



Original research



Prognostic relation of body mass index on extended aromatase inhibition treatment in postmenopausal patients with estrogen receptor positive breast cancer: A retrospective analysis of the SOLE trial

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ABSTRACT

Background: Obesity is associated with a greater risk of developing distant recurrences in patients with estrogen receptor-positive (ER+) breast cancer. This association is however poorly investigated in patients treated with extended endocrine treatment (ET). We therefore evaluated the prognostic role of BMI in the SOLE trial, where postmenopausal patients, after having completed 4–6 years of adjuvant ET, were treated with 5 additional years of continuous or intermittent letrozole.

Patients & methods: We considered the 3606 patients with ER+ /HER2- lymph node-positive BC with available BMI from the SOLE trial (NCT00553410). Distant-recurrence free interval (DRFI) was the main endpoint, and breast cancer-free interval (BCFI), disease-free survival (DFS) and overall survival (OS) secondary endpoints. Adjusted risk ratios (RR) for distant metastases were estimated with crude cumulative incidence models.

Results: 38.6 % of the patients were underweight or normal weight, 36.5 % overweight and 24.9 % obese. BMI was associated with age, tumor size, number of positive lymph nodes, menopausal status and type of prior ET. In the adjusted analyses, the prognostic value of BMI was dependent on prior ET and extended ET arm (second-order interaction p-value < 0.001 for DRFI, BCFI and DFS, but not for OS). For instance, in patients treated with both a selective estrogen receptor modulator and an aromatase inhibitor in the first five years, obesity, as

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compared to normal-weight, was associated with better ($RR_{DRFI}=0.61$, 95 %CI: 0.42–0.90) and worse ($RR_{DRFI}=2.31$, 95 %CI: 1.41–3.78) outcomes in the adjusted models, in patients treated with continuous and intermittent letrozole in the extended ET, respectively.

Conclusion: We observed that the prognostic relation of BMI changes according to the type of adjuvant ET and mode of administration of extended AI. This warrants further investigation.

1. Introduction

Obesity has reached epidemic proportions in Western countries, and it has been estimated that one out of two adults will have obesity by 2030 in the United States and by 2050 in the United Kingdom, with detrimental consequences for the general population [1,2]. Obesity, commonly defined by a body mass index (BMI) ≥ 30 kg/m², is a complex condition which is associated with a greater risk of developing 13 types of cancer among which breast cancer [3]. In addition, obesity has been associated with poor outcomes in all molecular subtypes, while overweight was only associated with worse prognosis in patients with estrogen receptor-positive (ER+) breast cancer [4–6].

Late distant recurrence, after 5 years from the initial diagnosis, is a major consequence of unsuccessful treatment in patients with ER+ breast cancer [7]. One of the strategies to reduce this risk of late recurrences is to extend adjuvant endocrine treatment [8]. Obesity has been identified as one of the determinants of distant recurrence. A recent analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that overweight and obesity are associated with increased distant recurrence and breast cancer mortality in all types of patients with early-stage breast cancer [9]. Additionally, Ewertz *et al.* showed in a large national study that women with obesity had a greater risk of distant recurrence 5–10 years after BC diagnosis [10]. A pooled analysis of post-diagnosis lifestyle factors including BMI assessed ~ 2 years after the diagnosis of ER+ breast cancer, showed that obesity was associated with a greater risk of late distant recurrence [11]. Although several trials have investigated the efficacy and the optimal duration of the extended ET [12–14], none of these studies focused on the association between BMI and late distant recurrence in patients treated with extended ET, according to the type and mode of administration of ET.

The Phase 3 SOLE trial (NCT00553410) compared extended adjuvant intermittent letrozole to continuous letrozole for 5 years in women with ER+ /HER2 non-amplified (HER2-) breast cancer who were postmenopausal at study inclusion and did not have evidence of any type of recurrence after having completed 4–6 years of adjuvant ET [14,15]. The trial hypothesis was that resistance to continuous letrozole could be reversed by withdrawing and reintroducing letrozole. The final trial results however showed no evidence that disease-free survival (DFS), the primary endpoint of the trial, was improved with the intermittent as compared to the continuous administration [14]. The investigators also conducted the SOLE estrogen substudy in a small number of patients to document the changes of circulating estrogen levels. The results showed that the estrogen levels decreased with the administration of letrozole and increased again 1.5 month after interrupting letrozole. The estrogen recovery levels were however higher in patients with overweight and obesity [14]. In this retrospective analysis, we aimed to investigate the association of BMI with the clinical and pathological variables of the patients and their tumor, and to investigate into more detail the prognostic value of BMI in the SOLE trial, also taking into consideration the type of initial ET the patients received.

2. Methods

2.1. Study design and participants

The SOLE trial (NCT00553410) consisted of 4884 patients with unilateral, lymph node-positive, hormone receptor-positive operable invasive breast cancer who were postmenopausal and did not have

evidence of any type of recurrence at study inclusion. All patients had completed 4–6 years of prior adjuvant ET with Selective Estrogen Receptor Modulators (SERM), a sequential use of SERM and Aromatase Inhibitors (AI) or only AI. Patients who had received prior luteinizing-hormone releasing-hormone (LHRH) analogues within the last year were eligible if they had definite evidence of postmenopausal status as defined in the protocol. Patients were randomized to receive 5 additional years of continuous letrozole (2.5 mg/day for 5 years) vs intermittent letrozole (2.5 mg/day for 9 months in years 1–4, followed by a 3-month interruption in each year, and then 2.5 mg/day without interruption in year 5). Randomization was stratified by previous adjuvant endocrine therapy (AI only vs SERM only vs both AI and SERM). Details of the study, including the definition of the menopausal status, have been reported previously [14,15].

