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ORIGINAL RESEARCH

Efficacy of adjuvant chemotherapy schedules for breast cancer according to body mass index: results from the phase III GIM2 trial

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Background: The phase III GIM2 trial showed improved disease-free survival (DFS) and overall survival (OS) with adjuvant dose-dense (DD) as compared with standard-interval (SI) chemotherapy in women with node-positive early-stage breast cancer (BC). This exploratory analysis aimed to investigate the benefit of different schedules according to body mass index (BMI) in this trial.

Patients and methods: This analysis explored the efficacy, in terms of DFS and OS, of different chemotherapy schedules according to BMI. Univariate and multivariable Cox proportional hazard models, adjusted for relevant prognostic factors, were used.

Results: Out of 2091 patients enrolled, 1925 with known baseline BMI were randomized in the DD versus SI comparison and therefore included in this analysis: 31.6% were overweight and 19.3% obese. Overweight and obesity were significantly associated with postmenopausal status, pT >2, and pN >2 tumors. After a median follow-up of 15.0 years (interquartile range 8.4-16.3 years), multivariable Cox survival models demonstrated no association of different BMI categories on DFS [adjusted hazard ratio (adjHR) 0.96, 95% confidence interval (CI) 0.80-1.15 and adjHR 1.11, 95% CI 0.91-1.35 for overweight and obese patients, respectively, compared to patients with normal BMI] or OS (adjHR 0.90, 95% CI 0.71-1.14 and adjHR 1.18, 95% CI 0.92-1.52 for overweight and obese patients, respectively). No significant interaction was found between BMI and treatment schedule in terms of DFS ($P_{\text{for interaction}} = 0.56$) or OS ($P_{\text{for interaction}} = 0.19$). The survival benefit of DD chemotherapy was observed irrespective of different BMI categories, with a more pronounced benefit for overweight and obese patients.

Conclusion: In node-positive BC patients, DD schedule should be considered the preferred schedule irrespective of BMI.

Key words: breast cancer, body mass index, chemotherapy, dose-dense

INTRODUCTION

The prevalence of obesity, defined by a body mass index (BMI) of 30 kg/m^2 or higher, has almost tripled since the 1980s.[1] Globally, obesity represents a significant public health challenge, particularly in high-income countries.[1,2] Overweight or obese women have up to 1.4-fold higher risks of developing breast cancer.[3] Furthermore, about two-

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thirds of postmenopausal patients and one-third of premenopausal patients with breast cancer are overweight or obese at the time of breast cancer diagnosis.[4] Several studies and meta-analyses have observed that elevated BMI at the time of breast cancer diagnosis is linked to poorer prognosis, with higher risk of breast cancer recurrence and mortality.[5-7] However, the precise mechanism responsible for the adverse impact of obesity on breast cancer outcomes is not still fully elucidated.

Biologically, the endocrine function of the adipose tissue results in producing some factors, including estrogens, leptin, and insulin-like growth factor, that stimulate changes in gene expression, supporting proliferation of cancer cells.[8,9] Moreover, hyperinsulinemia and impaired glucose metabolism observed in obese individuals lead to a chronically inflamed microenvironment, facilitating cancer cell growth and dissemination.[10] Non-biological elements may also contribute to increase the risk of breast cancer recurrence among obese women: chemotherapy under-dosing, higher frequency of tumors with larger size and nodal involvement at diagnosis, increased susceptibility to post-surgery complications, concomitant comorbidities, and the influence of body composition as a determinant of chemotherapy outcomes.[11-13]

Obesity in patients with breast cancer presents unique challenges during treatment; to date it is still controversial whether main results from clinical trials may be fully applicable according to different BMI categories.

Anthracycline plus taxane-containing adjuvant chemotherapy is considered the most effective treatment for early-stage breast cancer, reducing the annual risk of breast cancer mortality by at least one-third.[14] Long-term results from the randomized phase III GIM2 study showed that, for women with node-positive breast cancer, disease-free survival (DFS) and overall survival (OS) were significantly improved using dose-dense (DD) adjuvant anthracycline and taxane-based chemotherapy schedule compared with standard-interval (SI) schedule.[15]

The specific impact of BMI on the efficacy of different adjuvant chemotherapy schedules (DD or SI) remains a subject of debate; we report here results of an exploratory analysis aimed to investigate the benefit of different dosing schedules according to BMI categories in patients enrolled in the GIM2 trial.

PATIENTS AND METHODS

Study design and participants

Details of the GIM2 trial were previously reported.[15,16] Briefly, GIM2 was a multicenter open-label, randomized phase III trial, with a 2 × 2 factorial design aiming to address both the role of the addition of fluorouracil to a regimen with anthracycline and taxane, and the role of the DD schedule as adjuvant chemotherapy in patients with node-positive early breast cancer.

