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ORIGINAL ARTICLE

Association between neoadjuvant paclitaxel dose intensity and outcomes in early triple-negative and HER2-positive breast cancer: a real-world data analysis

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Background: Reduction of paclitaxel dose intensity (PDI) is frequent during neoadjuvant treatment of high-risk early triple-negative (TN) and human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC), due to toxicity. The association between PDI and cancer outcomes is uncertain.

Patients and methods: We collected across eight European cancer centers (DigiCore consortium) a cohort of early TN and HER2-positive BC patients who received neoadjuvant anthracyclines and weekly paclitaxel. For each subtype, we assessed whether a threshold of reduced PDI (through dose reduction, treatment delay or early cessation) was associated with reduced pathological complete response (pCR) rate. We then described the association between reduced PDI, invasive BC-free survival (IBCFS), and overall survival.

Results: We included 514 TNBC and 249 HER2-positive BC patients. PDI reductions were required in 82.9% and 63.9% of patients, respectively. The optimal cut-off separating high and low PDI was 69% and 72%, respectively. Low PDI was in TNBC (29.8% of patients), but not in HER2-positive BC (22.1% of patients), significantly associated with a reduced pCR rate, compared with high PDI (37.3% versus 55.1%) (odds ratio 0.48, 95% confidence interval 0.33-0.71, $P < 0.001$). In TNBC, the estimated IBCFS at 36 months was 77.9% in the PDI-low and 89.2% in the PDI-high group (hazard ratio 2.19, 95% confidence interval 1.29-3.73, $P = 0.004$).

Conclusions: Reduction of PDI is frequently required during neoadjuvant treatment in early TNBC and HER2-positive BC, and is associated with lower pCR rate and IBCFS in TNBC. Reduction of PDI needs careful consideration, balancing adverse events and potential impact. Confirmation in independent datasets is warranted.

Key words: breast cancer, neoadjuvant, paclitaxel, dose intensity

INTRODUCTION

Neoadjuvant treatment (NAT) is the preferred option in early triple-negative breast cancer (TNBC) and human epidermal growth factor receptor 2 (HER2)-positive BC subtypes at elevated risk of relapse. Achieving a pathological complete response (pCR) leads to improved long-term invasive BC-free survival (IBCFS) and overall survival (OS).[1-3] A total of 4 cycles of anthracyclines and cyclophosphamide (AC), preceded or followed by 12 cycles of

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weekly paclitaxel, is a common backbone of NAT in both subtypes.[2,4] The addition of concurrent therapies (anti-HER2 antibodies for HER2-positive BC, carboplatin and pembrolizumab for TNBC) improves the pCR rate and clinical outcomes.[5]

The occurrence of adverse events frequently requires adapting the NAT plan, through dose reductions, treatment delays, and/or discontinuations. Among these, peripheral neuropathy is a potentially irreversible toxicity that can affect up to 70% of patients treated with paclitaxel, inducing a profound impact on quality of life.[6] To date, paclitaxel dose intensity (PDI) reduction before high-grade toxicity occurs remains the main management strategy. Alarmingly, incomplete paclitaxel administration is necessary in 30%-40% of cases.[7] Achieving optimal PDI, defined as the standard amount of paclitaxel administered within the designated time frame, is thus a challenge in early TNBC and HER2-positive BC. Retrospective trials suggest that overall treatment intensity reductions reduce pCR in HER2-positive BC[8] and mixed BC subtypes,[9,10] but these studies were not calibrated to separate the effects of dose reduction of AC and taxanes, nor to consider the specific impacts of the three different ways dose intensity can be reduced. Real-world data studying the association between PDI and cancer outcomes would thus generate strong hypotheses for a frequent clinical issue.

Using a multicentric cohort of early TNBC and HER2-positive BC treated with a standard backbone of neoadjuvant AC and paclitaxel, the objectives of this study were to identify for each subtype an optimal cut-off below which PDI was associated with reduced pCR rate, and to assess the association with reduced IBCFS and OS.

METHODS

Study design

The Digital Institute for Cancer Outcome Research (DigiCore) is a European research network aiming to shape digital interoperability between its members.[11] Eight European cancer centers, members of DigiCore, conceived this study with a retrospective design, after checking their homogeneity of clinical practice (disease work-up, treatment plan, and follow-up) and data availability. The ESMO Guidance for Reporting Oncology real-World evidence (ESMO-GROW) guideline was used to optimally guide the study conduct (see Supplementary Methods, available at https://doi.org/10.1016/j.esmorw.2025.100158).[12]

Patient population

In each center, we included all patients diagnosed between 2018 and 2021 with early TNBC or HER2-positive BC and treated with neoadjuvant AC (dose-dense schedule or not) and weekly paclitaxel or carboplatin—paclitaxel, with or without anti-HER2-directed antibodies (trastuzumab with or without pertuzumab). TNBC was defined as absence or low expression of the estrogen receptor (ER <10%) and absence of ERBB2 amplification or overexpression. ER-low disease (ER <10%) was considered as TNBC, given its similar biological characteristics and prognosis.[13] All patients underwent breast and axillary surgery with curative intent after NAT, with pathological reports available at diagnosis and at surgery, and data available regarding each treatment cycle.