Patient selection for the post-hoc exploratory retrospective study is illustrated in the flow-chart (Supplementary Figure 1). Eligible patients for the retrospective study were taken from the intention-to treat (ITT) population of the SOLE trial with positive lymph nodes, ER+ /HER2-breast cancer (3793 of 4884 enrolled patients). BMI, collected by the health care provider at randomization, was the main inclusion criteria for the present study and it was available for 3606 of the 4884 patients (Supplementary Figure 1). A scheme of the patients from the SOLE trial considered for the present study is shown in Figure 1.

Ethics committees and appropriate national health authorities of each center approved the protocol, which included mandatory prospective submission of tissue for central pathology review. All patients provided written informed consent for trial participation and for future use of biological samples under IBCSG Translational Research Working Group oversight.

2.2. Statistical analysis

For all analyses, we considered the values obtained from the central pathology review for ER, progesterone receptor (PR) and HER2 receptor, and local pathology values if central pathology values were not available. BMI was categorized according to the World Health Organization (WHO) criteria (underweight: < 18.5 , normal weight 18.5 – 24.9, overweight 25 – 29.9, obesity ≥ 30 kg/m²) [16]. The association between baseline clinico-pathological characteristics and BMI was evaluated using Fisher exact test and Kruskal-Wallis test when comparing categorical and continuous variables against the three BMI categories.

Based on the reported associations of BMI with distant recurrences but not locoregional recurrences or non-breast second primary cancers [17], we considered distant-recurrence free interval (DRFI), defined as the time from randomization to the invasive recurrence of BC at a distant site, as the main study endpoint. Secondary endpoints considered in this work were: 1) breast cancer-free interval (BCFI) defined as the time from randomization to the recurrence of invasive BC or invasive contralateral BC; 2) disease-free survival (DFS) defined as the time from randomization to the first appearance of invasive recurrence of BC, invasive contralateral BC, second invasive non-breast malignancy, or death without recurrence; 3) overall survival (OS) defined as the time from randomization to death from any cause.

In the following analyses, competing risk analyses were adopted. Competing events for DRFI (main outcome) were: death without distant recurrence, secondary non-breast malignancy, contralateral invasive breast cancer, and loco-regional recurrence. Competing events for BCFI were: death without distant recurrence and secondary non-breast

malignancy [18]. Estimates of Crude Cumulative Incidences (CCIs) for BMI groups conditioned to prior ET and treatment arm were reported. Then, the prognostic effect of BMI was evaluated by transformation models on pseudo-values for CCIs of the outcomes [19].

The covariates included in the models were: treatment arm (intermittent vs continuous) prior ET (SERM only, both SERM and AI vs AI only), age, BMI, tumor grade (G2, G3 vs G1), tumor size (>2 cm vs ≤2 cm), number of positive lymph nodes (≥ 4 vs 1–3), and histology (invasive lobular carcinoma (ILC), mixed invasive of no-special type (NST)/ILC, other vs NST). According to the study objective, second order interactions between prior ET, treatment arm and BMI were evaluated. A flexible model parameterization was performed for the baseline risk function and the effect of age and BMI, using restricted cubic splines [20]. Also, the assumption of proportional risks through time was assessed by specifying an interaction term between covariates and time variable. Results were presented in terms of estimated Risk Ratios (RR) and respective 95 % CIs. Covariate effects were assessed by the Wald test and deemed statistically significant for $p < 0.05$. Statistical analyses were performed using R version 4.2.1 [21] with the package *geepack* [22] and *multcomp* [23].

3. Results

3.1. Distribution of patient characteristics according to BMI

BMI was available for 3606 patients with lymph-node positive ER+ / HER2- breast cancer enrolled in the SOLE trial (Figure 1). Thirty-five (1 %) were underweight, 1356 (37.6 %) were normal weight, 1315 (36.5 %) were overweight and 899 (24.9 %) were obese. Considering the small number of patients with underweight, these were grouped with patients with normal weight for the subsequent analyses. In Table 1 we report the clinico-pathological characteristics of the patients according to BMI category. There was a higher proportion of patients with overweight or obesity who were menopausal at diagnosis, had larger tumors (>2 cm), had more positive axillary lymph nodes (≥4) and were White/Caucasian, as compared to patients with underweight or normal weight. Patients with overweight or obesity were also older at trial randomization than patients with underweight or normal weight. BMI was also associated with prior ET: women with obesity being more represented in the patients who received AI only (27.4 %) as compared to those who received SERM only (22.2 %) and a combination of SERM and AI (23.6 %). This can be explained by the fact that BMI is associated

with age at diagnosis and menopausal status, and that postmenopausal women are in general more likely to receive an AI than a SERM. The proportion of postmenopausal women at diagnosis in our study was indeed 54 %, 74.7 % and 87.2 % in the SERM only group, the combined SERM and AI group, and the AI only group, respectively (Supplementary Table 1). Also, the age category distribution differed according to the prior ET category, with the proportion of older women being the highest in the AIs only group. Finally, BMI was associated with race, with Asian women, who represented 5.4 % of the cohort, more likely to be normal weight.

