The Causes and Consequences of Incomplete Paclitaxel Administration during the Neoadjuvant treatment of Early Triple negative and HER2 positive breast cancer (CIPNETH)

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DigiCore

Background and rationale

- Neoadjuvant treatment (NAT) is the preferred option in early triple-negative (TNBC) and HER2-positive (HER2+) BC at elevated risk of relapse.[1,2]

- Approximate half of cases achieve a pathological complete response (pCR) at surgery, leading to an advantage in invasive BC-free survival (IBCFS) and overall survival (OS).[2]

- Decades of clinical studies have settled four cycles of anthracyclines and cyclophosphamide (AC), preceded or followed by 12 cycles of paclitaxel, as the common backbone of NAT in both diseases.[2,3]

- Peripheral neuropathy is a notable adverse event linked to paclitaxel administration, that can afflict up to 70% of patients.[4]

1. Nagayama. JNCI 106, (2014) ; 2. Asselain. Lancet Oncol 19, 27–39 (2018); 3. Bines. Annals of Oncology 25, 1079–1085 (2014).; 4. Molassiotis. BMC Cancer 19, 132 (2019).

Background and rationale

- To date, paclitaxel dose-intensity (PDI) attenuation before the occurrence of high-grade toxicity remains the chief strategy in managing this side effect.[5]

- In clinical practice, reducing PDI is obtained by dose reductions, treatment delays or treatment discontinuations, alone or in combinations, all of which can potentially undermine the effectiveness of NAT.

- Alarmingly, this incomplete paclitaxel administration is deemed necessary in 30 to 40% of cases.[5]

- **To the best of our knowledge, no comprehensive study has been conducted to evaluate the impact of reduced PDI on the efficacy of NAT.**

5. Bhatnagar. Springerplus 3, 366 (2014)

CIPNETH study design

Key inclusion factors

Early TNBC and HER2+ BC

Treated with neoadjuvant chemotherapy

Diagnosed Jan 2018 - Dec 2021

Exclusion factors

History of another invasive malignancy

Bilateral invasive BC

Concomitant pregnancy

Neoadjuvant treatment plan

AC/EC - paclitaxel

± carboplatin, ± anti-HER2

No investigational product, anti-PD(L)1 or endocrine therapy

4 cycles of AC/EC, dose dense or not.
12 cycles of paclitaxel 80 mg/m².

Primary endpoint

To assess the impact of reduced PDI on pCR rate and IBCFS.

Secondary endpoints

- To assess the impact of reduced PDI on OS.
- To estimate if this impact differs according to the BC subtype.
- To explore the reasons of reduced PDI.

8 centers, member of the DigiCore consortium.
Extensive data quality control at the level of each patient.

Hypothesis : significant effect in TNBC, but not in HER2+ BC *(high sensitivity to concomitant anti-HER2)*.