Exclusion criteria encompassed a history of another primary malignancy (related to BC or not, except for non-melanoma skin cancer or *in situ* carcinoma), bilateral invasive BC, administration of another anticancer systemic treatment in the neoadjuvant setting, and concomitant pregnancy.

Definition of main outcomes

The primary objective of this study was to define in TNBC and HER2-positive BC an optimal cut-off below which PDI was associated with reduced pCR rate (defined as the absence of residual invasive disease in the breast and lymph nodes). We then considered if low PDI was associated with worse IBCFS (defined as the timespan between diagnosis and the earliest of recurrence of invasive BC or death) and OS (defined as the timespan between diagnosis and death). IBCFS was selected over invasive disease-free survival to remain specific of the BC outcomes, without considering the occurrence of an independent new cancer. Finally, we aimed to characterize the clinical factors and treatment-related adverse events associated with reduced PDI.

Measuring study objectives

For each patient, we collected information regarding demographics, comorbidities, tumor characteristics, cycles of neoadjuvant chemotherapy, treatment-related toxicity, surgery, adjuvant therapy, and follow-up. The Supplementary methods, available at https://doi.org/10.1016/j.esmorw.2025.100158, provide the common data model and extensive details regarding data collection. Except toxicity data, most variables were already available in structured datasets in the majority of the centers.

Data management

The study was approved by the ethics committee of each center. The pseudonymized data were recorded in a secured database (REDCap).[14] Each center carried out pre-specified data quality checks, highlighting missing data and inconsistencies across variables (see Supplementary methods, available at https://doi.org/10.1016/j.esmorw.2025.100158).

Paclitaxel dose intensity assessment

We considered the three main factors affecting PDI: (i) cycle-dose factor (CDF): dose at single cycle level expressed in mg/m^2 with respect to the standard of 80 mg/m^2; (ii) cycles-completeness factor (CCF): number of cycles administered with respect to the standard of 12 cycles; and (iii) time-adherence factor (TAF): total duration in days of paclitaxel treatment course with respect to the standard 77 days. The PDI was defined as the product of CDF, CCF, and

TAF. More details are in the Supplementary methods, available at https://doi.org/10.1016/j.esmorw.2025.100158.

Statistical analysis plan

Our assumptions were that low PDI would lead to a reduced pCR rate in TNBC, in contrast to HER2-positive BC, given the high sensitivity to HER2-directed therapies. We thus decided to consider both subtypes separately.

In each subtype, the CART (Classification and Regression Tree) algorithm was used to identify the cut-off separating low versus high PDI for pCR prediction, with the first splitting rule selected as the optimal value to distinguish patients with/without pCR.[15] To obtain a more robust value and minimize the risk of identifying an inappropriate local optimum, we used a bootstrap-based split selection approach similar to the bagging technique and selected the most frequent cut-off value.[16] In each subtype, this cut-off was then used to analyze IBCFS and OS.

Standard descriptive and inferential statistics were used to characterize the study cohort (see Supplementary methodology, available at https://doi.org/10.1016/j.esmorw.2025.100158). We used a univariate logistic regression model to estimate odds ratios (OR) of individual potential predictors of pCR, and a univariate Cox proportional hazards regression model to estimate hazard ratios (HR) for IBCFS and OS. When fitting multivariate models, only predictors showing statistically significant effects in the univariate regression were consecutively selected, after exclusion of collinearity. Further details are provided in the Supplementary methods, available at https://doi.org/10.1016/j.esmorw.2025.100158. All analyses were carried out in R (4.2.1).[17]

RESULTS

Patient characteristics and treatments received

We included 514 patients with TNBC and 249 patients with HER2-positive BC. The baseline clinicopathological characteristics and treatment modalities are summarized in Tables 1 and 2, respectively. In the TNBC and HER2-positive BC populations, the mean age was 50.3 and 52.3 years, respectively, while 51.8% and 43.2% of patients were premenopausal, respectively. The majority of patients had a grade 3 (78% and 74.4%, respectively) and clinical stage II (69.3% and 71.4%, respectively) disease. The incidence of a germline pathological *BRCA1* or *BRCA2* mutation was 19.1% in the TNBC and 2.4% in the HER2-positive BC tested cohorts. Across the global cohort, a minority of patients presented comorbidities.

Neoadjuvant dose-dense AC was administered in 48.9% and 33.8% of patients with TNBC and HER2-positive BC, respectively. In these same subtypes, 86.7% and 91.2% of patients completed the four recommended cycles. In TNBC, 63% of patients had received neoadjuvant carboplatin, whereas 33.7% of HER2-positive BC patients had received dual anti-HER2 therapy. Median duration of follow-up was 27.6 months (interquartile range 16.9-38.3 months).

Paclitaxel dose intensity. Adaptations of neoadjuvant paclitaxel are summarized in Table 2 and detailed in Supplementary Table S1, available at https://doi.org/10.1016/j.esmorw.2025.100158. PDI reductions were required in 82.9% and 63.9% of TNBC and HER2-positive BC, leading to a median PDI of 82% and 91%, respectively. Specifically, dose reduction was required in 26.7% and 20.9% of patients, interval prolongation in 68.5% and 40.2% of patients, and reduction in the number of cycles in 35.2% and 39.8% of patients, respectively.

