

RESEARCH ARTICLE

Cancer Therapy and Prevention

Body mass index as a predictive factor for efficacy of adjuvant taxane-based chemotherapy in early-stage breast cancer patients: A pooled analysis from adjuvant GEICAM Spanish Breast Cancer Group and TRIO Translational Research in Oncology Group studies

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Abbreviations: AC, Doxorubicin plus cyclophosphamide; AE, Adverse event; BC, Breast cancer; BCOS, Breast cancer overall survival; BCS, Breast conserving surgery; BMI, Body mass index; BSA, Body surface area; CI, Confidence interval; CT, Chemotherapy; EBC, Early-stage breast cancer; EC, Epirubicin plus cyclophosphamide; ER, Estrogen receptor; ET, Endocrine therapy; FAC, Fluorouracil plus doxorubicin plus cyclophosphamide; FEC, Fluorouracil plus epirubicin plus cyclophosphamide; G, Histopathologic grade; HER2, Human epidermal growth factor receptor 2; HR, Hazard ratio; iDFS, Invasive disease-free survival; N, Lymph node involvement; NCI-CTAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, Overall survival; PgR, Progesterone receptor; RCT, Randomized controlled trials; RDI, Relative dose intensity; T, Tumor size; TAC, Docetaxel plus doxorubicin plus cyclophosphamide; WHO, World Health Organization.

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Abstract

Adjuvant anthracyclines and taxanes reduce recurrence and death in early-stage breast cancer (EBC) patients, but toxicity is a concern. Studies show conflicting results on the correlation between body mass index (BMI) and outcomes. Limited data exist on the efficacy of adjuvant taxanes among BMI categories and the impact of different taxane-based chemotherapies (paclitaxel vs. docetaxel) on disease recurrence. Here, we present a pooled analysis of 13,486 EBC patients treated with adjuvant anthracyclines ± taxanes from seven GEICAM and TRIO trials (1996–2008) conducted. Patients were classified into four BMI categories: normal (<25.0), overweight (25.0–29.9), obese (30.0–34.9), and severely obese (≥35.0). BMI was evaluated as a predictive factor for the efficacy and toxicity of taxane-based chemotherapy. Our results show the following findings: patients' distribution by BMI was 44% normal, 33% overweight, 16% obese, and 8% severely obese. Seventy-nine percent received taxane-based chemotherapy. Ten-year invasive disease-free survival (iDFS) was 71%, 70%, 68%, and 64% for normal, overweight, obese, and severely obese patients, respectively. Obese and severely obese patients had significantly worse outcomes (HR 1.15 and 1.29, respectively). Invasive disease-free survival with docetaxel vs. non-docetaxel was significant in the normal BMI group, while iDFS with paclitaxel was significant in the obese group. Relevant toxicity was observed in 5%, 5.5%, 5.9%, and 9.3% of normal, overweight, obese, and severely obese patients who received docetaxel. In conclusion, heavier EBC patients had a worse prognosis with adjuvant taxane-based chemotherapy. Normal BMI patients benefited more from docetaxel, while obese patients benefited more from paclitaxel.

KEYWORDS

body mass index, docetaxel, early-stage breast cancer, paclitaxel, pooled analysis, survival

What's New?

Body mass index (BMI) potentially influences outcomes among women with early-stage breast cancer (EBC). Little is known, however, about relationships between BMI and disease prognosis for different adjuvant taxane-based chemotherapies. Here, the prognostic effect of BMI on disease recurrence was evaluated among EBC patients treated with adjuvant anthracyclines, with and without taxanes. Prognosis was found to be worse for obese and severely obese EBC patients who received adjuvant taxane-based chemotherapy. Patients with healthy BMI benefited from docetaxel, while obese patients benefited from paclitaxel. The findings suggest that BMI can help guide decisions regarding personalized adjuvant taxane-based treatment for EBC.

1 | BACKGROUND

Despite significant advancements in early diagnosis and local treatment for early-stage breast cancer (EBC), up to one in four patients may still develop metastases. The likelihood of recurrence is influenced by clinical and pathological variables as well as the breast cancer (BC) subtype.¹ Systemic adjuvant treatment is commonly used in EBC to reduce the rate of recurrence and death derived from the disease. Standard anthracycline and taxane regimens are currently recommended to improve the efficacy, but the tolerability and—more importantly—their long-term toxicity profiles remain a concern to

balance the likelihood of cure while maintaining patients' quality of life.^{2,3}

Several studies have investigated the relationship between body mass index (BMI) and outcomes in EBC patients treated with adjuvant chemotherapy, with conflicting findings,^{4–7} and limited data on the long-term efficacy of taxanes among the different BMI categories.⁸ Moreover, no studies have evaluated the prognostic effect of BMI on disease recurrence between the different adjuvant taxane-based chemotherapies (paclitaxel vs. docetaxel). Similarly, there are no conclusive results on the impact of BMI on the outcomes of EBC patients receiving adjuvant taxane-plus HER2-targeted-based regimens.⁹

2 | METHODS

We analyzed individualized data from a population of EBC patients diagnosed with operable disease, who were randomized in seven phase III clinical trials in the adjuvant setting and were treated with anthracyclines and taxanes. These studies were conducted to evaluate the role of concomitant or sequential taxanes (docetaxel or paclitaxel), both in patients with negative (N−) and positive (N+) lymph node involvement.

Patients with N+ EBC were included in the following studies: GEICAM/9703_BCIRG001 (docetaxel-doxorubicin-cyclophosphamide [TAC] ×6 cycles vs. fluorouracil-doxorubicin-cyclophosphamide [FAC] ×6 cycles),¹⁰ GEICAM/9906¹¹ (fluorouracil-epirubicin-cyclophosphamide [FEC] ×6 cycles vs. FEC ×4 cycles followed by weekly paclitaxel ×8 weeks), BCIRG005¹² (TAC ×6 cycles vs. doxorubicin-cyclophosphamide [AC] ×4 cycles followed by 3-weekly docetaxel ×4 cycles), and GEICAM/2003-10¹³ (epirubicin-cyclophosphamide [EC] ×4 cycles followed by docetaxel ×4 cycles vs. epirubicin-docetaxel [ET] ×4 cycles followed by capecitabine ×4 cycles). The studies including patients with N− EBC were GEICAM/9805¹⁴ (evaluated the same chemotherapy regimens than the GEICAM/9703_BCIRG001 study), GEICAM/2001-06_BCIRG 006¹⁵ (AC ×4 cycles followed by three-weekly docetaxel ×4 cycles vs. AC ×4 cycles followed by docetaxel-trastuzumab ×4 cycles, continuing with weekly trastuzumab until the completion of 1 year vs. docetaxel-carboplatin-trastuzumab ×6 cycles followed by weekly trastuzumab until 1 year), and GEICAM/2003-02¹⁶ (FAC ×6 cycles vs. FAC ×4 cycles followed by weekly paclitaxel ×8 weeks).