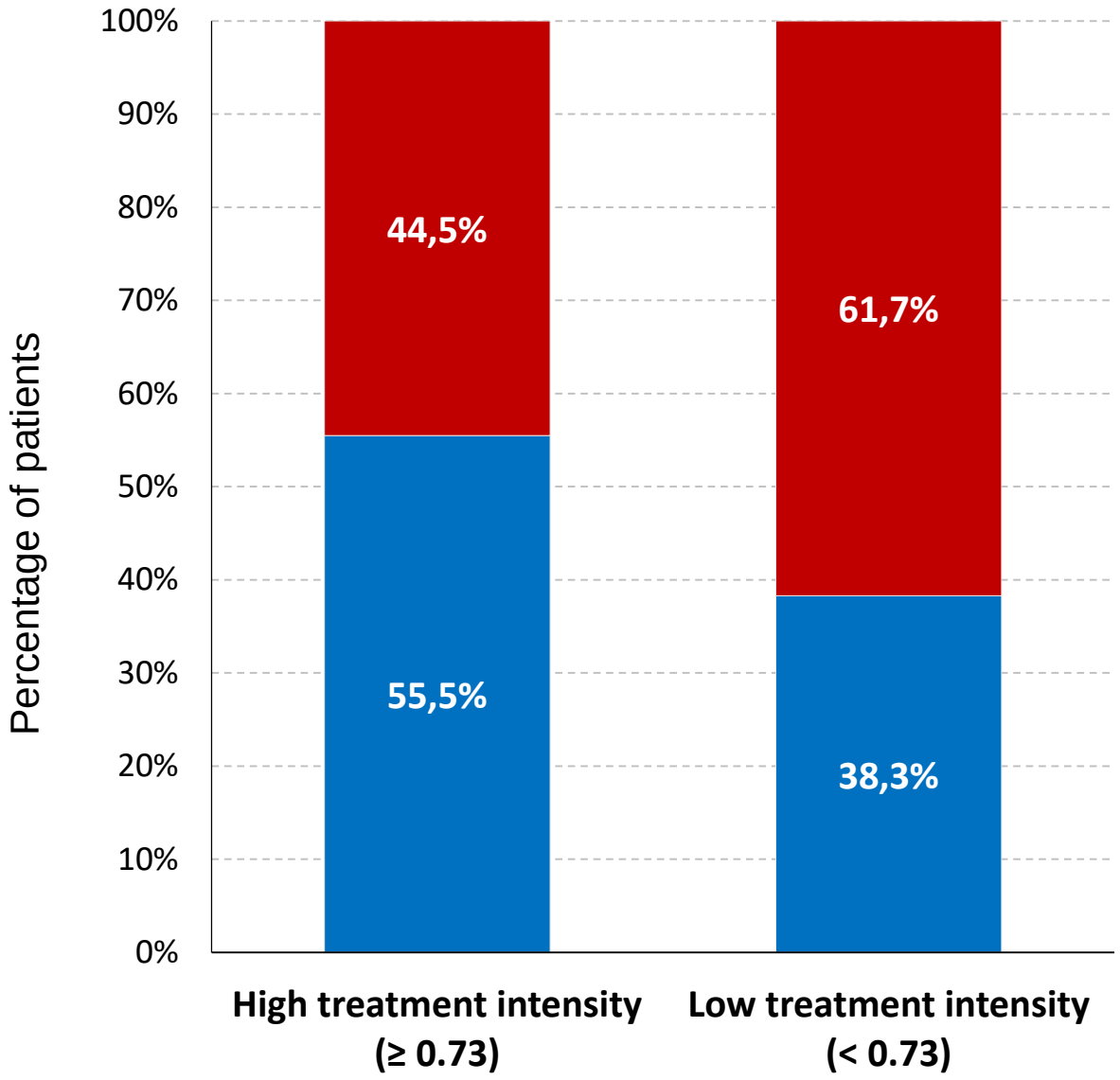
Baseline characteristics

		Overall (n = 763)	TNBC (n = 514)	HER2+ (n = 249)
Age at diagnosis		50.9 ± 12.8	50.3 ± 12.8	52.3 ± 12.6
Menopausal Status	Pre-menopausal	368 (49 %)	264 (51.8 %)	104 (43.2 %)
ECOG Performance Status	0	662 (86.8 %)	452 (87.9 %)	210 (84.3 %)
	1	98 (12.8 %)	59 (11.5 %)	39 (15.7 %)
	2	3 (0.4 %)	3 (0.6 %)	0 (0.0 %)
Diabetes		32 (4.2 %)	22 (4.3 %)	10 (4 %)
Active smoker		98 (12.9 %)	64 (12.5 %)	34 (13.7 %)
Alcohol abuse		9 (1.2 %)	4 (0.8 %)	5 (2 %)
Clinical T Stage	T1	130 (17.1 %)	84 (16.4 %)	46 (18.5 %)
	T2	486 (63.8 %)	333 (64.9 %)	153 (61.4 %)
	T3	81 (10.6 %)	59 (11.5 %)	22 (8.8 %)
	T4a-4c	31 (4.1 %)	14 (2.7 %)	17 (6.8 %)
	T4d (inflammatory)	34 (4.5 %)	23 (4.5 %)	11 (4.4 %)
Clinical N Stage	N0	369 (48.5 %)	278 (54.2 %)	91 (36.7 %)
	N1	313 (41.1 %)	176 (34.3 %)	137 (55.2 %)
	N2	55 (7.2 %)	43 (8.4 %)	12 (4.8 %)
	N3	24 (3.2 %)	16 (3.1 %)	8 (3.2 %)