Association between paclitaxel dose intensity and pCR

TNBC. pCR was obtained in 49.8% of patients. Using the CART algorithm, a PDI of $<$89% was significantly predictive of lower pCR rate, with 69% as optimal threshold (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmorw.2025.100158). Patients with TNBC were divided into two groups based on this threshold: 153 patients (29.8%) had received a low PDI ($<$69%), while 361 patients (70.2%) had received a high PDI ($\geq$69%). In univariate, the pCR rate was significantly lower among patients who received a low PDI compared with those who received a high PDI [pCR rates of 37.3% and 55.1%, respectively, OR 0.48, 95% confidence interval (CI) 0.33-0.71, $P < 0.001$] (Figure 1A and Supplementary Table S2, available at https://doi.org/10.1016/j.esmorw.2025.100158).

Considering individually the three factors influencing PDI, only a reduction in the number of administered cycles was associated with lower probability of pCR (HR 0.46, 95% CI 0.32-0.67, $P < 0.001$) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmorw.2025.100158). Administration of carboplatin was not associated with higher probability of pCR (OR 1.25, 95% CI 0.87-1.79; $P = 0.226$). The dose-dense schedule of anthracyclines did not reach a statistical association with higher probability of pCR (OR 1.38, 95% CI 0.98-1.96; $P = 0.069$). In the multivariate analysis, low PDI remained an independent significant predictor of lower pCR rate (OR 0.50, 95% CI 0.33-0.76; $P = 0.001$) (Supplementary Figure S2A, available at https://doi.org/10.1016/j.esmorw.2025.100158).

HER2-positive BC. pCR was obtained in 51% of patients. Using the CART algorithm, 72% was the optimal threshold to discriminate low and high PDI predicting pCR (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmorw.2025.100158). Patients with HER2-positive BC were divided into two groups based on this threshold: 55 patients (22.1%) had received a low PDI ($<$72%), while 194 patients (77.9%) had received a high PDI ($\geq$72%). This association was, however, not statistically significant, with a pCR rate of 40.0% and 54.1% in the low PDI and high PDI groups, respectively (OR 0.57, 95% CI 0.31-1.04; $P = 0.066$) (Figure 1B and Supplementary Table S2, available at https://doi.org/10.1016/j.esmorw.2025.100158). Interestingly, the dose-dense schedule of anthracyclines was associated with increased pCR rates (OR 1.87, 95% CI 1.08-3.23, $P = 0.026$). In a multivariate analysis, the absence of expression of hormone receptors was associated with increased pCR rates (OR 4.63, 95% CI 2.44-8.79, $P < 0.001$).

Table 1. Baseline clinicopathological characteristics

Variable	Level/units	Missing values (%)	TNBC (n = 514)	HER2+ (n = 249)
Age at diagnosis	(years)	0 (0)	50.3 ± 12.8 49 (40-61)	52.3 ± 12.6 52 (42-60)
Menopausal status (%)	Premenopausal Peri/postmenopausal	12 (1.6)	264 (51.8) 246 (48.2)	104 (43.2) 137 (56.8)
ECOG performance status (%)	0 1 2	0 (0.0)	452 (87.9) 59 (11.5) 3 (0.6)	210 (84.3) 39 (15.7) 0 (0.0)
Diabetes (%)		0 (0.0)	22 (4.3)	10 (4)
Active smoker (%)		1 (0.1)	64 (12.5)	34 (13.7)
Alcohol abuse (%)		0 (0.0)	4 (0.8)	5 (2)
Histological type (%)	Invasive ductal carcinoma; no special type Any special type mixture of types	0 (0)	493 (95.9) 6 (1.2) 15 (2.9)	236 (94.8) 5 (2) 8 (3.2)
Grade (%)	G1 G2 G3	25 (3.3)	2 (0.4) 108 (21.6) 390 (78)	2 (0.8) 59 (24.8) 177 (74.4)
UICC anatomic staging (%)	Stage I Stage II Stage III	3 (0.4)	50 (9.8) 355 (69.3) 107 (20.9)	14 (5.6) 177 (71.4) 57 (23)
Clinical T stage (%)	T1 T2 T3 T4a-4c T4d (inflammatory)	1 (0.1)	84 (16.4) 332 (64.7) 59 (11.5) 15 (2.9) 23 (4.5)	46 (18.5) 152 (61) 22 (8.8) 18 (7.2) 11 (4.4)
Clinical N stage (%)	N0 N1 N2 N3	2 (0.3)	278 (54.2) 176 (34.3) 43 (8.4) 16 (3.1)	91 (36.7) 137 (55.2) 12 (4.8) 8 (3.2)
HER2 status (%)	Negative IHC2+/ISH+ IHC3+	0 (0)	514 (100) 0 (0.0) 0 (0.0)	0 (0.0) 50 (20.1) 199 (79.9)
Estrogen receptor status (%)	Negative Positive	0 (0)	514 (100) 0 (0.0)	103 (41.4) 146 (58.6)
Progesterone receptor status (%)	Negative Positive	0 (0)	514 (100) 0 (0.0)	159 (63.9) 90 (36.1)
BRCA1/2 status (%)	Test not carried out or missing value Both *BRCA1*- and *BRCA2*- negative *BRCA1*- or *BRCA2*-positive		126 (24.5) 290 (56.4) 98 (19.1)	161 (64,7) 82 (32.9) 6 (2.4)

For continuous variables the mean ± standard deviation and median (interquartile range) is given. For categorical variables the absolute (relative) frequencies are given.
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, *in situ* hybridization; TNBC, triple-negative breast cancer; UICC, Union for International Cancer Control.