3.2. Prognostic association of BMI with DRFI

We investigated the risk of developing a distant recurrence according to BMI category, prior adjuvant ET and treatment assignment (intermittent versus continuous letrozole) considering the competing risks for this endpoint. After a median follow-up of 84 months, 339 distant recurrences were observed and the number of patients and events per treatment arm and prior type of ET are listed in Supplementary Table 2.

The analyses provided evidence for a second-order interaction for DRFI (Wald p-value for adjusted analysis < 0.0001), suggesting a joint modifying role of BMI, prior ET and treatment arm on distant recurrence (Figure 2, Supplementary Table 3). Of note, there was also evidence for a second-order interaction for the competing risk analyses of DRFI (Wald p-value for adjusted analysis < 0.039, Supplementary Figure 3, Supplementary Table 4). We will now present the results according to the prior ET the patients received.

For the patients who were treated with SERM only as prior ET, we observed a higher cumulative incidence of distant recurrence in overweight patients, as compared to normal weight, in both treatment arms (continuous and intermittent letrozole, Figure 2A). The adjusted relative risks confirmed this observation (continuous arm: RR=1.59, 95 % CI: 0.98–2.59 for overweight vs normal weight, intermittent arm: RR=2.30, 95 % CI: 1.49–3.57 for overweight vs normal weight), (Figure 2A,B; Supplementary Table 3). With regard to patients with obesity, we observed a lower risk compared to patients with normal weight in the adjusted analyses, but only in the intermittent letrozole arm (RR=0.61, 95 % CI: 0.42–0.90, Figure 2A,B). Analyses of the competing risks (which include death without distant recurrence, secondary non-breast malignancy, contralateral invasive breast cancer, and loco-regional recurrence), revealed that patients with overweight, as compared to patients with normal weight, were showing a lower risk for the

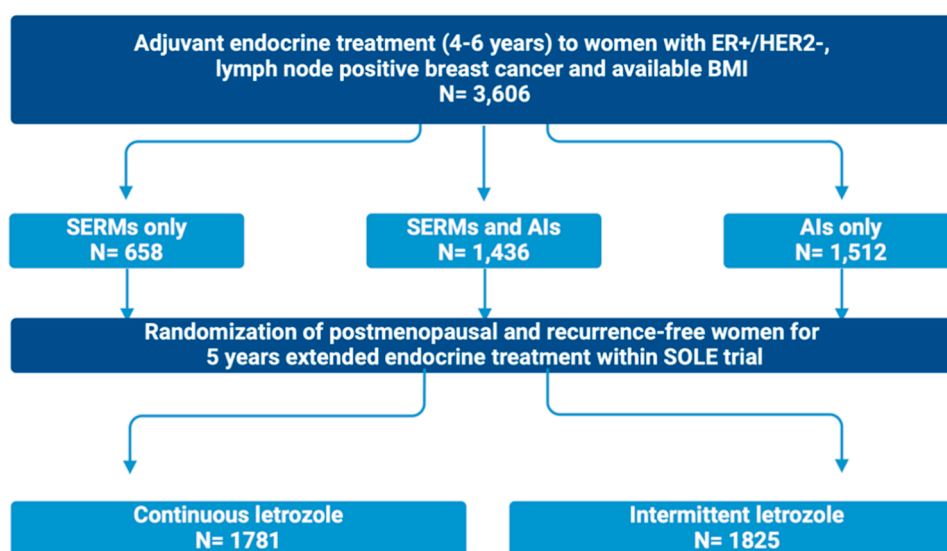


Fig. 1. Overview of the SOLE trial design and patient cohort for this retrospective analysis. Abbreviations: AI: aromatase inhibitor, BMI: body mass index, ER: estrogen receptor, SERM: Selective Estrogen Receptor Modulator.

Table 1
Patients and tumor characteristics according to BMI.