Early-stage breast cancer patients were eligible for enrollment if they had at least one axillary positive lymph node without radiological evidence of distant metastases. Estrogen and progesterone receptor expression was assessed locally and defined by a finding of at least 10% of positive cells by immunohistochemical analysis. Human epidermal growth factor receptor 2 (HER2) positivity, assessed locally, was defined by at least 10% of tumor cells with HER2 protein expression assessed by immunohistochemistry or *in situ* hybridization assay.

Eligible patients were randomized in a 1 : 1 : 1 : 1 ratio to one of the following groups: SI epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, on day 1, every 3 weeks followed by four cycles of paclitaxel 175 mg/m^2 on day 1, every 3 weeks (EC-P); SI fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2 (FEC-P) once every 3 weeks; DD EC-P every 2 weeks; and DD FEC-P every 2 weeks.

The study was approved by ethics committees of all participating institutions. Written, informed consent was obtained from all patients before study entry.

This trial is registered in ClinicalTrials.gov, NCT00433420.

Outcomes

This is an exploratory analysis aiming to evaluate the efficacy, in terms of DFS and OS, of different chemotherapy schedules (DD versus SI) according to different BMI categories.

Patients with known baseline BMI, assessed by a health care provider during clinical visits, were categorized according to the World Health Organization classification[17] as follows: underweight (BMI $\leq$18.5), normal weight (BMI $>$18.5 and $<$25), overweight (BMI $\geq$25 and $<$30), and obese (BMI $\geq$30). Due to the low frequency ($n = 29$, 1.5%) and potentially adverse prognosis, underweight patients were excluded from this analysis.[18]

Breast cancer subtypes were defined according to immunohistochemistry-defined characteristics in luminal-like, triple-negative, and HER2-positive.[15]

Statistical analysis

Long-term results of the GIM2 trial support that fluorouracil should not be added to EC-P regimen.[15] For this reason, the present analysis was conducted to estimate the prognostic and predictive role of BMI according to the schedule of chemotherapy administration (DD versus SI). We did not explore its impact in relation to the addition of fluorouracil to the anthracycline and taxane regimen.

Patients allocated to the five centers that provided only SI chemotherapy were excluded.

The associations between the BMI categories and the clinicopathologic characteristics were assessed using the chi-square test or Kruskal–Wallis test, for categorical or continuous variables as appropriate. To assess the impact of different BMI categories, DFS and OS were considered as primary and secondary endpoint as in the GIM2 trial.[15,16] DFS was calculated from the date of randomization to the date of local recurrence, distant metastases, contralateral or ipsilateral breast tumor (excluding ductal carcinoma *in situ*), second primary malignancy, or death from any cause,

whichever came first.[19] OS was calculated from the day of randomization to the date of death from any cause. DFS and OS of patients without an event were censored on the date of the last contact. Survival estimates were computed using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariable Cox proportional hazard models, adjusted for relevant prognostic factors, were used to explore the impact of BMI on chemotherapy schedule. The analyses were adjusted for standard clinico-pathologic variables such as age, histology, tumor size, nodal status, tumor grading, hormone receptor status, and HER2 status. Interaction between BMI categories and chemotherapy schedule was explored using Cox regression models, and statistical significance was tested with the likelihood ratio test. Second-order interaction of chemotherapy schedule, BMI, and luminal subtype was investigated given the very small available sample size for other subtypes.

Median follow-up time was estimated by the reverse Kaplan–Meier method. Relative dose intensity (RDI), expressed as a percentage of the planned dose, was calculated as the ratio of the received mean total dose to the planned dose of the treatment.

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0, and toxicities were compared among the tree BMI categories.

All reported P values are two-sided, and $P < 0.05$ was considered statistically significant. No adjustment for multiple testing was carried out. The present analysis was not pre-planned in the protocol; thus it must be considered exploratory. All statistical analyses were carried out using SAS version 9.4.

RESULTS

Baseline BMI and patient characteristics

Overall, 2091 patients were enrolled in the GIM2 trial. After exclusion of 88 patients enrolled in the five centers providing only SI chemotherapy, 49 (2.5%) patients with unknown BMI, and 29 (1.5%) underweight patients, 1925 patients were included in the present analysis.

Among the 1925 included patients, 907 (47.1%) were lean, 632 (32.8%) were overweight, and 386 (20.1%) were obese.

Clinical–pathological and treatment characteristics according to the three BMI categories are reported in Table 1. Demographic data were investigator-observed.