Dose-dense anthracyclines, however, were not anymore significantly associated with pCR, and had to be removed due to high correlation with age at diagnosis (Supplementary Figure S2B, available at https://doi.org/10.1016/j.esmorw.2025.100158).

Association between paclitaxel dose intensity and IBCFS

TNBC. The most common event was distant recurrence, occurring in 13.1% of patients in the low PDI group and 6.7% in the high PDI group. At 36 months, 77.9% of patients in the low PDI group and 89.2% in the high PDI group were alive and without BC recurrence (HR 2.19, 95% CI 1.29-3.73, $P = 0.004$) (Figure 2A). Moreover, achieving pCR after NAT was significantly associated with improved IBCFS (HR 0.20, 95% CI 0.10-0.40; $P < 0.001$) (Supplementary Figure S3A and Supplementary Table S3, available at https://doi.org/10.1016/j.esmorw.2025.100158). Similar to what was observed with pCR, the correlation between PDI and IBCFS was particularly driven by a reduction in the number of administered cycles (HR 2.17, 95% CI 1.28-3.68, $P = 0.004$). In patients who did not achieve pCR, adjuvant capecitabine was not associated with improved IBCFS (HR 1.02, 95% CI 0.57-1.83; $P = 0.95$) (Supplementary Table S3, available at https://doi.org/10.1016/j.esmorw.2025.100158). In a multivariate model, low PDI did not retain significance regarding association with IBCFS (HR 1.59, 95% CI 0.93-2.73, $P = 0.092$) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmorw.2025.100158).

HER2-positive BC. The most common event was distant recurrence, occurring in 3.6% of patients in the low PDI group and 2.1% in the high PDI group. At 36 months, 93.0% in the low PDI group and 92.5% in the high PDI group were alive and without BC recurrence (HR 0.78, 95% CI 0.17-3.57, $P = 0.75$) (Figure 2B). Achieving pCR after NAT, however, was significantly associated with improved IBCFS (HR 0.18, 95% CI 0.04-0.83, $P = 0.028$) (Supplementary Figure S3B and Supplementary Table S3, available at https://doi.org/10.1016/j.esmorw.2025.100158).

Association between paclitaxel dose intensity and OS

TNBC. Death occurred in 9.8% of patients in the low PDI group and 5.5% of patients in the high PDI group. At

Table 2. Treatment modalities

Variable	Level/units	Missing values (%)	TNBC (n = 514)	HER2+ (n = 249)
Neoadjuvant treatment setting (%)	AC → paclitaxel EC → paclitaxel Paclitaxel → AC Paclitaxel → EC	10 (1.3)	245 (47.9) 107 (20.9) 133 (26) 26 (5.1)	98 (40.5) 141 (58.3) 0 (0.0) 3 (1.2)
Schedule of anthracyclines−cyclophosphamide (%)	Standard Dose-dense	19 (2.5)	259 (51.1) 248 (48.9)	157 (66.2) 80 (33.8)
Number of anthracyclines−cyclophosphamide cycles (%)	4 Cycles 1-3 Cycles	14 (1.8)	442 (86.7) 68 (13.3)	218 (91.2) 21 (8.8)
Neoadjuvant carboplatin (%)	Not received Received	0 (0)	190 (37) 324 (63)	249 (100) 0 (0.0)
Neoadjuvant trastuzumab (%)	Not received Trastuzumab without pertuzumab Trastuzumab with pertuzumab	0 (0)	514 (100) 0 (0.0) 0 (0.0)	21 (8.4) 144 (57.8) 84 (33.7)
HER2+: neoadjuvant trastuzumab (node positive N1 to N3 only) (%)	Not received Trastuzumab without pertuzumab Trastuzumab with pertuzumab	0 (0)	— — —	12 (7.6) 87 (55.4) 58 (36.9)
Paclitaxel intensity reduction (%)	No reduction (standard) Any type of reduction (interval prolongation, dose or number of cycles reduction)	0 (0)	88 (17.1) 426 (82.9)	90 (36.1) 159 (63.9)
Overall paclitaxel dose intensity (PDI)	(ratio)	0 (0)	0.77 ± 0.20 0.82 (0.67; 0.92)	0.83 ± 0.20 0.91 (0.75; 0.99)
Tumor surgery type (%)	Mastectomy Wide local excision Other (not specified)	0 (0)	230 (44.7) 280 (54.5) 4 (0.8)	125 (50.2) 124 (49.8) 0 (0.0)
Lymph node surgery type (%)	Sentinel lymph node biopsy only Axillary lymph node Dissection Other (not specified)	0 (0)	275 (53.5) 236 (45.9) 3 (0.6)	83 (33.3) 162 (65.1) 4 (1.6)
Pathological T stage (%)	ypT0/is ypT1 ypT2 ypT3 ypT4	0 (0)	270 (52.5) 178 (34.6) 50 (9.7) 12 (2.3) 4 (0.8)	139 (55.8) 83 (33.3) 21 (8.4) 5 (2) 1 (0.4)
Pathological N stage (%)	yN0 yN1 yN2 yN3	1 (0.1)	422 (82.3) 56 (10.9) 27 (5.3) 8 (1.6)	199 (79.9) 39 (15.7) 8 (3.2) 3 (1.2)
Adjuvant capecitabine (%)	Received	0 (0)	139 (27)	0 (0.0)
TNBC without pCR: Adjuvant capecitabine (%)	Not received Received	0 (0)	121 (46.9) 137 (53.1)	— —
Adjuvant trastuzumab (%)	Not received Trastuzumab without Pertuzumab Trastuzumab with Pertuzumab Trastuzumab emtansine	0 (0)	513 (99.8) 1 (0.2) 0 (0.0) 0 (0.0)	17 (6.8) 133 (53.4) 51 (20.5) 48 (19.3)
HER2+ without pCR: adjuvant trastuzumab (%)	Not received Trastuzumab without Pertuzumab Trastuzumab with pertuzumab Trastuzumab emtansine	0 (0)	— — — —	10 (8.2) 51 (41.8) 14 (11.5) 47 (38.5)
Adjuvant endocrine therapy (%)	Received	0 (0)	13 (2.5)	130 (52.2)
Adjuvant radiotherapy (%)	Received	0 (0)	363 (70.6)	195 (78.3)