The patients with N− EBC enrolled in the GEICAM/9805, and GEICAM/2003-02 studies met at least one of the high-risk criteria described in the 1998 St. Gallen consensus recommendations: tumor size (T) >2 cm, negative results on tests for expression of estrogen receptor (ER) and progesterone receptor (PgR), tumor histopathologic grade (G) 2 or 3, or age <35 years. The patients with N+ EBC enrolled at BCIRG-001, BCIRG-005, GEICAM/2003-10 and GEICAM/9906 studies had at least one involved axillary lymph node from a minimum of six resected lymph nodes; the distribution between 1–3 and 4 or more positive lymph nodes categories was similar, except in the GEICAM/2003-10 study, where patients had up to three positive lymph nodes. Human epidermal growth factor receptor 2 positive (HER2+), high-risk, N− or N+ patients were enrolled in the BCIRG-006 study.

If the patient's calculated body surface area (BSA) was >2.2 m², the dose administered was capped at a BSA of 2.2 m².

The current analysis was approved by an institutional review board.

2.1 | Patients

These phase III trials accrued patients between 1996 and 2008. After completion of chemotherapy, tamoxifen, aromatase inhibitors, or the switching strategy (tamoxifen followed by an aromatase inhibitor) were administered for 5 years for patients with hormone receptor positive (HR+) tumors. Radiotherapy was mandatory in the case of

breast-conserving surgery (BCS) and was administered after mastectomy according to each institution's guidelines.

These patients received at least one dose of the corresponding study treatment, which could be based on taxane administration or not. For the purpose of our analysis, patients were classified into four categories according to BMI (kg/m²) at the time of study baseline assessment. In accordance with the World Health Organization (WHO) recommendation: underweight (<18.5), normal (18.5 to 24.9), overweight or pre-obesity (25.0 to 29.9), obesity class I (30.0 to 34.9), obesity class II (35.0 to 39.9) and obesity class III (≥40.0). This variable was simplified to four categories: normal (<25.0), overweight (25.0 to 29.9), obese (30.0 to 34.9), and severely obese (≥35.0). (155 patients [1.1%]) were underweight. These latter patients were included in the normal category because we performed a sensitivity analysis and there were no differences. The fourth category was added based on current evidence of the poorest prognosis in this subset of patients.

All patients included in this pooled analysis had a score on the Karnofsky performance scale of 80% or more (60% or more in GEICAM/9805 study).

Other clinicopathological variables included in this pooled analysis were: age, menopausal status, histological tumor type (invasive ductal carcinoma vs. other histologies), histological grade (1 and 2 vs. 3), T (≤2 vs. >2 cm), nodal involvement (N0 vs. N1 vs. N2), HR status (negative vs. positive), HER2 status (positive vs. negative vs. unknown), and Ki-67 proliferation index (≤20% vs. >20%). For biomarker definition (ER, PgR, HER2, and Ki-67), central determination was preferred, if available, over local determination.

2.2 | Objectives and endpoints

This pooled analysis evaluated the impact of BMI on the four following groups based on the adjuvant chemotherapy regimen administered: (a) docetaxel-based chemotherapy vs. non-docetaxel-based chemotherapy, (b) paclitaxel-based chemotherapy vs. non-paclitaxel-based chemotherapy, (c) taxane-based chemotherapy vs. non-taxane-based chemotherapy, and (d) all patients regardless of chemotherapy.

The primary objective was to determine the invasive disease-free survival (iDFS), according to the BMI categories and adjuvant chemotherapy regimens administered. The iDFS was defined as the time from the date of randomization to the date of diagnosis of any of the following events: ipsilateral invasive BC recurrence, loco-regional invasive BC recurrence, distant BC recurrence, death attributable to any cause, contralateral invasive BC, or second primary invasive non-breast malignancy.

The secondary objectives considered for this manuscript were to determine the BC overall survival (BCOS), overall survival (OS) and the percentage of patients with clinically relevant adverse events (AEs) of grade 3 or higher, according to the BMI categories and adjuvant chemotherapy regimens administered. BCOS was defined as the time from the date of randomization to the date of death from BC, and OS was defined as the time from the date of randomization to the date of death from any cause. BCOS and OS were evaluated for the same categories and groups as for the primary objective.

Clinically relevant AEs of grade 3 or higher were analyzed according to BMI categories and the following groups based on the adjuvant chemotherapy: (a) docetaxel-based chemotherapy vs. non-docetaxel-based chemotherapy, (b) paclitaxel-based chemotherapy vs. non-paclitaxel-based chemotherapy, (c) taxane-based chemotherapy vs. non-taxane-based chemotherapy. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE), and AEs of grade 3 or higher were considered clinically relevant. Three categories were defined based on the number of these AEs of grade 3 or higher: (i) no clinically relevant toxicity (patients had 0 AEs of grade 3–4), (ii) mild clinically relevant toxicity (patients had 1, 2 or 3 AEs of grade 3–4), and (iii) high clinically relevant toxicity (patients had >3 AEs of grade 3–4 or at least one AE of grade 5).

In addition, a comparison of dosing patterns according to the BMI categories was performed, using the proportion of patients having a relative dose intensity (RDI) of 85%, where <85% was considered as reduced dose intensity.

2.3 | Statistical analyses

All analyses were based on patients who received at least one dose of study treatment and had available BMI data. All analyses were also performed in subsets described above according to the taxane-based chemotherapy schedule.

The mean total dose per cycle was defined as the sum of the total dose of the treatment considered for each cycle divided by the number of cycles. RDI was the ratio of the received mean total dose to the planned dose of the treatment considered. RDI was expressed as a percentage of the planned dose.

The Kaplan–Meier method was used to estimate iDFS, BCOS, and OS, and BMI categories were compared using the log-rank test. The Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Full Cox regression models were stratified by study and adjusted for major prognostic factors at baseline, including age, menopausal status, tumor size, nodal status, histopathological grade, hormone receptor status, HER2 status, and overall undertreatment (yes/no) as potential confounders. Interaction tests between BMI and groups of treatments were also performed.

The data were analyzed at the Statistical Department of GEICAM using SAS, version 9.4 (SAS Institute Inc.). All statistical tests were two-sided and were assessed at $\alpha = 0.05$ significance level unless otherwise stated; adjustment by multiple hypothesis testing was not considered, taking into account the exploratory nature of these analyses.

3 | RESULTS

3.1 | Patients' characteristics

The study population comprised 13,486 patients with the distribution of BMI according to the four categories as follows: 5868 (43.5%) in the normal category, 4485 (33.3%) in the overweight category, 2094

(15.5%) in the obese category, and 1039 (7.7%) in the severely obese category. If we consider the type of chemotherapy that these patients received, 10,638 (78.9%) were treated with taxane-based chemotherapy, 7703 (83.2%) with docetaxel, and 1557 (16.8%) with paclitaxel. Non-taxane-based chemotherapy was administered to 2848 patients (Table S1).

The majority of patients were from Europe (67.4%) and North America (22.1%), with the remainder coming from (Oceania [4.9%], Asia [4.5%], and Africa [1%]). Baseline demographic and disease characteristics are described in Table 1. The median age of patients at primary BC diagnosis was 50 years, with 92.4% of them below 65 years. More than half the patients had tumor size $\geq T2$ ($n = 7419$; 55%) and $N+$ ($n = 9620$; 71.3%). Forty-five percent of tumors were of G3, and 19% of tumors were evaluated for Ki-67 proliferation index, with 4.7% ($n = 636$) $n \geq 20\%$. 53.8% of tumors ($n = 7241$) expressed ER, and 49.6% ($n = 6581$) expressed PgR. HER2 positivity was 28.3% ($n = 3815$), with HER2 status being unknown in 2042 cases.