Increasing median age was observed according to different BMI categories, with a median age of 47.1 years (41.0-55.3 years), 54.8 years (47.6-60.5 years), and 58.4 years (51.9-63.4 years) for lean, overweight, and obese patients, respectively ($P < 0.0001$). Regarding prognostic factors, patients with tumor >2 cm (i.e. pT >2) were significantly more represented among overweight (50.6%) or obese (55.2%) subgroups as compared to lean patients (46.3%) ($P < 0.002$). All patients included in the GIM2 trial had node-positive disease: overweight and obese patients had significantly higher nodal stage (pN ≥2, 42.1% and 47.6%, respectively), compared to lean women (35.8%) ($P < 0.0001$). Breast-conserving surgery was more frequently chosen in patients with higher BMI (around 65%) compared to lean patients (58%) ($P = 0.004$).

RDI was similar in the different BMI categories being 98.1% in the lean group, 97.7% in the overweight group, and 97.1% in the obese group.

No major differences were reported among lean, overweight, and obese patients according to chemotherapy schedule (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.103650).

Survival outcomes according to BMI categories: intention to treat population

After a median follow-up of 15.0 years (interquartile range 8.4-16.3 years), a total of 732 DFS events were observed: 315 (34.7%), 240 (38%), and 177 (45.9%) in the lean, overweight, and obese groups, respectively. In terms of type of first DFS event, 406 patients developed a distant recurrence: 182 (57.8%), 131 (54.6%), and 93 (52.5%) in the lean, overweight, and obese groups, respectively. Second primary non-breast cancers were more frequently diagnosed in overweight or obese patients (12.1% and 11.3%, respectively) compared to lean patients (8.3%). Obese patients were more likely to experience death without recurrence as DFS event (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.103650).

Compared to lean patients, overweight and obese women had a higher risk of experiencing a DFS event [unadjusted hazard ratio (HR) 1.11, 95% confidence interval (CI) 0.94-1.31 and HR 1.37, 95% CI 1.14-1.65, respectively, $P = 0.003$]. Multivariable analysis adjusted for prognostic factors demonstrated no association between BMI and DFS [adjusted HR (adjHR) 0.96, 95% CI 0.80-1.15 and adjHR 1.11, 95% CI 0.91-1.35 for overweight and obese patients, respectively] (Figure 1A).

Overall, 436 OS events were observed: 180 (19.8%) among lean, 137 (21.7%) among overweight, and 119 (30.8%) among obese patients.

Similarly, overweight and obese patients were at higher risk of death compared to lean patients (unadjusted HR 1.11, 95% CI 0.89-1.38 and HR 1.59, 95% CI 1.26-2.01 for overweight and obese patients, respectively). However, when adjusting for prognostic factors, no difference in survival was observed across BMI categories (adjHR 0.90, 95% CI 0.71-1.14 and adjHR 1.18, 95% CI 0.92-1.52 for overweight and obese patients, respectively) (Figure 1B).

Comparison of the efficacy of DD and SI treatment according to BMI categories

No significant interaction was found between BMI and treatment schedule in terms of DFS ($P_{\text{for interaction}} = 0.56$) nor OS ($P_{\text{for interaction}} = 0.19$).

The benefit of DD chemotherapy was observed irrespective of different BMI categories in terms of DFS (adjHR 0.87, 95% CI 0.70-1.09; adjHR 0.72, 95% CI 0.56-0.93; and

Table 1. Patient, disease, and treatment characteristics according to BMI category

	Normal weight $n = 907$	Overweight $n = 632$	Obese $n = 386$	*P*
Age at randomization				<0.0001
Median, years (IQR)	47.1 (41.0-55.3)	54.8 (47.6-60.5)	58.4 (51.9-63.4)	
Age				<0.0001
<50	553 (61.0)	204 (32.3)	78 (20.2)	
≥50	354 (39.0)	428 (67.7)	308 (79.8)	
Type of surgery				0.004
Mastectomy	381 (42.0)	219 (34.7)	134 (34.7)	
Lumpectomy	526 (58.0)	413 (65.4)	252 (65.3)	
Histological type				0.338
Ductal	738 (81.4)	503 (79.6)	314 (81.4)	
Lobular	103 (11.4)	80 (12.7)	53 (13.7)	
Other	66 (7.3)	49 (7.8)	19 (4.9)	
Tumor stage				0.002
pT1	506 (55.8)	311 (49.2)	169 (43.8)	
PT2	343 (37.8)	272 (43.0)	182 (47.2)	
pT3-4	54 (6.0)	48 (7.6)	31 (8.0)	
Unknown	4 (0.4)	1 (0.2)	4 (1.0)	
Nodal status				<0.0001
pN1	583 (64.3)	366 (57.9)	202 (52.3)	
pN2	221 (24.4)	147 (23.3)	114 (29.5)	
pN3	103 (11.4)	119 (18.8)	70 (18.1)	
Histological grade				0.104
G1	60 (6.6)	28 (4.4)	23 (6.0)	
G2	430 (47.4)	273 (43.2)	173 (44.8)	
G3	390 (43.0)	313 (49.5)	184 (47.7)	
Unknown	27 (3.0)	18 (2.9)	6 (1.6)	
HER2 status				0.058
Negative	537 (59.2)	407 (64.4)	253 (65.5)	
Positive	213 (23.5)	137 (21.7)	87 (22.5)	
Unknown	157 (17.3)	88 (13.9)	46 (11.9)	
Hormone receptor status				0.320
Negative	152 (16.8)	99 (15.7)	68 (17.6)	
Positive	736 (81.2)	510 (80.7)	304 (78.8)	
Unknown	19 (2.1)	23 (3.6)	14 (3.6)	
Ki67 status				0.404
0-14	221 (24.4)	145 (22.9)	99 (25.7)	
15-20	80 (8.8)	54 (8.5)	22 (5.7)	
>20	432 (47.6)	298 (47.2)	183 (47.4)	
Unknown	174 (19.2)	135 (21.4)	82 (21.2)	
Arm				0.607
FEC-P	449 (49.5)	323 (51.1)	185 (47.9)	
EC-P	458 (50.5)	309 (48.9)	201 (52.1)	
Arm				0.332
DD	469 (51.7)	309 (48.9)	184 (47.7)	
SI	438 (48.3)	323 (51.1)	202 (52.3)	
Relative dose intensity of the combination, % (IQR)	98.1 (94.2-99.7)	97.7 (94.3-99.6)	97.1 (92.7-99.4)	0.004