For continuous variables the mean ± standard deviation and median (interquartile range) is given. For categorical variables the absolute (relative) frequencies are given.
AC, Adriamycin and cyclophosphamide; EC, epirubicin and cyclophosphamide; HER2, human epidermal growth factor receptor 2; pCR, pathological complete response; TNBC, triple-negative breast cancer.

36 months, 86.1% in the low PDI group and 93.1% in the high PDI group were alive (HR 1.78, 95% CI 0.91-3.47, $P = 0.093$) (Figure 2C). Achieving pCR after NAT was significantly associated with improved OS (HR 0.22, 95% CI 0.10-0.51, $P < 0.001$) (Supplementary Figure S3C and Supplementary Table S4, available at https://doi.org/10.1016/j.esmorw.2025.100158).

HER2-positive BC. Death occurred in 1.8% of patients in the low PDI group and 0.0% of patients in the high PDI group. At 36 months, 95.8% in the low PDI group and 100.0% in the high PDI group were alive. The low number of events prevented from carrying out statistical analyses (Figure 2D and Supplementary Figure S3D, Supplementary Table S3, available at https://doi.org/10.1016/j.esmorw.2025.100158).

Treatment safety and correlation with PDI

Among the global cohort, the main adverse events related to paclitaxel are summarized in Supplementary Figure S5, available at https://doi.org/10.1016/j.esmorw.2025.100158, and associations between PDI modifications and adverse events are reported in Figure 3. Caution is warranted in their interpretation given the high heterogeneity of quality of

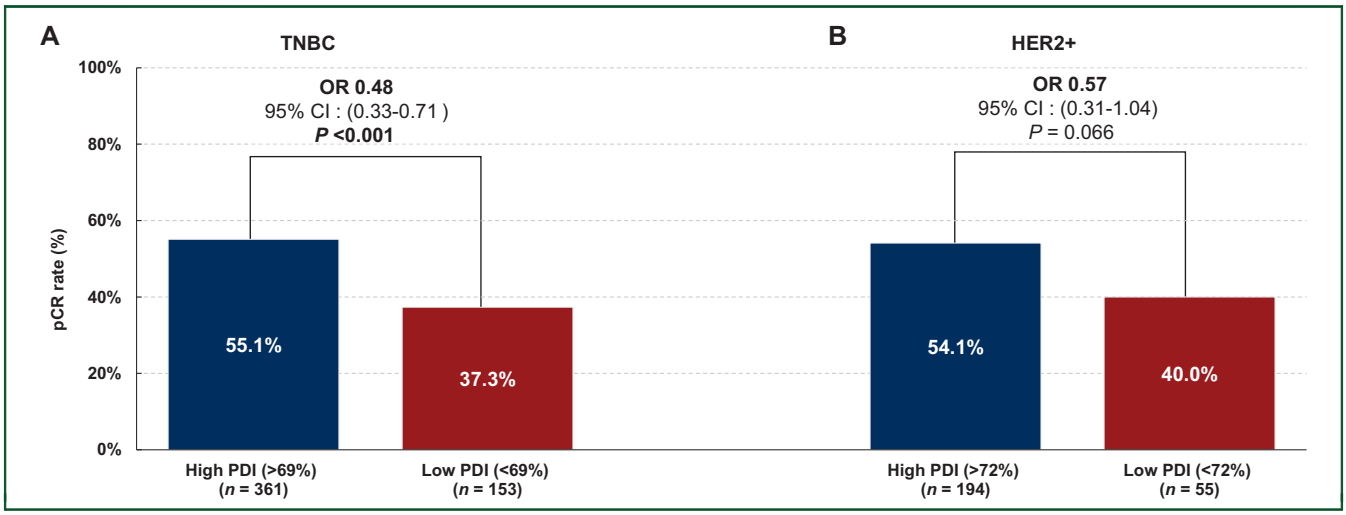

Figure 1. Pathological complete response rate according to the paclitaxel dose intensity, in (A) the TNBC population, and (B) the HER2-positive BC population. BC, breast cancer; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OR, odds ratio; pCR, pathological complete response; PDI, paclitaxel dose intensity; TNBC, triple-negative breast cancer.