3.2 | Efficacy

3.2.1 | Invasive disease-free survival results

With a median follow-up time of 9.8 years (range 0–15.7 years), the frequency of iDFS events at 10 years increased from normal to severely obese weight categories (27.5% to 34.3%). Distant metastases, loco-regional recurrence, and a second primary invasive malignancy of non-breast origin were the most common events (Table S2). The iDFS at 10 years was 71.2%, 69.7%, 67.9%, and 64.1% in normal weight, overweight, obese, and severely obese patients, respectively, considering all patients who received chemotherapy, and was statistically significant in obese (HR 1.15; 95% CI 1.05–1.26; p -value = 0.002) and severely obese (HR 1.29; 95% CI 1.15–1.45; p -value <0.001) BMI categories when compared to patients with normal weight. Similar results were observed in the following groups based on the adjuvant chemotherapy received, with worse iDFS seen in the obese and severely obese BMI categories: docetaxel-based (obese: HR 1.14; 95% CI 1.00–1.29; p -value = 0.042, and severely obese: HR 1.26; 95% CI 1.07–1.47; p -value = 0.004), non-paclitaxel-based (obese: HR 1.33; 95% CI 1.03–1.72; p -value = 0.029, and severely obese: HR 1.85; 95% CI 1.35–2.54; p -value <0.001) chemotherapy regimens. Finally, in the group of patients with taxane-based chemotherapy, those in the obese and severely obese BMI categories had worse iDFS with statistically significant differences (obese: HR 1.15; 95% CI 1.03–1.27; p -value = 0.011, and severely obese: HR 1.31; 95% CI 1.14–1.49; p -value <0.001) (Tables 2 and S3).

In the comparison of docetaxel-based chemotherapy vs. non-docetaxel-based chemotherapy by BMI category, only patients within the normal weight group showed a better iDFS when treated with docetaxel-based chemotherapy (69.6% vs. 62.0%) with a statistically significant difference (HR 0.73; 95% CI 0.59–0.89; p -value = 0.003). In contrast, in patients who received paclitaxel-based chemotherapy vs. non-paclitaxel-based chemotherapy by BMI category, only patients

TABLE 1 Baseline characteristics of patients and their breast cancer at diagnosis.

	Normal weight N = 5868	Overweight N = 4485	Obese N = 2094	Severely obese N = 1039	Total N = 13,486
Median age, years (range)	46 (22–74)	51 (23–76)	54 (23–75)	54 (26–76)	50 (22–76)
Cut-off age of 65 years, n (%)					
<65	5620 (95.8)	4099 (91.4)	1830 (87.4)	908 (87.4)	12,457 (92.4)
≥65	248 (4.2)	386 (8.6)	264 (12.6)	131 (12.6)	1029 (7.6)
Cut-off age of 50 years, n (%)					
<50	3740 (63.7)	1942 (43.3)	678 (32.4)	337 (32.4)	6697 (49.7)
≥50	2128 (36.3)	2543 (56.7)	1416 (67.6)	702 (67.6)	6789 (50.3)
Menopausal status, n (%)					
Postmenopausal	2204 (37.6)	2515 (56.1)	1411 (67.4)	710 (68.3)	6840 (50.7)
Premenopausal	3664 (62.4)	1970 (43.9)	683 (32.6)	329 (31.7)	6646 (49.3)
Tumor size (cm)					
Median (range)	2.10 (0–15)	2.30 (0.1–25.5)	2.40 (0.01–24)	2.50 (0.13–14)	2.20 (0–25.5)
≤2, n (%)	2884 (49.1)	1955 (43.6)	834 (39.8)	391 (37.6)	6064 (45.0)
>2, n (%)	2984 (50.9)	2527 (56.4)	1260 (60.2)	648 (62.4)	7419 (55.0)
Number of involved lymph nodes, n (%)					
0	1736 (29.6)	1253 (27.9)	611 (29.2)	265 (25.5)	3865 (28.7)
1–3	2524 (43.0)	1956 (43.6)	882 (42.1)	449 (43.2)	5811 (43.1)
≥4	1608 (27.4)	1275 (28.4)	601 (28.7)	325 (31.3)	3809 (28.2)
Histopathological grade, n (%)					
G1	459 (7.8)	354 (7.9)	162 (7.7)	76 (7.3)	1051 (7.8)
G2	2354 (40.2)	1849 (41.3)	837 (40.0)	440 (42.4)	5480 (40.7)
G3	2685 (45.8)	1959 (43.7)	938 (44.9)	483 (46.5)	6065 (45.0)
GX	362 (6.2)	320 (7.1)	154 (7.4)	39 (3.8)	875 (6.5)
Estrogen receptor, n (%)					
Positive	3132 (53.4)	2382 (53.2)	1164 (55.7)	563 (54.3)	7241 (53.8)
Negative	2729 (46.6)	2097 (46.8)	926 (44.3)	474 (45.7)	6226 (46.2)
Progesterone receptor, n (%)					
Positive	2802 (48.6)	2222 (50.4)	1029 (50.0)	528 (51.6)	6581 (49.6)
Negative	2960 (51.4)	2189 (49.6)	1029 (50.0)	496 (48.4)	6674 (50.4)
Hormone receptors, n (%)					
Positive	3499 (60.2)	2703 (60.9)	1277 (61.6)	622 (60.4)	8101 (60.7)
Negative	2309 (39.8)	1736 (39.1)	797 (38.4)	408 (39.6)	5250 (39.3)
HER2, n (%)					
Negative	2384 (40.6)	1949 (43.5)	914 (43.6)	453 (43.6)	5700 (42.3)
Positive	1660 (28.3)	1075 (24.0)	475 (22.7)	250 (24.1)	3460 (25.7)
Unknown	1824 (31.1)	1461 (32.6)	705 (33.7)	336 (32.3)	4326 (32.1)
Ki-67 proliferation index, n (%)					
<20%	757 (12.9)	684 (15.3)	338 (16.1)	154 (14.8)	1933 (14.3)
≥20%	285 (4.9)	214 (4.8)	93 (4.4)	44 (4.2)	636 (4.7)
Unknown	4690 (82.2)	3587 (80.0)	1663 (79.4)	841 (80.9)	10,917 (81.0)
Type of chemotherapy					
No taxane based					2848 (21.1%)
Taxane based					10,638 (78.9%)
Docetaxel					7703*
Paclitaxel					1557

Note: Patients from GEICAM/2003-10 study were not included in the docetaxel group because this drug was administered in both the experimental and control arms.

TABLE 2 Invasive disease-free survival (iDFS) per drug and BMI category.