Patient and tumor characteristics	Underweight/ Lean N = 1391	Overweight N = 1315	Obese N = 899	p-value
Age at randomization (continuous), years				< 0.001
Mean (SD)	59 (9)	61 (9)	61 (9)	
Median (IQR)	58 (53–65)	61 (55–67)	62 (55–67)	
Range	34–86	38–90	35–85	
Race				0.001
White/Caucasian	1206 (86.6)	1210 (92.1)	854 (95.0)	
Black	5 (0.4)	3 (0.2)	5 (0.6)	
Asian	142 (10.2)	46 (3.5)	8 (0.9)	
Other	39 (2.8)	55 (4.2)	32 (3.6)	
Missing	0	1	0	
Menopausal status at diagnosis				0.001
Premenopausal	327 (23.6)	247 (18.9)	152 (16.9)	
Perimenopausal	59 (4.3)	40 (3.1)	32 (3.6)	
Postmenopausal	1000 (72.2)	1023 (78.1)	714 (79.5)	
Missing	6	5	1	
Number of positive lymph-nodes				0.026
1–3	971 (69.8)	903 (68.7)	579 (64.5)	
≥ 4	421 (30.2)	411 (31.3)	319 (35.5)	
Missing	0	1	1	
Tumor grade				0.191
1	296 (22.2)	282 (22.4)	174 (20.1)	
2	759 (56.9)	731 (58.1)	537 (61.9)	
3	278 (20.9)	245 (19.5)	156 (18.0)	
Missing	59	57	32	
Tumor size (continuous), cm				< 0.001
Mean (SD)	2.42 (1.63)	2.59 (1.67)	2.76 (1.98)	
Median (IQR)	2.00 (1.40–3.00)	2.20 (1.50–3.00)	2.20 (1.50–3.10)	
Range	0.10–13.50	0.00–15.00	0.00–19.00	
Tumor size				0.001
≤ 2 cm	745 (53.7)	590 (45.0)	394 (44.1)	
> 2 cm	642 (46.3)	721 (55.0)	499 (55.9)	
Missing	5	4	6	
Ki67 (%)				0.201
Mean (SD)	19 (10)	20 (11)	20 (12)	
Median (IQR)	17 (12–24)	18 (13–25)	18 (13–26)	
Range	1–99	0–99	1–80	
Missing	194	151	116	
Ki67 index				0.634
< 10 %	145 (12.1)	127 (10.9)	87 (11.1)	
≥ 10 %	1053 (87.9)	1037 (89.1)	696 (88.9)	
Missing	194	151	116	
Hormone receptor status				0.219
ER+ /PR+	1255 (90.5)	1206 (91.9)	830 (92.4)	
ER+ /PR-	132 (9.5)	106 (8.1)	68 (7.6)	
ER+ /PR unknown	5	3	1	
Tumor histology				0.102
NST	1053 (75.6)	1051 (79.9)	718 (79.0)	
ILC	239 (17.2)	172 (13.1)	131 (14.6)	
Mixed NST/ILC	50 (3.6)	50 (3.8)	27 (3.0)	
Other	50 (3.6)	42 (3.2)	31 (3.4)	
Local therapy				0.112
Mastectomy with RT	454 (32.6)	432 (32.9)	300 (33.4)	
Mastectomy no RT	218 (15.7)	185 (14.1)	102 (11.3)	
BCS with RT	706 (50.7)	689 (52.4)	490 (54.5)	
Other	14 (1.0)	9 (0.7)	7 (0.8)	
Previous chemotherapy				0.615
No	295 (21.2)	281 (21.4)	281 (21.4)	
Yes	1097 (78.8)	1034 (78.6)	1034 (78.6)	

Table 1 (continued)

Patient and tumor characteristics	Underweight/ Lean N = 1391	Overweight N = 1315	Obese N = 899	p-value
Previous endocrine therapy				0.005
SERMs only	267 (19.2)	238 (18.1)	139 (15.5)	
SERMs and AIs	609 (43.8)	535 (40.7)	361 (40.2)	
AIs only	516 (37.1)	542 (41.2)	399 (44.4)	
Time from end of previous endocrine therapy to randomization				0.785
≤ 1 month	989 (71.0)	940 (71.5)	651 (72.4)	
> 1 month	403 (29.0)	375 (28.5)	248 (27.6)	
Duration of previous endocrine therapy				0.227
< 4.5 years	212 (15.2)	234 (17.8)	168 (18.7)	
4.5–5.5 years	1059 (76.1)	972 (73.9)	656 (73.0)	
> 5.5 years	120 (8.6)	109 (8.3)	75 (8.3)	
Missing	1	0	0	

Abbreviations: AIs: aromatase inhibitors; BCS: breast conservative surgery; BMI: body mass index; ER: estrogen receptor; ILC: invasive lobular carcinoma; IQR: interquartile range; NST: invasive carcinoma of no special type; PgR: progesterone receptor; RT: radiotherapy; SD: standard deviation; SERMs: selective estrogen receptor modulators.

competing events but only in the continuous letrozole arm (Supplementary Figure 3; Supplementary Table 4). There was no statistical evidence that overweight or obesity was associated with a higher risk of competing events compared to normal weight in this group of patients.

For patients treated with a combination of SERM and AI as prior ET, we observed that patients with obesity had a higher risk of distant recurrence compared to patients with normal weight, but only in the intermittent letrozole arm. This was maintained in the adjusted analyses (RR=2.31, 95 % CI: 1.41–3.78, Figure 2A,B). Regarding the competing risk analysis, patients with overweight, as compared to patients with normal weight, were showing a lower risk for the competing events, but only in the intermittent letrozole arm (Supplementary Figure 2; Supplementary Table 4). Here again, there was no statistical evidence that overweight or obesity was associated with a higher risk of competing events. As the duration of AI given in this group is variable (median=4, range: 3–5 years), we also explored a model where we added the exact duration of the AI received as prior ET as a variable. The results were very similar to the ones obtained by the model without that variable and therefore do not add statistical evidence for a possible impact of the duration of the prior AI treatment on the results (Supplementary Figures 3 and 4 and Supplementary Tables 5 and 6).

For the patients treated with AIs only as prior ET, we observed a lower cumulative incidence of distant recurrence for patients with overweight, only in the intermittent letrozole arm. However, patients with overweight or obesity had a lower risk of distant recurrence compared to patients with normal weight in both arms in the adjusted analyses (continuous arm: RR=0.64, 95 % CI: 0.46–0.89 for overweight vs normal; continuous arm: RR=0.65, 95 % CI: 0.47–0.89 for obese vs normal; intermittent arm: RR=0.38, 95 % CI: 0.29–0.50 for overweight vs normal weight; intermittent arm: RR=0.63, 95 % CI: 0.46–0.87) (Supplementary Table 3). There was no statistical evidence that overweight or obesity was associated with a higher risk of competing events.