capture of these data. Peripheral neuropathy occurred in 30.1% of patients, with 73.5% of them being of grade 1 or 2. Grade 3-4 neutropenia occurred in 30.7% of patients during the cycles of paclitaxel. Paclitaxel dose reductions (24.8% of patients) were associated with neuropathy, neutropenia, and miscellaneous reasons in 30.7%, 27.5%, and 27.0% of cases, respectively. Interval prolongation (59.2% of patients) was most frequently associated with neutropenia (39.6% of cases) and miscellaneous reasons outside neuropathy, liver toxicity, and allergy (i.e. at the physician's discretion or not notified, 65.7% of cases). Early paclitaxel cessation (36.7% of patients) was most frequently associated with the occurrence of peripheral neuropathy (25.4% of cases) (Figure 3). Among the global cohort, in a multivariate analysis, a reduction of PDI was significantly associated with Eastern Cooperative Oncology Group (ECOG) performance status $\geq$1, diabetes, incompleteness of the AC regimen, the occurrence of grade 2 or higher neuropathy, grade 3-4 neutropenia or anaphylaxis (Supplementary Table S5, available at https://doi.org/10.1016/j.esmorw.2025.100158). Based on these data, we carried out a sensitivity analysis in TNBC, demonstrating that the association between pCR rate and PDI was independent of AC completeness (Supplementary Table S6, available at https://doi.org/10.1016/j.esmorw.2025.100158).

DISCUSSION

Using real-world data from eight cancer centers with homogeneous clinical practice, we specifically investigated the prognostic impact of reduced PDI in early TNBC and HER2-positive BC. We considered PDI as a composite of the dose at each cycle, the number of cycles, and the adherence to timing of the schedule.

Despite including a majority of patients with aggressive BC and without comorbidities, only 17.1% and 36.1% of patients with TNBC and HER2-positive BC, respectively, received paclitaxel without any dose intensity modification. Considering our thresholds of low PDI optimized for pCR prediction, 28.6% and 22.1% of TNBC and HER2-positive BC even received a PDI reduction of >31% and 28%, respectively. In TNBC, low PDI had a statistically and clinically meaningful association with lower pCR rate (37.3% versus 55.5%), and decrease in 3-year IBCFS rate (77.9% versus 89.2%). The association with pCR rate was independent of other clinico-pathological factors. In HER2-positive BC, however, low PDI was not statistically associated with a lower pCR rate (40.0% versus 54.1%), while no differences were seen in 3-year IBCFS. These results are in line with our initial hypotheses, given the high sensitivity of this disease to HER2-directed therapies. Nevertheless, this subtype remains heterogeneous, as our results confirm previous findings of increased chemosensitivity of hormone receptor-negative HER2-positive BC, compared with hormone receptor-positive HER2-positive BC.[18]

Encapsulating in a single metric the different methods leading to reduced chemotherapy dose intensity is well established. Weycker et al.[19] considered relative dose intensity, defined as the amount of drug administered per unit of time as a fraction of the standard amount per unit of time. A relative dose intensity <85% of the entire NAT regimen was considered low. Our TNBC data are in line with this, but we specifically focused on paclitaxel, which frequently requires adaptation for toxicity management. Very interestingly, considering independently the three factors influencing dose intensity, we could specifically highlight a negative impact of reduction of number of cycles of paclitaxel. To the best of our knowledge, until now no published data provided data allowing to suggest this differential impact.

The results of our study suggest that TNBC patients with lower tolerance to standard neoadjuvant chemotherapy are at higher risk of poorer outcomes, but treatment guidelines meanwhile evolved: escalation of NAT for BC through the addition of pembrolizumab for TNBC and pertuzumab for