BMI, body mass index; DD, dose-dense; EC-P, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, followed by paclitaxel 175 mg/m^2; FEC-P, florouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2, followed by paclitaxel 175 mg/m^2; G, grade; IQR, interquartile range; HER2, human epidermal growth factor receptor 2; SI, standard-interval.

adjHR 0.70, 95% CI 0.51-0.93, for lean, overweight, and obese patients, respectively) (Figure 2A-C).

Similarly, in terms of OS, the benefit of DD chemotherapy was observed irrespectively of different BMI categories, with a more pronounced benefit for overweight and obese patients (adjHR 0.91, 95% CI 0.67-1.21; adjHR 0.60, 95% CI 0.42-0.85; and adjHR 0.61, 95% CI 0.42-0.88) (Figure 3A-C).

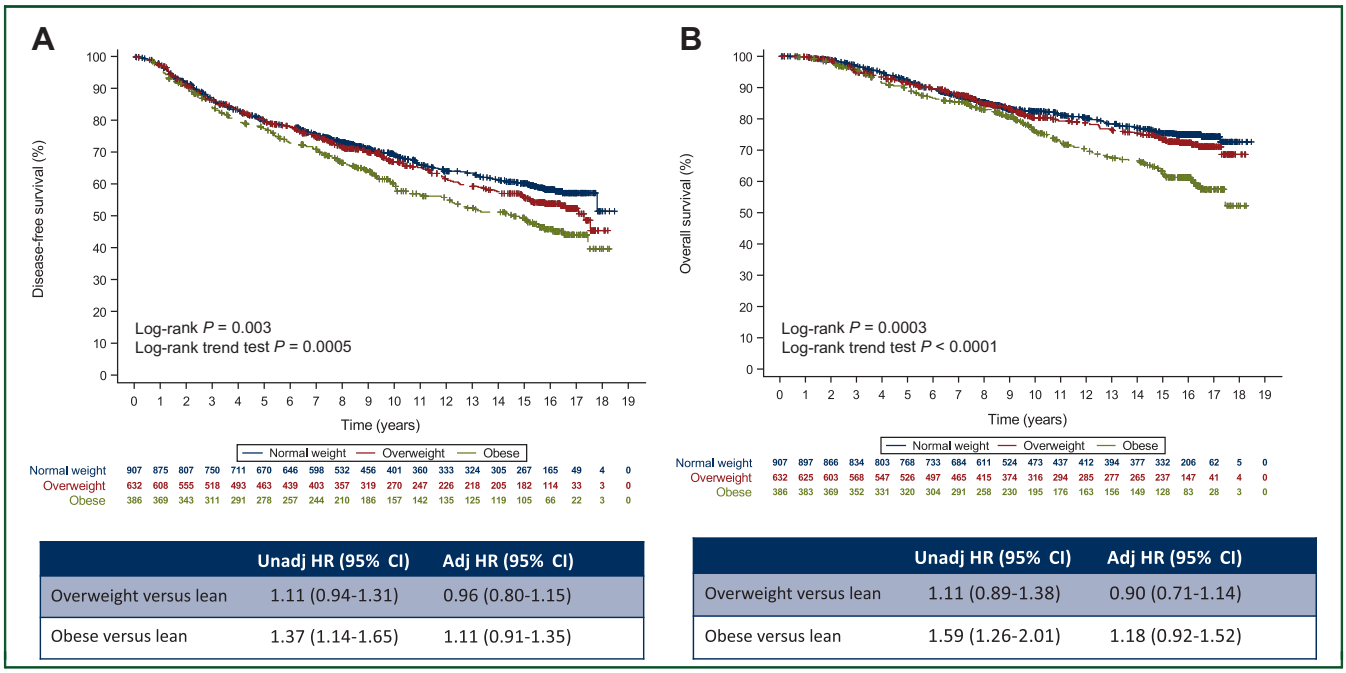
Survival outcomes according to BMI categories in patients with luminal-like tumors

Among 1053 luminal-like breast cancer, 480 (45.6%), 358 (34%), and 215 (20.4%) were classified as lean, overweight, and obese, respectively.