Normal	Overweight	Obese	Severely obese
All patients			
71.2%	69.7%	67.9%	64.1%
	HR 1.04 (0.97–1.12)	HR 1.15 (1.05–1.26)	HR 1.29 (1.15–1.45)
	<i>p</i> -value = 0.257	<i>p</i> -value = 0.002	<i>p</i> -value <0.001
<i>N</i> = 5868	<i>N</i> = 4485	<i>N</i> = 2094	<i>N</i> = 1039
Adjuvant non-docetaxel-based chemotherapy patients			
62.0%	65.5%	62.4%	67.2%
	HR 0.90 (0.73–1.11)	HR 1.03 (0.80–1.34)	HR: 0.79 (0.55–1.15)
	<i>p</i> -value = 0.334	<i>p</i> -value = 0.804	<i>p</i> -value = 0.219
<i>N</i> = 510	<i>N</i> = 442	<i>N</i> = 206	<i>N</i> = 97
Adjuvant docetaxel-based chemotherapy patients			
69.6%	67.4%	66.0%	63.5%
	HR 1.06 (0.96–1.17)	HR 1.14 (1.00–1.29)	HR 1.26 (1.07–1.47)
	<i>p</i> -value = 0.221	<i>p</i> -value = 0.042	<i>p</i> -value = 0.004
<i>N</i> = 3486	<i>N</i> = 2478	<i>N</i> = 1135	<i>N</i> = 604
Adjuvant non-paclitaxel-based chemotherapy patients			
77.2%	74.0%	71.9%	65.0%
	HR 1.09 (0.87–1.37)	HR 1.33 (1.03–1.72)	HR 1.85 (1.35–2.54)
	<i>p</i> -value = 0.436	<i>p</i> -value = 0.029	<i>p</i> -value <0.001
<i>N</i> = 686	<i>N</i> = 517	<i>N</i> = 271	<i>N</i> = 119
Adjuvant paclitaxel-based chemotherapy patients			
78.5%	76.6%	77.8%	71.2%
	HR 1.06 (0.84–1.33)	HR 1.05 (0.78–1.40)	HR 1.40 (0.95–2.05)
	<i>p</i> -value = 0.612	<i>p</i> -value = 0.758	<i>p</i> -value = 0.085
<i>N</i> = 620	<i>N</i> = 572	<i>N</i> = 262	<i>N</i> = 103
Adjuvant non-taxane-based chemotherapy patients			
70.7%	70.1%	67.8%	66.0%
	HR 0.99 (0.85–1.15)	HR 1.17 (0.98–1.40)	HR 1.23 (0.97–1.56)
	<i>p</i> -value = 0.892	<i>p</i> -value = 0.091	<i>p</i> -value = 0.088
<i>N</i> = 1196	<i>N</i> = 959	<i>N</i> = 477	<i>N</i> = 216
Adjuvant taxane-based chemotherapy patients			
71.3%	69.5%	67.7%	63.3%
	HR 1.06 (0.98–1.15)	HR 1.15 (1.03–1.27)	HR 1.31 (1.14–1.49)
	<i>p</i> -value = 0.164	<i>p</i> -value = 0.011	<i>p</i> -value <0.001
<i>N</i> = 4672	<i>N</i> = 3526	<i>N</i> = 1617	<i>N</i> = 823

within the obese group showed a better iDFS when treated with paclitaxel-based chemotherapy, 77.8% vs. 71.9% (HR 0.72; 95% CI 0.52–0.98; *p*-value = 0.039). In addition, a trend favoring paclitaxel-based chemotherapy was observed in patients within the severely obese (71.2% vs. 65%), but not statistically confirmed (Figures 1, 2, S1 and S2 and Table S4).

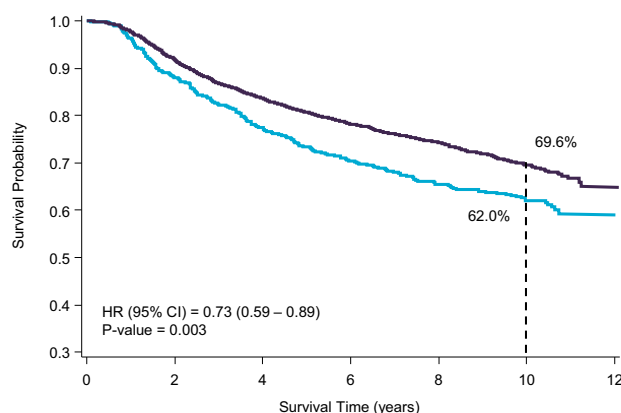
3.2.2 | Univariate and multivariate analyses

These analyses were performed in the following populations:

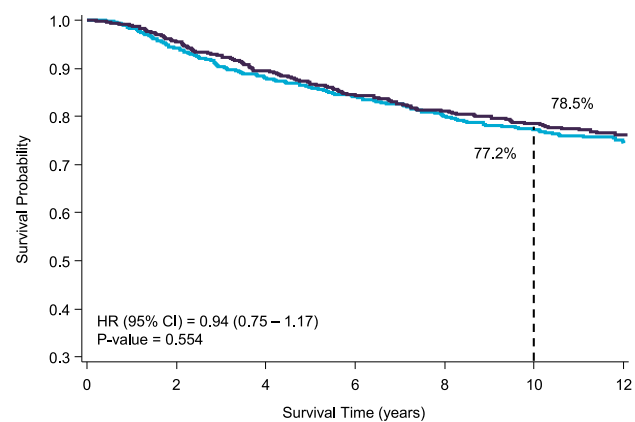
(a) docetaxel-based vs. non-docetaxel-based chemotherapy,

(b) paclitaxel-based vs. non-paclitaxel-based chemotherapy, and
(c) taxane-based vs. non-taxane-based chemotherapy. Some already known factors related to poor prognosis were confirmed in both univariate and multivariate analyses, and regardless of the chemotherapy regimen given, established clinicopathological factors associated with prognosis were lymph node involvement (1–3 and >3 positive lymph nodes), $T > 2$ cm, and histopathological G3. Both hormone receptor negativity and overexpression of HER2 were not confirmed as poor prognostic factors in all populations. On the other hand, the severely obese BMI category was an independent poor prognostic factor in nearly all populations but in docetaxel-based vs. non-docetaxel-based chemotherapy. Further information is necessary to explain this data.

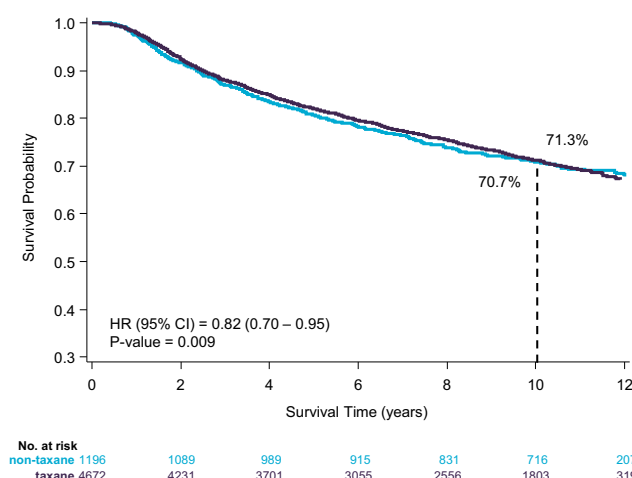
(A) Docetaxel vs. non-docetaxel



(B) Paclitaxel vs. non-paclitaxel



(C) Taxane vs. non-taxane

**FIGURE 1** Kaplan–Meier curves for invasive disease-free survival in patients with normal BMI category.

The age at initial BC diagnosis was shown to be a good prognostic factor (Table 3).