Regarding the other variables included in the model, we observed that intermediate and high grade (as compared to low grade), ILC and mixed histology (as compared to NST), 4 or more positive lymph nodes (as compared to less than 4 lymph nodes) as well as a tumor size above 2 cm (as compared to less than 2 cm) were associated with an greater risk of distant recurrence (Figure 2C). As previously described [24], age

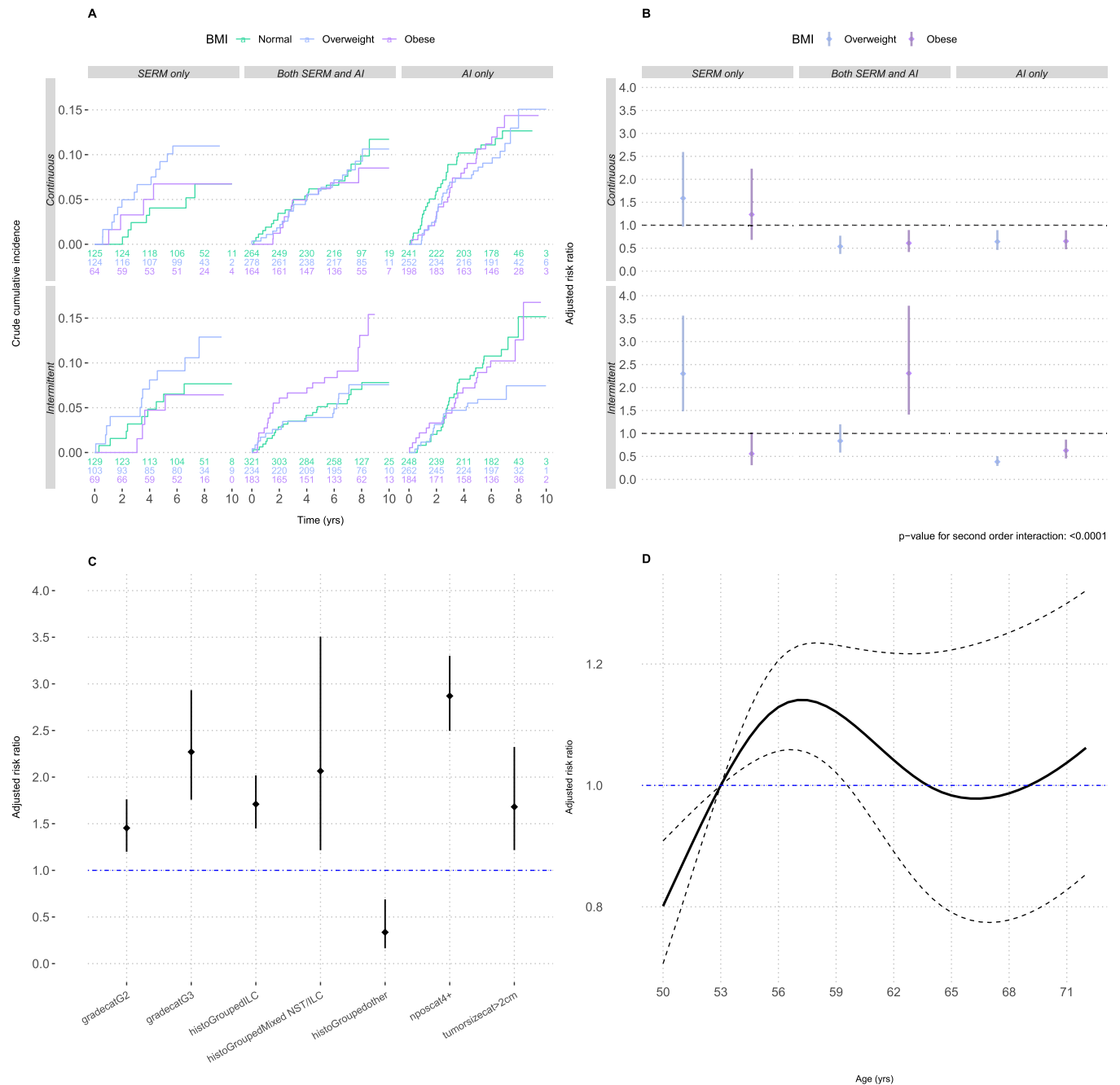


Fig. 2. Prognostic association of categorical BMI with DRFI. (A) Unadjusted non-parametrical estimates of CCI of distant recurrences conditioned on prior endocrine treatment, treatment arm and BMI category. (B) Forest plot of the estimated risk ratios of distant recurrences between patients with normal weight and overweight (blue) and between patients with normal weight and obesity (purple) adjusted for tumor size, grade, histology, number of positive lymph nodes, and age. Patients with normal weight are the reference category. (C) Estimated risk ratios for the other covariates in the multivariable model: tumor grade, tumor size, histology, and number of positive lymph nodes. (D) Plot of the non-linear effect of age, modelled with a restricted cubic spline. The risk ratios (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95 % CIs. Abbreviations: BMI: body mass index; CCI: crude cumulative incidence; CIs: confidence intervals.

was non-linearly associated with the risk of distant recurrence ($p = 0.016$, Figure 2D). Regarding the competing risks, increasing age, as expected, was associated with an increased risk, but grade 3 (as compared to grade 1), and ILC histology (as compared to NST) were associated with a lower risk.