Women who were obese at diagnosis had a higher risk of experiencing a DFS event (adjHR 1.08, 95% CI 0.85-1.38 and adjHR 1.32, 95% CI 1.01-1.73 for overweight and obese patients, respectively) compared to lean patients. No difference in OS was observed comparing overweight and obese to lean patients (adjHR 0.86, 95% CI 0.62-1.19 and adjHR 1.35, 95% CI 0.96-1.89 for overweight and obese patients, respectively) (Figure 4A and B).

Comparison of the efficacy of DD and SI treatment according to BMI in patients with luminal-like tumors

No statistically significant second-order interaction between tumor subtype, BMI categories, and chemotherapy



	Unadj HR (95% CI)	Adj HR (95% CI)
Overweight versus lean	1.11 (0.94-1.31)	0.96 (0.80-1.15)
Obese versus lean	1.37 (1.14-1.65)	1.11 (0.91-1.35)

	Unadj HR (95% CI)	Adj HR (95% CI)
Overweight versus lean	1.11 (0.89-1.38)	0.90 (0.71-1.14)
Obese versus lean	1.59 (1.26-2.01)	1.18 (0.92-1.52)

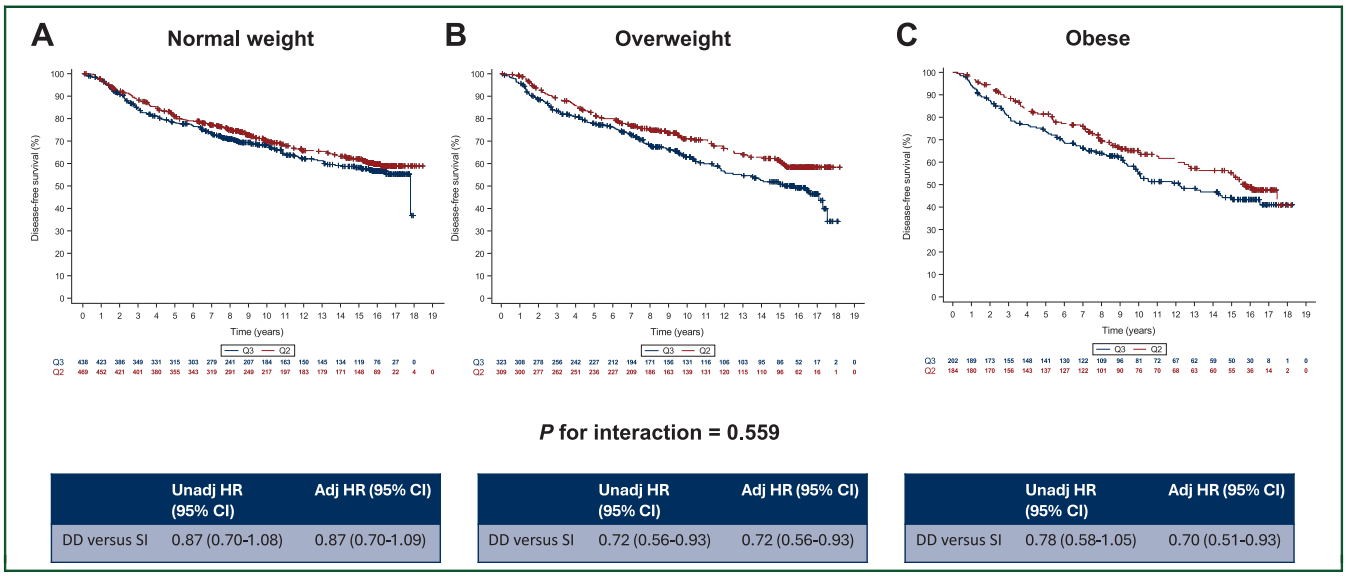
Figure 1. DFS (A) and OS (B) according to BMI category (unadjusted and adjusted analysis). Adjustment made for treatment, age, histology, pT, pN, grade, receptors, and HER2.
BMI, body mass index; CI, confidence interval; DFS, disease-free survival; HER2, human epidermal growth factor receptor 2; OS, overall survival.

schedule was observed for both DFS ($P_{\text{for interaction}} = 0.962$) and OS ($P_{\text{for interaction}} = 0.858$).