3.2.3 | Overall survival results

The OS at 10 years results were 83%, 81.9%, 80%, and 74.7% in patients in the normal weight, overweight, obese, and severely obese BMI categories, respectively, considering all patients who received adjuvant chemotherapy, regardless of chemotherapy type. The differences were statistically significant in obese (HR 1.24; 95% CI 1.11–1.40; p -value <0.001) and severely obese (HR 1.46; 95% CI 1.27–1.69; p -value <0.001, when compared with the normal weight population). The 10-year OS showed no statistically significant differences in any BMI category in the group receiving non-docetaxel-based chemotherapy, but differences were observed in patients who received docetaxel-based chemotherapy. In the obese and severely obese categories, worse 10-year OS was seen when compared with the normal weight BMI category (obese: HR 1.22; 95% CI 1.04–1.43; p -

value = 0.016, and severely obese: HR 1.44; 95% CI 1.18–1.74; p -value <0.001). Patients with normal weight treated with docetaxel-based chemotherapy had a better 10-year OS of 81.4% (HR 0.70; 95% CI 0.54–0.91; p -value = 0.008) vs. 76.5% of patients with non-docetaxel-based chemotherapy. No significant differences in OS were seen in any other BMI category when comparing docetaxel-based chemotherapy vs. non-docetaxel-based chemotherapy.

Statistically significant differences were observed in the obese BMI category; 89.5% vs. 82.2% (HR 0.62; 95% CI 0.41–0.94; p -value = 0.025) when 10-year OS was compared in patients receiving paclitaxel-based chemotherapy vs. non-paclitaxel-based chemotherapy.

Patients receiving taxane- vs. non-taxane-based chemotherapy demonstrated similar results to those seen in the docetaxel- vs. non-docetaxel-based chemotherapy. Patients in both obese and severely obese BMI categories had significantly worse 10-year OS when compared to the normal weight BMI category (obese 80.2%; HR 1.24; 95% CI 1.08–1.42; p -value = 0.002, and severely obese 74.7%; HR 1.48; 95% CI 1.26–1.75; p -value <0.001) (Tables S5 and S6).

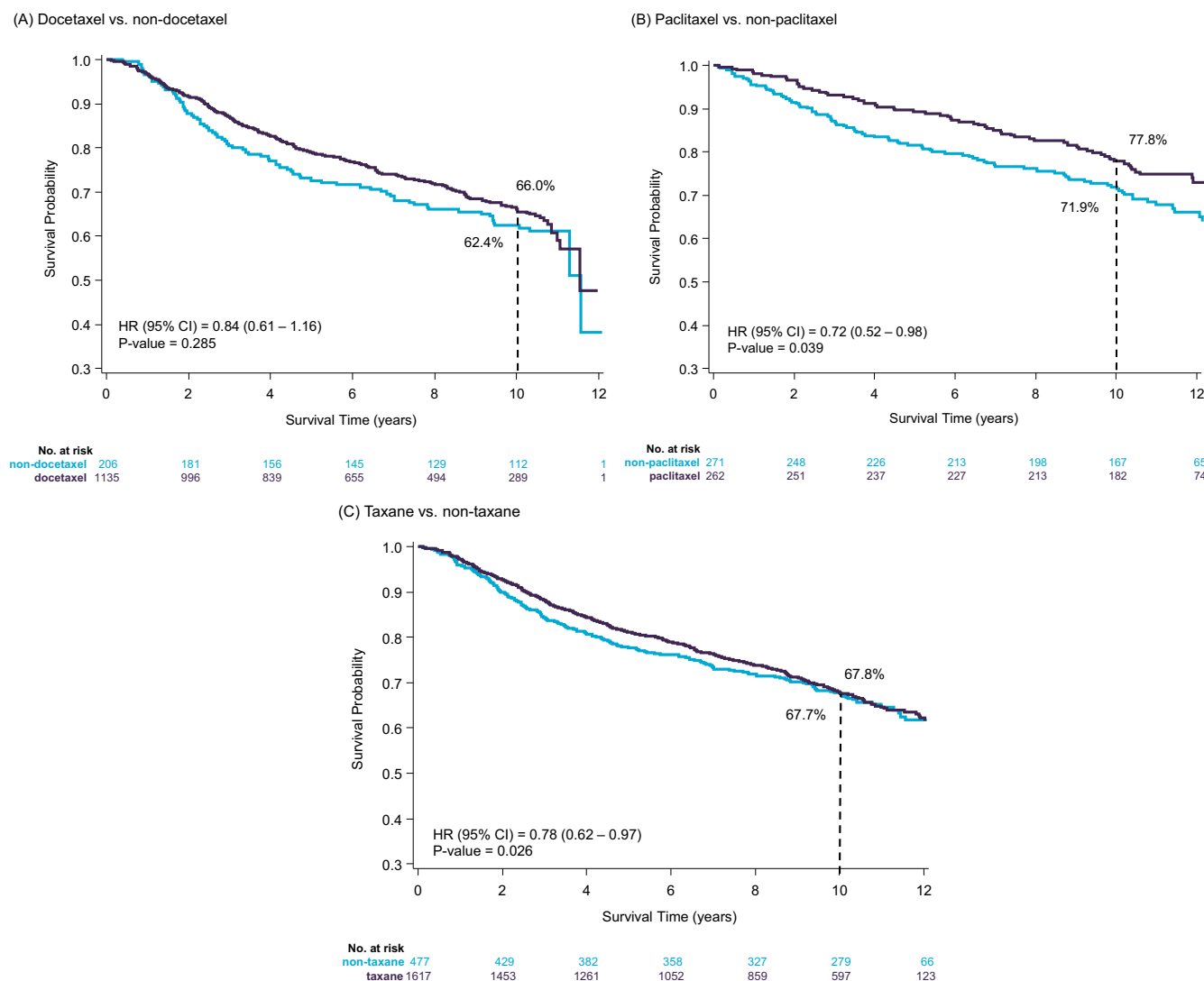


FIGURE 2 Kaplan-Meier curves for invasive disease-free survival in patients with obese BMI category.

3.2.4 | Breast cancer overall survival results

For the whole population, regardless of the type of adjuvant chemotherapy received, those patients in the obese and severely obese BMI categories had significantly worse 10-year BC overall survival (BCOS) rates when compared to the normal weight population (obese HR 1.16; 95% CI 1.02–1.32; p -value = 0.030, and severely obese HR 1.33; 95% CI 1.13–1.56; p -value = 0.001). The BCOS rates were 85.5%, 84.5%, 83.5%, and 79.9% in normal weight, overweight, obese, and severely obese BMI categories, respectively.

Statistically significant differences were observed in the docetaxel-based adjuvant chemotherapy group for patients in obese and severely obese BMI categories when compared to normal weight 80.8% in the obese patients (HR 1.21; 95% CI 1.02–1.45; p -value = 0.032) and 76.4% in the severely obese patients (HR 1.41; 95% CI 1.14–1.74; p -value = 0.002). Furthermore, normal weight patients treated with docetaxel-based chemotherapy had a better 10-year BCOS (84.1%) than normal weight patients treated with non-

docetaxel-based chemotherapy (78.9%) (HR 0.62; 95% CI 0.46–0.82; p -value = 0.001).