Neoadjuvant treatment

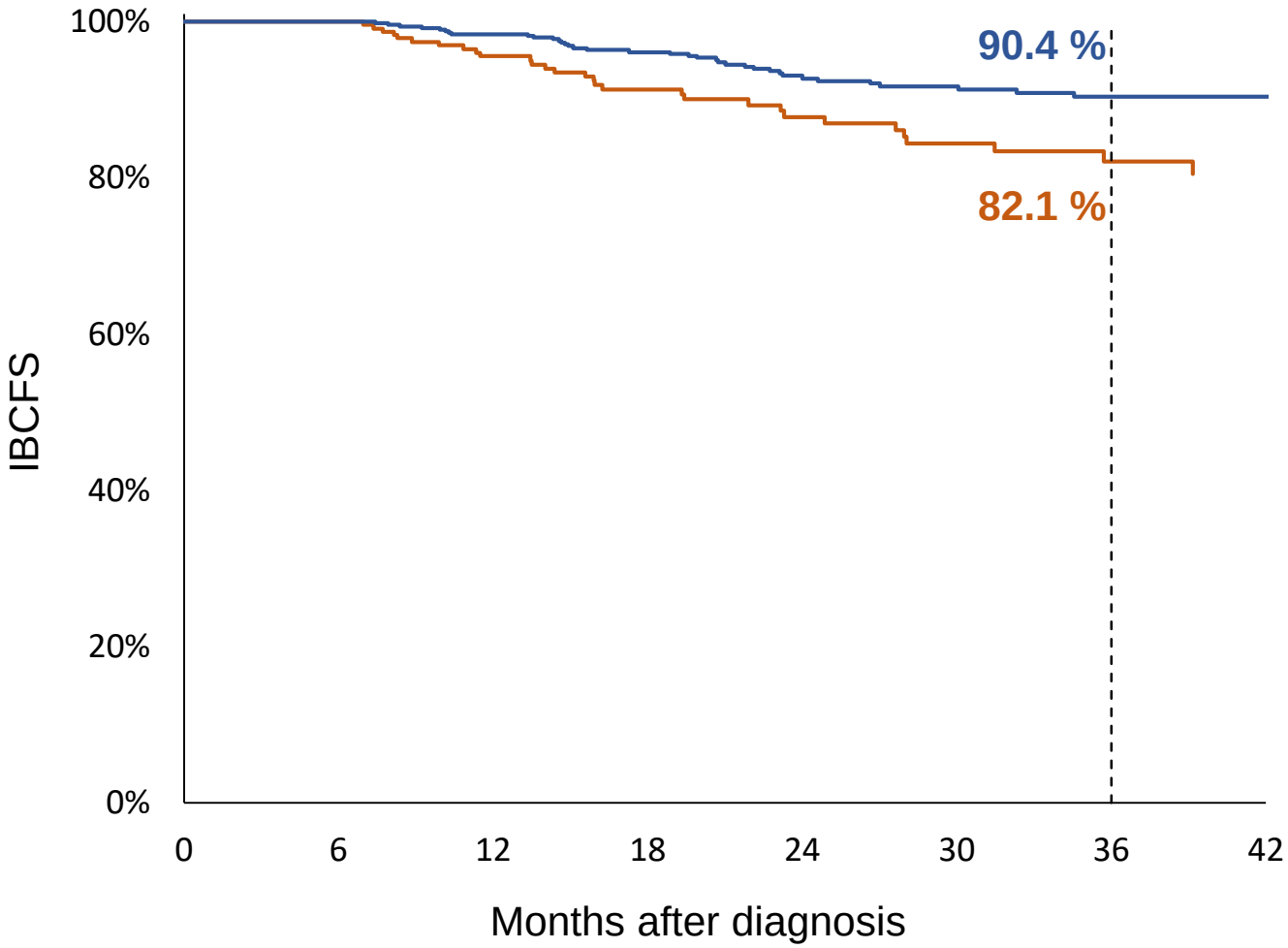
		Overall (n = 763)	TNBC (n = 514)	HER2+ (n = 249)
Molecules	AC -> Paclitaxel	343 (45.6 %)	245 (47.9 %)	98 (40.5 %)
	EC -> Paclitaxel	248 (32.9 %)	107 (20.9 %)	141 (58.3 %)
	Paclitaxel -> AC	133 (17.7 %)	133 (26 %)	0 (0.0 %)
	Paclitaxel -> EC	29 (3.9 %)	26 (5.1 %)	3 (1.2 %)
Anthracyclines	Dose-dense	328 (44.1 %)	248 (48.9 %)	80 (33.8 %)
Neoadjuvant carboplatin		324 (42.5 %)	324 (63 %)	0 (0.0 %)
Neoadjuvant anti-HER2	Trastuzumab without Pertuzumab	144 (18.9 %)	0 (0.0 %)	144 (57.8 %)
	Trastuzumab with Pertuzumab	84 (11 %)	0 (0.0 %)	84 (33.7 %)
Paclitaxel Intensity Reduction	No reduction (standard)	178 (23.3 %)	89 (17.3 %)	89 (35.7 %)
	Interval prolongation only	199 (26.1 %)	165 (32.1 %)	34 (13.7 %)
	Dose reduction only	32 (4.2 %)	17 (3.3 %)	15 (6 %)
	Early cessation only	82 (10.7 %)	48 (9.3 %)	34 (13.7 %)
	Interval prolongation & Dose reduction	73 (9.6 %)	62 (12.1 %)	11 (4.4 %)
	Dose reduction & Early cessation	17 (2.2 %)	7 (1.4 %)	10 (4 %)
	Interval prolongation & Early cessation	120 (15.7 %)	80 (15.6 %)	40 (16.1 %)
	All three types of reduction	62 (8.1 %)	46 (8.9 %)	16 (6.4 %)
Number of Paclitaxel Cycles	12 cycles	482 (63.2 %)	333 (64.8 %)	149 (59.8 %)