Similar observations were made when considering BMI as a continuous variable (Supplementary Figures 5 and 6, Supplementary Tables 7 and 8).

To conclude, we observed that the association of BMI with distant recurrences (and with competing risks) depends on the prior ET

treatment and the treatment arm (continuous versus intermittent letrozole administration).

3.3. Prognostic association of BMI with the other endpoints

We further investigated the impact of BMI on the remaining endpoints of the SOLE trial, starting with BCFI. For this endpoint, a second-order interaction was observed ($p < 0.0001$). The cumulative incidence plots and multivariable model for BCFI (Figure 3, Supplementary Table 7) showed very similar results to those obtained for DRFI, with the

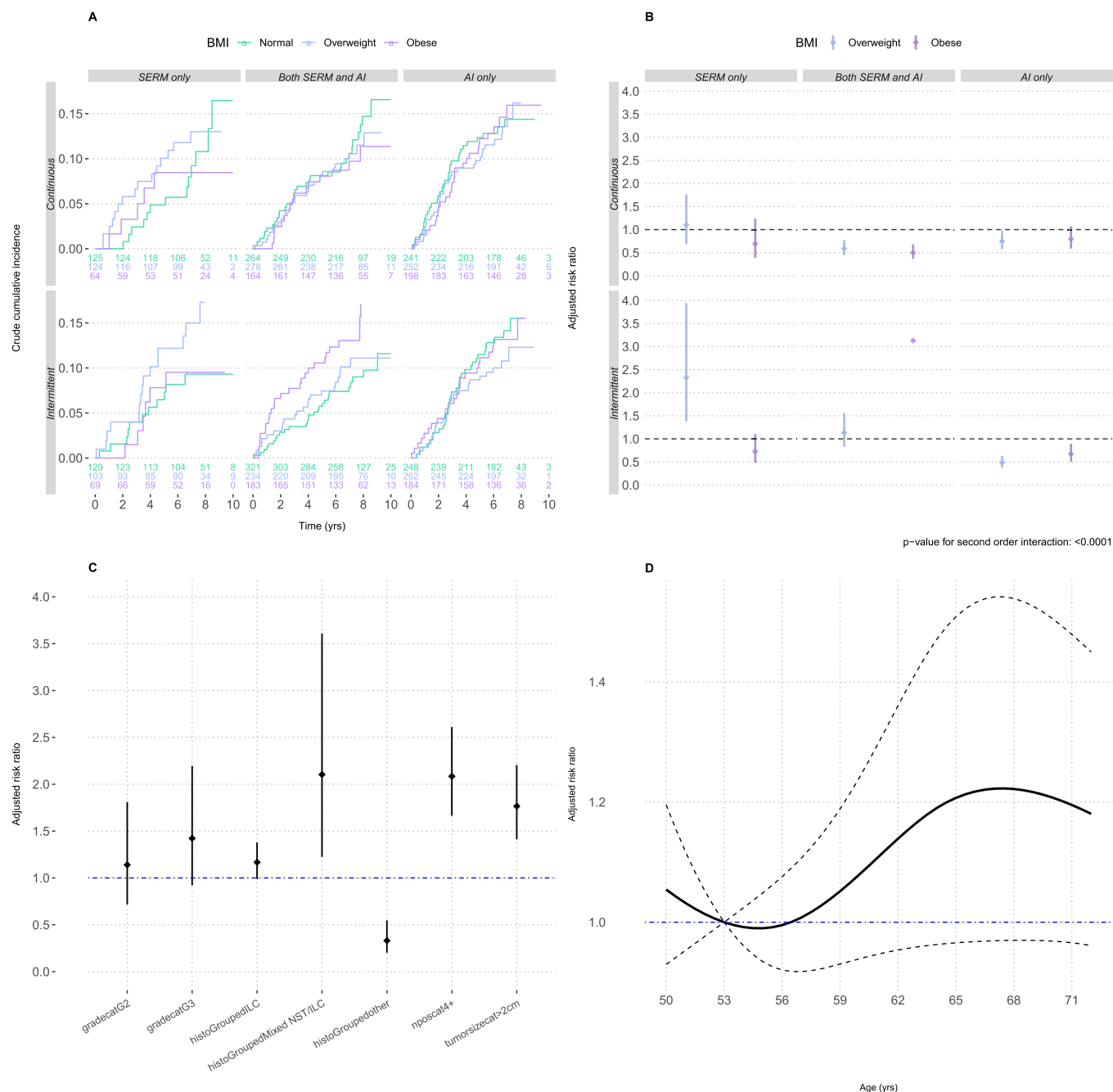


Fig. 3. Prognostic association of categorical BMI with BCFI. (A) Unadjusted non-parametrical estimates of CCI of BC recurrences conditioned on prior endocrine treatment, treatment arm and BMI category. (B) Forest plot of the estimated risk ratios of BC recurrences between patients with normal weight and overweight (blue) and between patients with normal weight and obesity (purple) adjusted for tumor size, grade, histology, number of positive lymph nodes, and age. Patients with normal weight are the reference category. (C) Estimated risk ratios for the other covariates in the multivariable model: tumor grade, tumor size, histology, and number of positive lymph nodes. (D) Plot of the non-linear effect of age, modelled with a restricted cubic spline. The risk ratios (solid line) are computed with respect to a subject of 53 years of age as the reference. Dashed lines represent the 95 % CIs. Abbreviations: BC: breast cancer; BCFI: breast cancer free interval; BMI: body mass index; CCI: crude cumulative incidence; CIs: confidence intervals.