Among patients with luminal-like tumors, the benefit of DD chemotherapy was observed among all BMI categories, with a benefit that seemed more pronounced with higher BMI (adjHR 0.89, 95% CI 0.65-1.22; adjHR 0.76, 95% CI 0.54-1.08; and adjHR 0.68, 95% CI 0.46-1.01 for lean, overweight, and obese patients, respectively) (Supplementary Figure S1A-C, available at https://doi.org/10.1016/j.esmoop.2024.103650). Similar results were observed for OS (adjHR 0.94, 95% CI 0.62-1.42; adjHR 0.58, 95% CI 0.36-0.95; and adjHR 0.74, 95% CI 0.46-1.18 for lean, overweight, and obese patients, respectively) (Supplementary Figure S1D-F, available at https://doi.org/10.1016/j.esmoop.2024.103650).

Toxicity

Overall, most frequent adverse events of any grade were asthenia, anemia, neuropathy, myalgia, and bone pain,

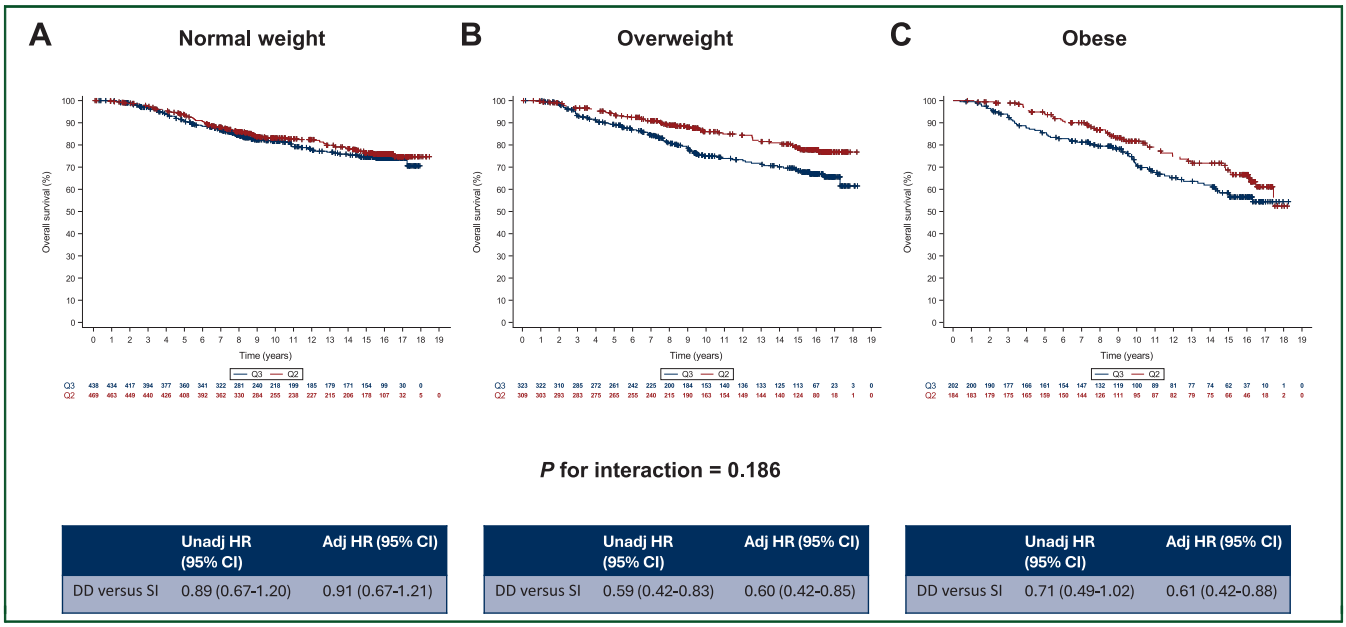


	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.87 (0.70-1.08)	0.87 (0.70-1.09)

	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.72 (0.56-0.93)	0.72 (0.56-0.93)

	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.78 (0.58-1.05)	0.70 (0.51-0.93)

Figure 2. DFS benefit of chemotherapy schedule in normal weight (A), overweight (B) and obese (C) patients.
BMI, body mass index; CI, confidence interval; DD, dose-dense; DFS, disease-free survival; HR, hazard ratio; SI, standard-interval.