Patients in the severely obese BMI category also had a worse 10-year BCOS rate when compared to the normal weight BMI category when treated with non-paclitaxel-based chemotherapy (rate 76.3%, HR 2.04; 95% CI 1.32–3.15; p -value = 0.001). Furthermore, in the taxane-based chemotherapy group, statistically significant differences were observed in the obese and severely obese categories, with lower 10-year BCOS rates (obese 83.3%; HR 1.19; 95% CI 1.02–1.39; p -value = 0.023, and severely obese 79.8%; HR 1.38; 95% CI 1.15–1.66; p -value = 0.001; Tables S7 and S8).

3.3 | Safety

The adverse events (AEs) of grade ≥ 3 of high clinical relevance were reported in 4.6%, 4.7%, 5.8%, and 7.2% of patients in the normal weight, overweight, obese, and severely obese BMI categories,

TABLE 3 Invasive disease-free survival (IDFS) per drug and variable.

	Docetaxel vs. non-docetaxel			Paclitaxel vs. non-paclitaxel			Taxanes vs. non-taxanes					
	Univariate HR (95% CI)		p-value	Univariate HR (95% CI)		p-value	Univariate HR (95% CI)		p-value			
	Multivariate HR (95% CI)			Multivariate HR (95% CI)								
Age ^a	0.98 (0.96–1.00)	0.024	0.92 (0.89–0.95)	<0.001	1.02 (0.98–1.05)	0.365	0.95 (0.90–1.01)	0.077	0.99 (0.97–1.00)	0.119	0.93 (0.90–0.95)	<0.001
Non-docetaxel vs. docetaxel/ Non-paclitaxel vs. paclitaxel/ Non-taxane vs. taxane	0.81 (0.70–0.92)	0.002	0.79 (0.69–0.90)	<0.001	0.85 (0.75–0.98)	0.023	0.85 (0.74–0.97)	0.019	0.83 (0.75–0.91)	<0.001	0.81 (0.74–0.89)	<0.001
BMI	Reference		Reference		Reference		Reference		Reference		Reference	
Normal	1.04 (0.95–1.13)		1.04 (0.95–1.14)		1.07 (0.91–1.26)		1.07 (0.91–1.27)		1.04 (0.97–1.12)		1.06 (0.98–1.14)	
Overweight	0.446		0.359		0.402		0.406		0.257		0.157	
Obese	1.12 (1.00–1.26)		1.11 (0.98–1.24)		1.19 (0.98–1.44)		1.16 (0.95–1.43)		1.15 (1.05–1.26)		1.14 (1.04–1.26)	
Severely obese	0.043		0.094		0.076		0.153		0.002		0.006	
	1.16 (1.01–1.34)		1.12 (0.97–1.30)		1.65 (1.30–2.10)		1.59 (1.23–2.06)		1.29 (1.15–1.45)		1.26 (1.12–1.42)	
	0.041		0.122		<0.001		<0.001		<0.001		<0.001	
HER2	Reference		Reference		Reference		Reference		Reference		Reference	
Negative	1.14 (0.79–1.64)		1.06 (0.73–1.54)		1.24 (1.03–1.49)		1.20 (0.99–1.45)		1.14 (0.99–1.32)		1.07 (0.93–1.24)	
Positive	0.498		0.756		0.024		0.058		0.069		0.356	
Unknown	1.03 (0.77–1.38)		1.05 (0.79–1.42)		1.08 (0.83–1.40)		1.11 (0.85–1.45)		1.10 (0.93–1.30)		1.11 (0.94–1.31)	
	0.837		0.725		0.580		0.445		0.288		0.234	
Histological grade	Reference		Reference		Reference		Reference		Reference		Reference	
G1-G2	1.36 (1.25–1.48)		1.31 (1.20–1.42)		1.30 (1.13–1.50)		1.12 (0.96–1.30)		1.33 (1.24–1.42)		1.24 (1.16–1.33)	
G3	<0.001		<0.001		<0.001		0.157		<0.001		<0.001	
Gx	1.17 (1.00–1.37)		1.19 (1.02–1.39)		1.06 (0.80–1.41)		1.01 (0.75–1.34)		1.19 (1.05–1.35)		1.16 (1.02–1.32)	
	0.044		0.031		0.693		0.970		0.008		0.021	
Hormone receptors	Reference		Reference		Reference		Reference		Reference		Reference	
Positive	0.95 (0.87–1.03)		0.94 (0.87–1.02)		1.53 (1.31–1.78)		1.36 (1.16–1.61)		1.08 (1.01–1.16)		1.03 (0.96–1.11)	
Negative	0.211		0.138		<0.001		<0.001		0.036		0.394	
Menopausal status	Reference		Reference		Reference		Reference		Reference		Reference	
Premenopausal	1.01 (0.93–1.09)		1.25 (1.10–1.41)		1.19 (1.04–1.36)		1.27 (1.03–1.57)		1.06 (0.99–1.13)		1.27 (1.14–1.40)	
Postmenopausal	0.809		<0.001		0.013		0.029		0.08		<0.001	
Nodal status ^b	Reference		Reference		Reference		Reference		Reference		Reference	
0	1.58 (1.31–1.91)		1.59 (1.32–1.92)		1.59 (1.32–1.92)		1.59 (1.32–1.92)		1.59 (1.32–1.92)		1.62 (1.34–1.94)	
1–3	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
>3	2.98 (2.48–3.58)		2.85 (2.37–3.42)		<0.001		2.96 (2.47–3.55)		2.96 (2.47–3.55)		2.82 (2.35–3.39)	
	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Tumor size	Reference		Reference		Reference		Reference		Reference		Reference	
≤2 cm	1.54 (1.42–1.68)		1.36 (1.25–1.48)		1.48 (1.29–1.70)		1.42 (1.23–1.63)		1.54 (1.44–1.64)		1.37 (1.28–1.46)	
>2 cm	<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	
Under-treated	Reference		Reference		Reference		Reference		Reference		Reference	
No	1.29 (1.16–1.43)		1.34 (1.20–1.49)		1.31 (1.05–1.62)		1.30 (1.04–1.62)		1.21 (1.11–1.32)		1.24 (1.13–1.39)	
Yes	<0.001		<0.001		0.016		0.020		<0.001		<0.001	

^aAge has been divided by 5.^bNodal status was not included in the group paclitaxel vs. non-paclitaxel because the models were stratified by study. There were only two studies in this group, one of which had patients with negative nodal status and the other had patients with positive nodal status.

TABLE 4 Comparison of adverse events (AEs) by treatment regimens and BMI category.