pCR rate by paclitaxel dose intensity



Paclitaxel	n	OR (95% CI)	p-value
High intensity (≥ 0.73)	528		
Low intensity (< 0.73)	235	**0.50** (0.36 ; 0.68)	**<0.001**

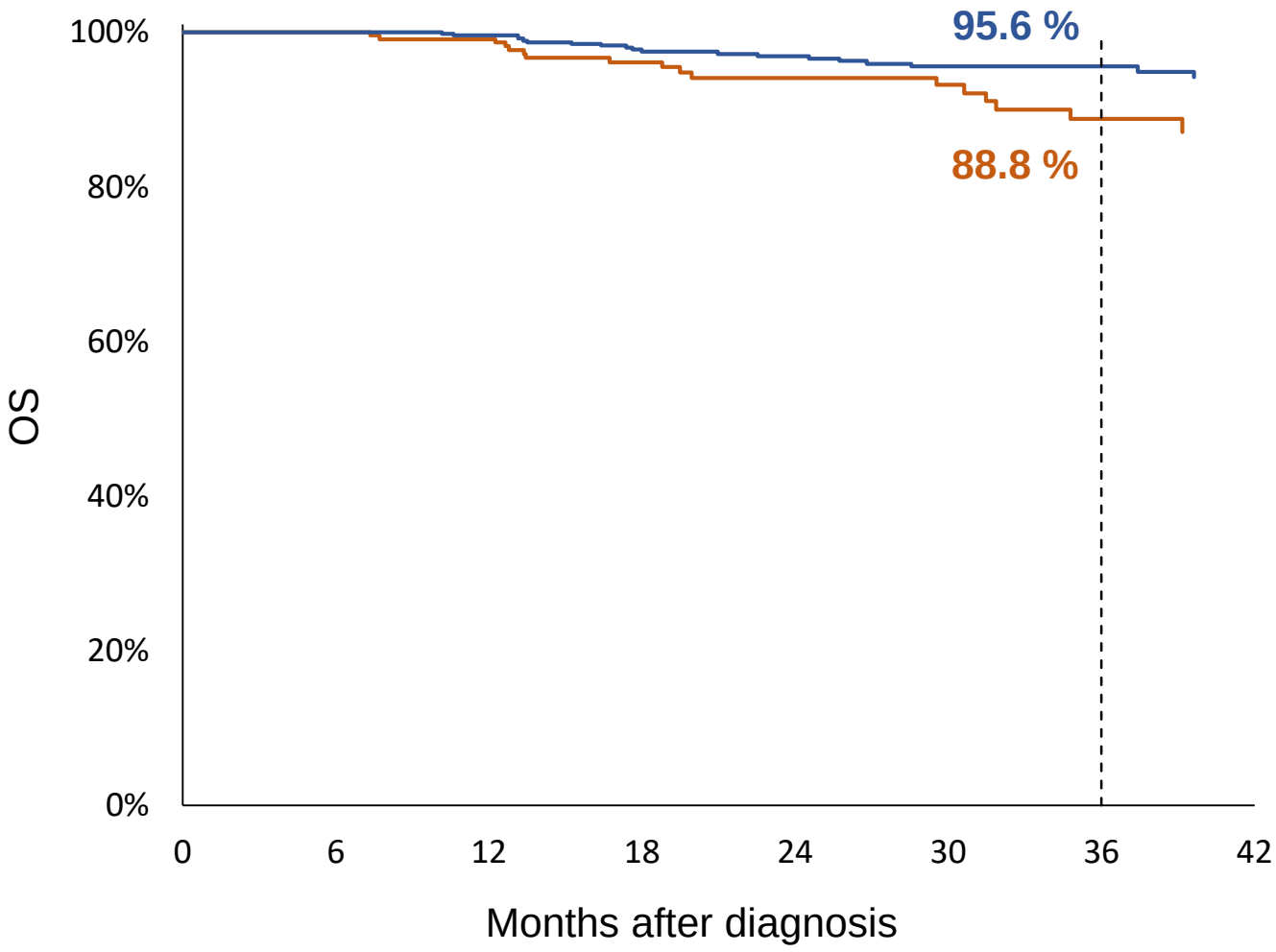
IBCFS by paclitaxel dose intensity



Paclitaxel	n	HR (95% CI)	p-value
High intensity (≥ 0.73)	528		
Low intensity (< 0.73)	235	**2.00** (1.23 ; 3.23)	**0.005**