exception that there was no statistical evidence anymore of patients with overweight having received SERM only as prior ET to have a worse survival compared to lean patients in the continuous letrozole arm. The competing risk analysis, where competing events are death without distant recurrence and secondary non-breast malignancy, was also in line with the competing analysis of DRFI with the exception that here patients with obesity had a higher risk of competing events as compared to lean patients in the group of patients treated with SERM only as prior ET and in the continuous letrozole arm (RR = 4.92 (1.76, 13.77)). Here, the second-order interaction for the competing risks did not reach

statistical significance ($p = 0.11$, [Supplementary Figure 7, Supplementary Table 8](#)). Further analyses showed a significant non-linear impact of continuous BMI (p -value: <0.0001), among prior ET and treatment arm groups ([Supplementary Figures 8 and 9, Supplementary Tables 7 and 8](#)).

We also observed similar results for DFS as for DRFI and BCFI, with again a second-order interaction ($p = 0.001$, [Supplementary Figure 10, Supplementary Table 9](#)). In general, the RRs were less pronounced (i.e., closer to 1) and here there was no significant difference anymore between the patients with obesity versus normal weight in all patients treated with AIs only as prior ET, as well as in those treated with SERM

only followed by intermittent letrozole. Here again, a significant non-linear effect of continuous BMI was observed (Supplementary Table 9, Supplementary Figure 11).

In the multivariable model for incidence of death for any cause (Supplementary Figures 12 and 13; Supplementary Table 10), the observations were different from those made for the previous endpoints. Here, patients with obesity treated with adjuvant SERMs followed by continuous letrozole showed a higher risk as compared to patients with normal weight. Also, a general trend for higher risk of death was observed for patients with overweight and patients with obesity as compared to patients with normal weight in all the remaining groups.

To conclude, we did observe for the BCFI and DFS endpoints, but not for OS, that the association of BMI was still dependent on the prior ET as well as on the treatment arm, with some differences regarding DRFI.

4. Discussion

In this retrospective study of the SOLE trial, we first evaluated the association of BMI with clinico-pathological features and then with distant recurrence as primary endpoint. The association of obesity with unfavorable tumor characteristics, such as larger tumor size and increased axillary lymph node involvement, has been extensively documented and was also observed in our analysis [25–29]. These associations are most probably the consequence of a delay in the physical detection of a palpable mass in larger breasts, combined with socio-economic factors and healthcare behaviors associated with obesity as well as with differences in biology. Overweight and obesity have also been consistently associated with older age at diagnosis and with menopause [25–29], which is also the case in our series.

Regarding the association of BMI with prognosis, we chose distant recurrences as our primary endpoint given the documented association of BMI with distant but not loco-regional recurrences [17]. We observed a second order interaction between BMI, type of prior ET and modality of administration of extended letrozole (intermittent versus continuous), which to our knowledge has not yet been reported before. It is important to realize that the variable “prior ET” is not only relevant for the type of ET the patient received initially, but also for the age and menopausal status distribution at diagnosis. Indeed, while all patients had to be postmenopausal at the time of inclusion in the SOLE trial, this was not mandatory at primary diagnosis and differences were observed across the prior ET groups with 74 %, 51 % and 35 % of the patients who were younger than 60 years at diagnosis, and 54 %, 75 % and 87 % who were postmenopausal in the group of SERM only, of SERM and AI, and, AI only group, respectively. This is relevant for the levels and the source of estrogens at diagnosis, the levels of estrogen being much higher and mainly originating from the ovaries in premenopausal women and much lower and mostly originating from the adipose tissue in postmenopausal women. It is important to note that all our analyses were adjusted for age and exploratory analyses substituting age for menopausal status revealed similar results (data not shown). We could therefore postulate that while the “prior ET” variable represents different patient populations in terms of age and menopausal status, the type of ET might still be relevant regarding prognosis.

In our analysis, we showed that a worse prognosis in patients with overweight or obesity was only evident in a few subgroups of patients such as in those treated with SERM only followed by intermittent or continuous letrozole or in those treated with both SERM and AI followed by intermittent letrozole. These observations might not only result from the extended ET with letrozole but possibly also from a possible differential agonist-antagonist balance of tamoxifen, that the patients have received as first adjuvant therapy, according to estrogen concentrations [30–34].

On the contrary, a lower risk of distant recurrence in patients with overweight or obesity treated with AIs only followed by continuous or intermittent letrozole was observed compared to patients with normal weight. This suggests that in this patient population, which was mostly

postmenopausal at primary diagnosis with estrogens consequently produced by the adipose tissue and at higher levels than in patients with normal weight, a first adjuvant therapy with AI followed any mode of administration of letrozole was more effective in controlling distant recurrences than in patients with normal weight. While these results could be surprising based on the literature [9,17], we should obviously remain cautious in the interpretation of the results given the relatively small number of patients and events in some of the different subgroups of prior ET and treatment arm. Also, there are many documented mechanisms of endocrine resistance and disease progression, some related to obesity and some not related, and we obviously do not know which mechanism was responsible of the distant recurrences observed in the patients of the SOLE trial.