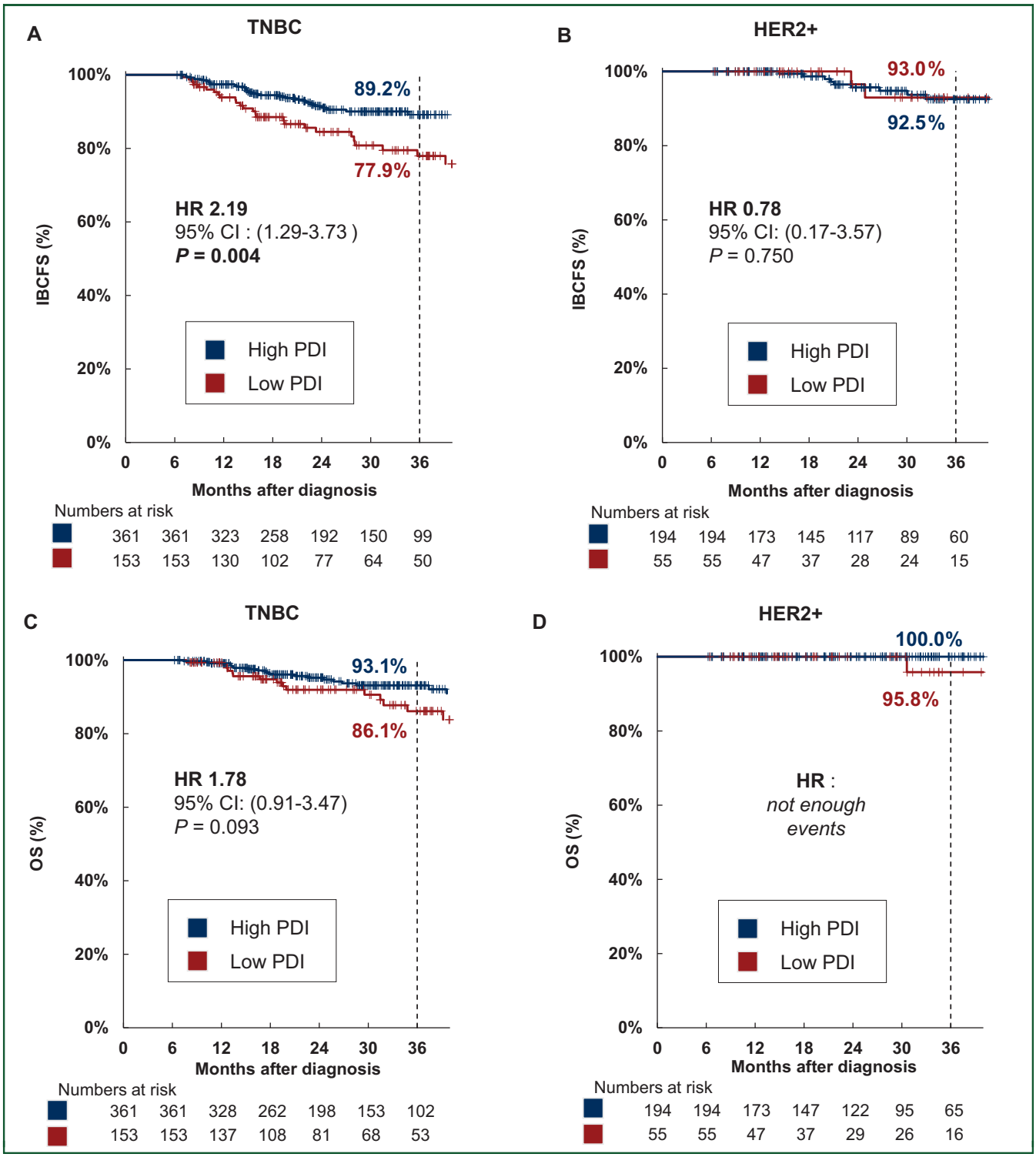

Figure 2. (A) Kaplan–Meier estimates of invasive BC-free survival, according to the paclitaxel dose intensity, in the TNBC population. (B) Kaplan–Meier estimates of invasive BC-free survival, according to the paclitaxel dose intensity, in the HER2-positive BC population. (C) Kaplan–Meier estimates of overall survival, according to the paclitaxel dose intensity, in the TNBC population. (D) Kaplan–Meier estimates of overall survival, according to the paclitaxel dose intensity, in the HER2-positive BC population.

BC, breast cancer; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PDI, paclitaxel dose intensity; TNBC, triple-negative breast cancer.

HER2-positive BC at high risk of recurrence improves the outcomes.[20-22] Furthermore, patients with residual disease after NAT are now a well-defined subgroup at higher risk of relapse, eligible for more intense adjuvant systemic therapy: adjuvant capecitabine, and olaparib in case of a germline *BRCA1/2* pathogenic variant, both lead to improved OS over placebo in TNBC,[23,24] whereas trastuzumab emtansine leads to improved outcomes over trastuzumab with or without pertuzumab in HER2-positive BC.[25] Ongoing adjuvant trials further aim to select patients at high risk of recurrence in