	Normal	Overweight	Obese	Severely obese
Docetaxel vs. non docetaxel				
No clinically relevant toxicity	45.7% vs. 79.2%	47.7% vs. 78.5%	47.0% vs. 73.8%	42.7% vs. 68.0%
Mild clinically relevant toxicity	49.3% vs. 19.6%	46.8% vs. 20.1%	47.0% vs. 24.8%	48% vs. 32.0%
High clinically relevant toxicity	5.0% vs. 1.2%	5.5% vs. 1.4%	5.9% vs. 1.5%	9.3% vs. 0%
Paclitaxel vs. non paclitaxel				
No clinically relevant toxicity	52.3% vs. 50.7%	51.2% vs. 51.6%	56.1% vs. 62.7%	49.5% vs. 57.1%
Mild clinically relevant toxicity	46.0% vs. 46.1%	45.1% vs. 45.6%	39.7% vs. 32.8%	46.6% vs. 37.8%
High clinically relevant toxicity	1.8% vs. 3.2%	3.7% vs. 2.7%	4.2% vs. 4.4%	3.9% vs. 5%
Taxane vs. non taxane				
No clinically relevant toxicity	44.8% vs. 62.9%	46.4% vs. 64.0%	47.7% vs. 67.5%	43.7% vs. 62.0%
Mild clinically relevant toxicity	50.1% vs. 34.8%	48.2% vs. 33.9%	45.6% vs. 29.4%	47.9% vs. 35.2%
High clinically relevant toxicity	5.1% vs. 2.3%	5.4% vs. 2.1%	6.6% vs. 3.1%	8.4% vs. 2.8%
Paclitaxel vs. docetaxel				
No clinically relevant toxicity	52.3% vs. 45.7%	51.2% vs. 47.7%	56.1% vs. 47.0%	49.5% vs. 42.7%
Mild clinically relevant toxicity	46.0% vs. 49.3%	45.1% vs. 46.8%	39.7% vs. 47.0%	46.6% vs. 48.0%
High clinically relevant toxicity	1.8% vs. 5%	3.7% vs. 5.5%	4.2% vs. 5.9%	3.9% vs. 9.3%

respectively. No clinically and mild clinically relevant AEs were similar in all four categories. Patients who received docetaxel-based, taxane-based, or non-paclitaxel-based chemotherapy had higher proportions of both mild and high clinically relevant AEs. The differences between the types of chemotherapy are described in Table 4.

3.4 | Treatment administration according to BMI categories

To evaluate whether there were differences in the administered treatment dose based on BMI categories, we assessed the relative dose intensity (RDI) of each agent within each combination chemotherapy, considering a cut-off of 85% ($\geq 85\%$ vs. $< 85\%$).

In non-taxane-based, non-paclitaxel-based, and non-docetaxel-based groups, there were more severely obese patients that received RDI $< 85\%$ for any of the given drugs when comparing to other BMI categories (10% vs. $\sim 4\%$).

In taxane-based, paclitaxel-based, and docetaxel-based chemotherapy groups, the patients with a RDI $< 85\%$ for any given drug were more frequently in obese and severely obese categories (19%–20% in obese and 22%–23% in severely obese vs. 12%–15% in normal weight and overweight categories). This finding was not seen in the paclitaxel-based chemotherapy group where the proportion of patients with a RDI $< 85\%$ was lower in normal weight and overweight BMI categories, and slightly lower in the severely obese category (Table S9).

4 | DISCUSSION

Systemic adjuvant chemotherapy is generally recommended to a large proportion of high-risk EBC to reduce the risk of recurrence and

death. Current taxane-based regimens improve the outcome of EBC, but increased toxicity is seen when compared to anthracycline-only-based combinations.^{2,3}

In this comprehensive pooled analysis, encompassing seven well-executed randomized clinical trials (RCT) and compiling data from 13,486 early breast cancer (EBC) patients, we aimed to clarify the long-term outcomes and safety considerations. Our conclusions highlight the varied long-term outcomes, including iDFS, OS, and BCOS, among breast cancer patients undergoing adjuvant chemotherapy based on individual BMI. The prognosis is worse in heavier vs. normal BMI patients, and the magnitude of the difference increased across our defined BMI categories. We confirm our previously reported results (with four out of seven of the trials compiled in this pooled analysis; GEICAM/9906, GEICAM/9805, GEICAM/2003-02, and BCIRG-001) of an association between severely obese and prognosis in patients receiving adjuvant anthracycline-taxane-based chemotherapy.⁶ High BMI, as a prognostic factor, has been widely reported as a marker of chemoresistance in EBC patients.^{17–21} The biological explanation for the relationship between obesity and BC outcomes remains unclear. It is known that severely obese patients are more likely to experience toxicity-related dose reduction or to receive suboptimal initial doses despite guideline recommendations.^{22,23}

In our series, we conclude that normal BMI but not heavier patients receiving docetaxel-based chemotherapy compared to non-taxane chemotherapy achieved a better 10-years iDFS, OS and BCOS. All long-term efficacy outcomes were statistically significant improved in the docetaxel-treated normal-BMI population (a trend worse prognosis for iDFS and BCOS and a statistically significant difference in OS in the overweight subgroup).

Possible explanations for our results in the docetaxel treated population include suboptimal dosing of docetaxel in obese patients and also that the lipophilic pharmacokinetic property of docetaxel implies

a higher affinity for the adipose tissue, resulting in a higher volume of distribution and decreased efficacy amongst tumor tissue in heavier patients.²⁴ Our results are similar to those of a study in BC patients treated with adjuvant chemotherapy, where reduced DFS and OS were seen with increasing BMI category in the docetaxel-containing group, but not in the non-docetaxel one.⁷

To our knowledge, this is the first study to demonstrate an improved outcome with respect to 10-yr iDFS, OS, and BCOS in both obese and severely obese patients who received paclitaxel- vs. non-paclitaxel-based chemotherapy. Both iDFS and OS with paclitaxel were clearly better in the obese group (with a strong trend in the severely obese group, as well as BCOS in heavier people) while no significant differences were seen in the normal BMI group irrespective of inclusion of paclitaxel or not. These observations of higher efficacy in terms of iDFS and OS with paclitaxel in obese patients are consistent when paclitaxel results are adjusted (using a stratified Cox proportional hazard model) compared with docetaxel studies. The higher efficacy of paclitaxel in the obese cohort was seen irrespective of dose delivery.

The different efficacy of docetaxel and paclitaxel in heavier patients was unexpected as both agents are lipophilic drugs showing a high affinity to adipose tissues, thus drug distribution in heavier patients would be expected to be comparable.²⁵ The observed differences in long-term outcomes between docetaxel and paclitaxel were unexpected; given the retrospective nature of this pooled analysis, these findings should be considered hypothesis-generating and warrant further investigation. Even though paclitaxel is also a lipophilic drug, different pharmacokinetic properties have been described between the two taxanes. It has been reported that BMI does not influence the exposure to paclitaxel.²⁶

Another possible explanation for different outcomes seen between docetaxel-based and paclitaxel-based treatment may be differences in dose per surface area mandated for both taxanes in a given trial, where a relative lower initial dose for docetaxel was used for safety concerns. Some studies have reported no differences in toxicity with paclitaxel when dosed as per basal body weight^{27–29} supporting that the oncologists may be comfortable using a full dose of paclitaxel but not of docetaxel. Moreover, these trials were carried out before the ASCO recommendation for chemotherapy dosing in obese patients.²⁴

The different safety categories distribution between paclitaxel and docetaxel may support this hypothesis; when comparing adverse events categories, there was a higher percentage of docetaxel-treated patients experiencing high clinically relevant toxicity (9.3% vs. 3.9% in the severely obese group).

Clinicopathologic factors known to be associated with a worse prognosis were confirmed in the multivariate analyses regardless of the chemotherapy received. There is a biased interpretation of the prognostic value of HER2 status because in all trials, except BCIRG006, most studies did not stratify by HER2 status, and in many trials, the HER2 status was unknown. Hormone receptor negative disease was clearly associated with a worse prognosis in all BMI categories in the paclitaxel vs. non-paclitaxel comparison. However, the

poorer prognostic value of HR-negative status was not established in the docetaxel vs. non-docetaxel regimens analysis. Data from other series analyses are needed to confirm whether a worse outcome exists in patients with HR-negative disease receiving docetaxel-based therapies.