	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.89 (0.67-1.20)	0.91 (0.67-1.21)

	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.59 (0.42-0.83)	0.60 (0.42-0.85)

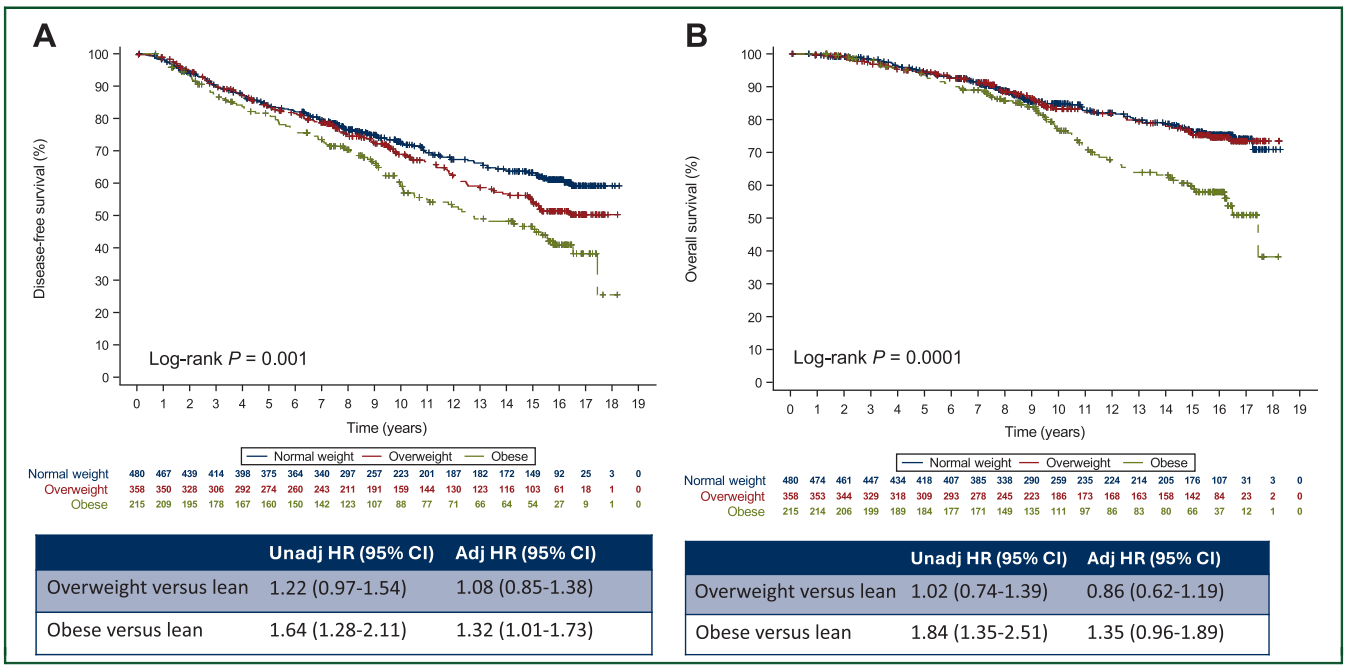
	Unadj HR (95% CI)	Adj HR (95% CI)
DD versus SI	0.71 (0.49-1.02)	0.61 (0.42-0.88)

Figure 3. OS benefit of chemotherapy schedule in normal weight (A), overweight (B) and obese (C) patients.
BMI, body mass index; CI, confidence interval; DD, dose-dense; HR, hazard ratio; OS, overall survival; SI, standard-interval.

occurring in >40% of the patients, whereas most frequent grade 3-4 adverse events were neutropenia, nausea, vomiting, asthenia, and neuropathy. The distribution of adverse events was similar across BMI subgroups. Anyway, when comparing different BMI categories, obese patients seemed to experience increased incidence of grade 3-4 non-hematological adverse events as compared to overweight and lean patients, particularly regarding diarrhea (1.6% versus 0.2% versus 0.1%, respectively), bone pain (4.7% versus 2.1% versus 2.0%, respectively), and neuropathy (5.4% versus 3.0% versus 2.2%, respectively). A full detail of adverse events according to BMI categories is displayed in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2024.103650.

DISCUSSION

This exploratory analysis of the randomized phase III GIM2 trial aimed at investigating the prognostic value of BMI and its association with the efficacy of different adjuvant chemotherapy schedules in patients with node-positive breast cancer. We found that, when adjusting for prognostic factors, overweight and obese patients did not have a higher risk of experiencing DFS and OS events compared to



	Unadj HR (95% CI)	Adj HR (95% CI)
Overweight versus lean	1.22 (0.97-1.54)	1.08 (0.85-1.38)
Obese versus lean	1.64 (1.28-2.11)	1.32 (1.01-1.73)

	Unadj HR (95% CI)	Adj HR (95% CI)
Overweight versus lean	1.02 (0.74-1.39)	0.86 (0.62-1.19)
Obese versus lean	1.84 (1.35-2.51)	1.35 (0.96-1.89)

Figure 4. DFS (A) and OS (B) according to BMI category in patients with luminal tumors (unadjusted and adjusted analysis). Adjustment made for treatment, age, histology, pT, pN, and grade.
BMI, body mass; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

those with a normal BMI, and the benefit of DD schedule was observed irrespective of different BMI categories.