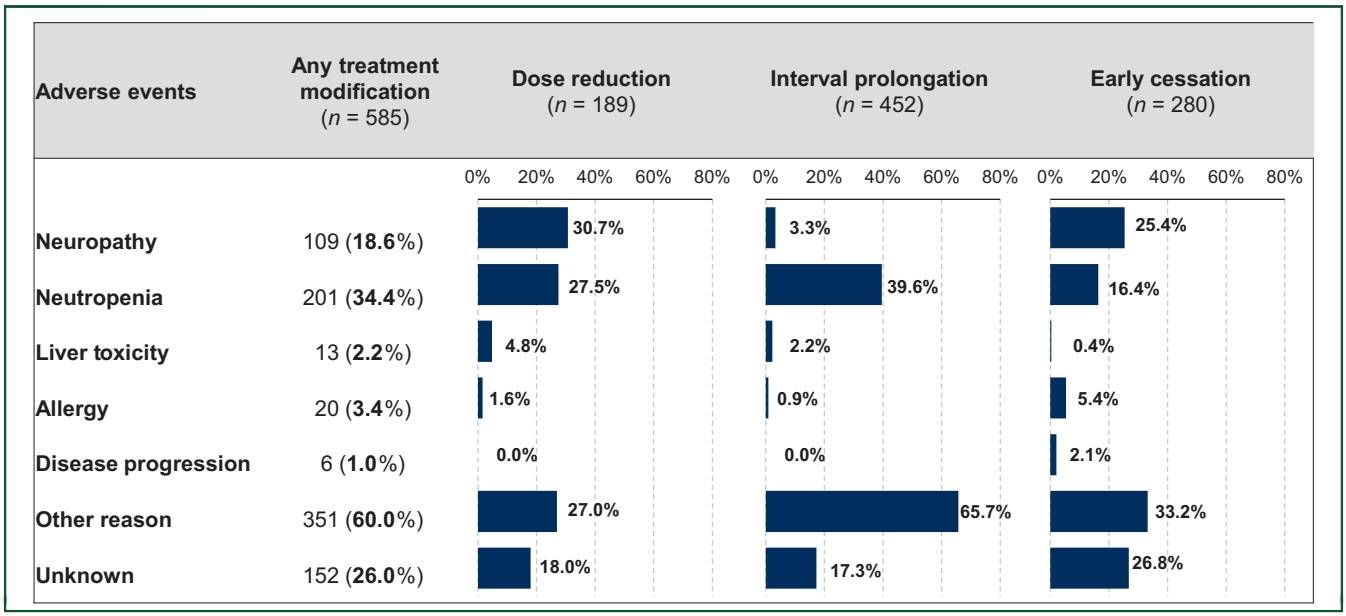

Figure 3. Associations between modifications in paclitaxel dose intensity and adverse events. Caution is warranted when inferring causality given the retrospective nature of the analysis.

the post-neoadjuvant setting.[26-31] To the best of our knowledge, however, escalation trials never formally reported on the potential paradoxical impact of reduced treatment exposure through lower tolerance to more intense treatment combinations: paradoxically, patients with lower tolerance to neoadjuvant chemotherapy could in the future be more selected for escalation adjuvant strategies. Strategies to reduce the risk of lowering PDI in the neoadjuvant setting (among which cooling of the extremities is the most widely used)[32] could thus lead to several benefits in TNBC, improve the tolerance of the NAT and long-term cancer outcomes, and potentially spare unnecessary adjuvant treatments to a significant number of patients who would be negatively affected by paclitaxel-related toxicity. Financial toxicity could thus also be reduced, both in the neoadjuvant and adjuvant settings. It also remains unknown if the risk of recurrence is equivalent when considering patients with residual disease after low or high neoadjuvant PDI. Indeed, the latter could reflect true chemoresistant disease. Interestingly, low PDI was associated with incompleteness of the AC regimen, suggesting common risk of lower tolerance to both parts of the treatment plan. Nevertheless, early cessation of AC was not associated with impaired treatment outcomes in TNBC.

Our study has several limitations: first, general caution should always be considered when analyzing data of retrospective nature. This certainly holds true regarding the assessment of toxicity and some comorbidities, lacking standardized medical notes. Second, we reliably collected pCR rate, but some centers did not use in daily practice the more informative Residual Cancer Burden classification. Third, we collected relatively few HER2-positive BC patients, as some centers more frequently administered the docetaxel—carboplatin—anti-HER2 regimen. While results of the HER2-positive BC population should thus be interpreted with caution, a true difference between TNBC and HER2-positive BC could exist, as recent successful de-escalation strategies with chemotherapy-free regimens in HER2-positive BC demonstrate the extreme sensitivity of this disease to anti-HER2 therapies.[33] Fourth, while the general cohorts were homogeneous for NAT plans, we acknowledge heterogeneity regarding the adjuvant treatments. Indeed, many patients did not receive the most effective post-NAT schedules (capecitabine for non-pCR TNBC, trastuzumab emtansine for non-pCR HER2-positive BC). This could have impacted the association between PDI and long-term cancer outcomes. Fifth, given the multiple adaptations of the paclitaxel injections encountered in our patients, we could not study with confidence the specific impact of reducing the dose to 60 mg/m^2, a measure commonly carried out in clinical practice. Lastly, the standard treatment of early TNBC at high risk of relapse evolved to the combination of chemotherapy and pembrolizumab, and combination of paclitaxel with carboplatin is now standard of care.

Analyzing independent cohorts is thus mandatory, to confirm our threshold for reduced PDI in both subtypes, to confirm its negative impact on patient outcomes in TNBC, to further study if this has an impact in HER2-positive BC, and to consider the prevalence of low PDI and its prognostic impact in TNBC treated with combined chemotherapy and immunotherapy. Recent real-world data with the chemo-immunotherapy regimen also highlighted the association of chemotherapy adaptation with pCR rate.[34] We are currently performing a second independent study to tackle these questions.

In conclusion, reduction of PDI (through dose delay, dose reduction or treatment interruption) is frequently carried out during NAT of early TNBC and HER2-positive BC, with a significant and clinically meaningful negative impact on pCR rate and IBCFS in TNBC. Reduction of PDI should always be

carefully considered, balancing the risk of adverse events and potential impact on outcomes, especially in TNBC. Strategies to minimize low PDI should be a research priority.

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DISCLOSURE

MB was employed by IPO Porto at the time of data generation and interpretation, but is since then an employee of IQVIA. HF is an employee of IQVIA. All other authors have declared no conflicts of interest.

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