A potential avenue for future research would be to track BMI changes over time through advanced stages of breast cancer, especially considering the “obesity paradox,” where overweight and obese cancer patients appear to exhibit better survival outcomes.³⁰ Monitoring BMI in these early breast cancer patients could provide valuable insights into the complex interactions between BMI, the type of adjuvant taxane received, and disease progression.

There are important limitations in this study including the retrospective nature of the analysis, although all patients in the current study were participants in prospective randomized clinical trials with BMI being recorded at baseline. However, our analysis could not take into account any weight changes that may have occurred during the period of study follow-up. The association of BMI changes after treatment and survival have been reported and with conflicting results.^{5,31–33} The majority of the studies reported that weight gain is associated with a worse prognosis, but excessive loss of BMI can also be a factor for poor prognosis in the long-term. Recently, Chen and collaborators reported the association of BMI change and survival in a pooled analysis from the docetaxel-based studies BCIRG-001 and BCIRG-005 trials.³⁴ Though severe obesity was associated with worse outcome, BMI loss exceeding 10% was also an independent prognostic factor for adverse OS.³⁵

The strength of our study includes protocol-mandated treatment and follow-up in accordance with those of randomized clinical trials, the large number of patients included here, inclusion of the incidence of AEs, and the sensitivity analysis including patients with RDI >85%. Our results suggest that paclitaxel, but not docetaxel, may be the optimal adjuvant taxane agent for obese and severely obese EBC patients. In addition, docetaxel-based adjuvant regimens instead of paclitaxel-based regimens may preferably be considered within the normal BMI EBC population; nevertheless, other studies are needed to confirm our findings.

5 | CONCLUSIONS

To conclude, this pooled-analysis of seven randomized clinical trials highlights the differential efficacy of adjuvant taxane-based chemotherapy regimens according to BMI, and perhaps, baseline BMI should be a considered variable when selecting the most appropriate adjuvant therapy for a given patient.

AUTHOR CONTRIBUTIONS

José A. García-Saenz: Conceptualization; writing – original draft; writing – review and editing; investigation; supervision. **Gonzalo Spera:** Investigation; writing – review and editing. **Marina Pollán:** Investigation; supervision; writing – review and editing. **Begoña Bermejo:** Writing – review and editing; investigation. **Manuel Ruiz-**

Borrego: Investigation; writing – review and editing. **Arlene Chan:** Investigation; writing – review and editing. **Miguel Martín:** Conceptualization; investigation; writing – review and editing; supervision. **Ángel Guerrero-Zotano:** Investigation; writing – review and editing. **Lourdes Calvo:** Writing – review and editing; investigation. **Álvaro Rodríguez-Lescure:** Investigation; writing – review and editing. **María Marín:** Investigation; writing – review and editing. **Linnea Chap:** Investigation; writing – review and editing. **John Crown:** Writing – review and editing; investigation. **Tadeusz Pienkowski:** Investigation; writing – review and editing. **Valerie Bee:** Writing – review and editing; investigation. **Maribel Casas:** Formal analysis; writing – review and editing. **Óscar Polonio:** Writing – original draft; writing – review and editing. **Susana Bezares:** Investigation; supervision; writing – original draft; writing – review and editing. **Dennis Slamon:** Investigation; writing – review and editing.

ACKNOWLEDGMENTS

We acknowledge the patients who participated in the analysis and their families and all the participating investigators. We also acknowledge the support of the GEICAM staff.

CONFLICT OF INTEREST STATEMENT

Dr. Jose Ángel García has received consulting fees from Seagen, AstraZeneca, Daiichi Sankyo, Novartis, Gilead, and Menarini; speakers' honoraria from Celgene, Eli Lilly, Eisai, MSD, Exact Sciences, Tecnofarma, Nolver (Adium), Asofarma and Roche; institution and research funding from AstraZeneca and travel support from Gilead, AstraZeneca and Daiichi Sankyo. Dr. Begoña Bermejo has received consulting fees from AstraZeneca, Daiichi Sankyo, Lilly, Roche, MSD and Menarini; speakers' honoraria from Lilly, MSD, Pfizer, Novartis, AstraZeneca, Roche, and Gilead; and travel support from Gilead and Pfizer. Dr. Miguel Martín has received consulting fees from AstraZeneca, Amgen, Taiho Oncology, Roche/Genentech, Novartis, PharmaMar, Eli Lilly, PUMA, Taiho Oncology, and Pfizer; speakers' honoraria from AstraZeneca, Amgen, Roche/Genentech, Novartis, Daiichi Sankyo, and Pfizer; and contracted research fees from Roche, Novartis, and PUMA. Dr. Ángel Guerrero has received institutional grant by Pfizer, advisory by Novartis, Palex, Pfizer, AstraZeneca, Pierre Fabre, travel grant by Roche, Pfizer and Novartis and speaker honoraria by Novartis, Pfizer, Lilly, Pfizer, AstraZeneca. Dr. Álvaro Rodríguez-Lescure has received speaker honoraria by Pfizer, Novartis, AstraZeneca, Daiichi-Sankyo and Seagen and advisory by Pfizer, Novartis, Roche, AstraZeneca, Daiichi-Sankyo, Pierre Fabre and Seagen. Dr. John Crown has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Pfizer, Pierre Fabre, and Novartis; advisory boards from MSD, Immunocore, and AstraZeneca; and travel support from MSD, Pfizer, Roche, Daiichi Sankyo, Astrazeneca, Regeneron, and Novartis. Dr. Tadeusz Pienkowski has received lecture fees from Roche. Dr. Denis Slamon declares being part of the 1200 Pharma Board of Directors, BioMarin Pharmaceutical Inc. Board of Directors, TORL Biotherapeutics Board of Directors, and receiving grant/contract and stock from AstraZeneca as a consultant, consulting fees from Amgen Inc., and stock from Merck. Novartis consultant, grant/contract, and sponsored speaking

events. Pfizer Consultant, sponsored speaking engagements, Grant/contract, and stock. The other authors have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee for Research with medicines (CEIm, acronym in Spanish) of Hospital Parc Taulí de Sabadell with number 2023/5095 on September 26, 2023.

Trial registration: [ClinTrials.gov](https://clinicaltrials.gov) identifiers: GEICAM/9703–BCIRG001: NCT00688740; GEICAM/9805: NCT00121992; GEICAM/9906: NCT00129922; BCIRG005: NCT00312208; GEICAM/2001-06–BCIRG006: NCT00021255; GEICAM/2003-02: NCT00129389; GEICAM/2003-10: NCT00129935.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: García-Saenz JA, Spera G, Pollán M, et al. Body mass index as a predictive factor for efficacy of adjuvant taxane-based chemotherapy in early-stage breast cancer patients: A pooled analysis from adjuvant GEICAM Spanish Breast Cancer Group and TRIO Translational Research in Oncology Group studies. *Int J Cancer*. 2025;157(4):709-721. doi:10.1002/ijc.35432