The global raise in obesity rates leads to a significant public health issue.[20] Excess weight, obesity, and metabolic syndrome are recognized as developmental risk factors for up to 35% of all cancer cases, including breast cancer.[3,21]

A pooled analysis of the Southwest Oncology Group (SWOG) clinical trials observed an increasing trend from 23% to 42% in obesity among patients participating in clinical trials between 1985 and 2020, mirroring US adult obesity rates.[22] In the GIM2 trial, nearly half of the population was overweight or obese at diagnosis, underlining the critical relevance of this condition among women with breast cancer diagnosis also in Italy.

As already known from literature, in our study higher BMI was associated with larger mean tumor size and higher nodal involvement at the time of breast cancer diagnosis.

Previous studies underscored the overall negative effect of obesity on outcomes in breast cancer patients.[7,23] However, the negative prognostic effect of BMI in much larger case series appears to be modest: recently, an individual patient-level analysis including 7334 patients enrolled in five adjuvant randomized trials conducted by the Mammella InterGruppo (MIG) and GIM observed that higher baseline BMI was a negative prognostic factor (adjHR 1.18, 95% CI 1.05-1.33), with a specific pattern of recurrence that remains consistently elevated up to 15 years from diagnosis.[24]

Our findings revealed that, at a median follow-up of 15 years, overweight and obese patients did not have a higher risk of experiencing DFS and OS events compared to those with a normal BMI when adjusting for prognostic factors. Nevertheless, we observed that obese patients, who were generally older, had a higher risk of non-recurrence-related mortality compared to lean women; this may be attributed to the presence of other competing risks of death. In our cohort, we observed a modest negative prognostic effect of BMI, which disappeared when adjusting for prognostic factors such as tumor size and nodal status, which are imbalanced in the distribution of subgroups.

The absence of a significant interaction between BMI and treatment schedule suggests that the benefit of DD chemotherapy is consistent across different BMI groups. Furthermore, at the multivariate analysis, adjusting for relevant prognostic factors, a trend towards an improved DFS and OS for patients with higher BMI treated with DD chemotherapy was observed. This highlights the importance of avoiding undertreatment in this patient group, as the benefit of DD remains consistently evident. To note, in our study, no significantly lower RDI or intensity was given to obese patients, in contrast to prior studies showing that obese patients are more likely to be undertreated due to chemotherapy dose adjustment or delays.[11,25]

Breast cancer survivors are at increased risk for developing subsequent second primary cancers compared with the general population. A recent study observed that for every 5 kg/m^2 increase in BMI, the risk of any second cancer diagnosis increased by 7% (relative risk [RR] 1.07, 95% CI 1.01-1.14); 13% (RR 1.13, 95% CI 1.05-1.21) for obesity-related cancers, 11% (RR 1.11, 95% CI 1.02-1.21) for a second breast cancer, and 15% (RR 1.15, 95% CI 1.04-1.27) for a second estrogen receptor-positive breast cancer. In our study, patients with higher BMI had increased risk of second primary cancers (12.1% and 11.3% in overweight and obese patients, respectively) as compared to women with normal weight (8.3%). This highlights the need to improve primary prevention programs for these patients as well as adherence to screening procedures with more tailored prevention strategies. A large recent meta-analysis found that the presence of metabolic abnormalities (i.e. metabolic syndrome) is associated with an increased breast cancer risk in adult women.[26] These results point to a link between metabolic syndrome, obesity, and breast cancer, and suggest that the presence of metabolic abnormalities should be included in future studies evaluating the effect of obesity on survival in breast cancer patients.

In terms of toxicity, evidence reported that obese patients had toxicity rates that were similar or lower than non-obese patients. Results from this study are overall in line with literature data. We observed a non-significant increase in some G3-G4 non-hematological adverse events in obese patients as compared to overweight or lean women. Nevertheless, small absolute numbers did not allow to assess if potential factors may be associated with increased toxicity in this population.

Our study presents some potential limitations. This is an exploratory analysis not pre-planned in the original statistical plan. BMI was the only measure of adiposity available for these patients, and it has been recognized that it should not be the ideal surrogate for adiposity.[27] Many of the patients included in this analysis would be currently eligible to receive adjuvant abemaciclib, which is the current standard of care for patients with hormone receptor-positive high-risk breast cancer.[28] After all, our findings are derived from a specific geographical context, and caution must be exercised when attempting to generalize these results to a broader, global population.

Nevertheless, our analysis has some strengths: it is based on a population of patients enrolled in a large randomized phase III clinical trial, which reduces the potentially confounding effects of heterogeneous patient samples and different treatment regimens; moreover, the long follow-up that is essential to capture late recurrences typical of luminal cohorts.[29]

In conclusion, findings of this analysis suggest that, when considering adjuvant chemotherapy for patients with node-positive high-risk breast cancer, clinicians can confidently recommend the DD schedule as the preferred choice, irrespective of patients' BMI.

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