While the association between obesity and a higher risk of recurrence is supported by many studies [4–6], the association of BMI with recurrence and survival is under-investigated in the ER+ /HER2- patient subgroup treated with extended ET. The only trial which retrospectively dedicated a study on this topic was the ABCSG- 6a trial, which investigated the addition of 3 years of anastrozole versus nil after the initial ET in the ABCSG-6 trial (where postmenopausal patients were treated with tamoxifen versus tamoxifen plus aminoglutethimide, a non-steroidal AI). Their analysis suggested that the extended ET would only benefit patients with normal weight but not patients with overweight or obesity. Our results can however not be compared to those from the ABCSG-6a trial since: (i) all patients were already postmenopausal at the start of the adjuvant therapy, (ii) the trial investigated another AI, anastrozole, than in the SOLE trial, and (iii) all patients received extended ET in the SOLE trial. While AI act by suppressing estrogen synthesis, not all AIs are equal and it has been demonstrated that letrozole is a more potent AI than anastrozole, being more effective in decreasing plasma levels of estradiol and estrone sulfate [35]. Consequently, anastrozole might not be potent enough to decrease estrogen levels in patients with overweight or obesity, as suggested also by the retrospective analysis of the ABCSG-12 trial [36].

Several studies reported that patients with overweight and obesity have an increased risk of developing contralateral breast recurrences and second primary cancers at other sites than breast [37]. The analysis of the competing events in our study does not directly support this, as we do not have statistical evidence of a higher risk for competing events in our DRFI and BCFI analyses of patients with overweight or obesity compared to normal weight, except for patients treated with SERM only as prior ET followed by continuous letrozole. This could suggest that extended ET helps in preventing these events.

While our study has several unique features, such as the fact that it represents a retrospective analysis of a clinical trial, that BMI was available for most patients and that the follow up extended until ~15 years after the diagnosis of BC, it also has several limitations. Firstly, the treatment the patients received in the first 4–6 years before being randomized in the SOLE trial is not randomized. Therefore, caution is required regarding the interpretation of the prior ET treatment. Secondly, BMI was only recorded at the time of enrollment in the SOLE trial, approximately 5 years after BC diagnosis and BMI at the time of BC diagnosis was not available. Although several studies showed that BMI is associated with worse prognosis irrespective of when it is recorded [38], longitudinal evaluation of BMI might have been of interest. Thirdly, obesity is a multifactorial metabolic disorder. While BMI remains the most practical and most widely used measure of obesity, it does not consider body composition and fat distribution, nor metabolic, hormonal or microbiota abnormalities. It therefore remains to be investigated what is driving the complex associations we observed between BMI, prior ET and extended ET in this analysis. While this is not possible in this trial, it raises the necessity to collect additional data in future clinical trials, such as body composition, metabolic and hormonal measurements, as well as information on lifestyle, and preferentially at different points in time. Finally, this trial was conducted at the time the CDK4/6 inhibitors were not approved yet. While so far there is no

evidence for differential efficacy of CDK4/6 inhibitors in the adjuvant setting [39], results from the retrospective analysis in the monarchE [40] and NATALEE [41] trials according to BMI are still awaited.

To conclude, in the present study, we showed that the prognostic relationship of BMI in postmenopausal patients with ER+ /HER2- BC is more complex than initially anticipated as it may vary by the type of adjuvant ET and the modality of administration of extended ET. These results suggest that tailoring ET sequence approaches could be potentially based on BMI. Future studies should however be conducted to validate these observations and clarify the effect of BMI in this setting, and these studies should ideally include alternative measures of adiposity, together with metabolic and hormonal measurements.

CRedit authorship contribution statement

Boracchi Patrizia: Writing – review & editing, Methodology, Formal analysis. **Viale Giuseppe:** Writing – review & editing, Investigation. **Maetens Marion:** Writing – review & editing, Resources, Project administration. **Regan Meredith M.:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Floris Giuseppe:** Writing – review & editing, Investigation. **Dell’Orto Patrizia:** Writing – review & editing, Investigation. **Munzone Elisabetta:** Writing – review & editing, Investigation. **Hitre Erika:** Writing – review & editing, Investigation. **Desmedt Christine:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Conceptualization. **Colleoni Marco:** Writing – review & editing, Investigation. **Neven Patrick:** Writing – review & editing, Investigation. **Biganzoli Elia:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jerusalem Guy:** Writing – review & editing, Investigation. **Aebi Stefan:** Writing – review & editing, Investigation. **Richard François:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Kammer Roswitha:** Writing – review & editing, Investigation. **Marano Giuseppe:** Writing – review & editing, Methodology, Formal analysis. **Gombos Andrea:** Writing – review & editing, Investigation. **Biganzoli Giacomo:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Thompson Alastair:** Writing – review & editing, Investigation. **Isnaldi Edoardo:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data sharing

After publication, access to deidentified individual participant data may be requested by researchers by submitting a proposal (to stat-center@ibcsg.org), which will be reviewed for scientific merit and feasibility in accordance with the Guidelines for Collaborative research (https://www.ibcsg.org/images/Member/Public/Documents/Guidelines_for_Collaborative_Research_for_ETOP_IBCSG_Partners_Foundation_Dec_2022.pdf) and data sharing policy (https://www.ibcsg.org/images/Member/Public/Documents/Data_Sharing_Policy_for_IBCSG_Trials_Dec_2022.pdf) for IBCSG trials.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejca.2025.115438](https://doi.org/10.1016/j.ejca.2025.115438).

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