Median follow-up time : 28.1 months

OS by paclitaxel dose intensity

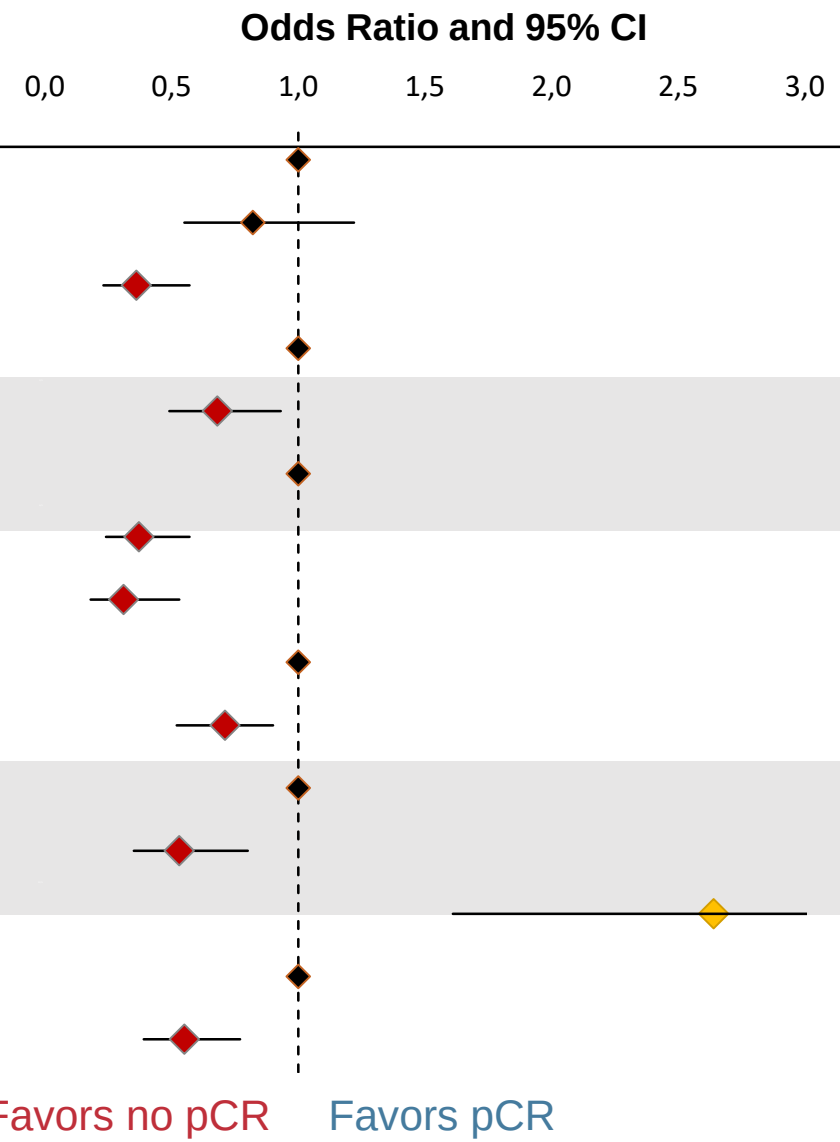


Paclitaxel	n	HR (95% CI)	p-value
High intensity (≥ 0.73)	528		
Low intensity (< 0.73)	235	**2.19** (1.14 ; 4.21)	**0.019**

Median follow-up time : 28.1 months

Multivariate analysis of pCR rate

		n	pCR (%)	Multivariate logistic regression model OR (95% CI)	p-value
Age at diagnosis	<40 years	161	97 (60.2 %)		
	40-60 years	398	212 (53.3 %)	**0.82** (0.55; 1.22)	0.330
	≥60 years	204	74 (36.3 %)	**0.36** (0.23; 0.57)	<**0.001**
Body Surface Area	<1.8 m^2	478	257 (53.8 %)		
	≥1.8 m^2	285	126 (44.2 %)	**0.68** (0.49; 0.93)	**0.016**
Clinical T Stage	T1	130	91 (70.0 %)		
	T2	486	231 (47.5 %)	**0.37** (0.24; 0.57)	**<0.001**
	T3/4	146	61 (41.8 %)	**0.31** (0.18; 0.53)	**<0.001**
Clinical N Stage	N0	369	202 (54.7 %)		
	N1/2/3	392	180 (45.9 %)	**0.71** (0.52; 0.98)	**0.039**
Biological Subtype	TNBC	514	256 (49.8 %)		
	Luminal HER2+	147	56 (38.1 %)	**0.53** (0.35; 0.80)	**0.002**
	Non luminal HER2+	102	71 (69.6 %)	**2.64** (1.61; 4.31)	**<0.001**

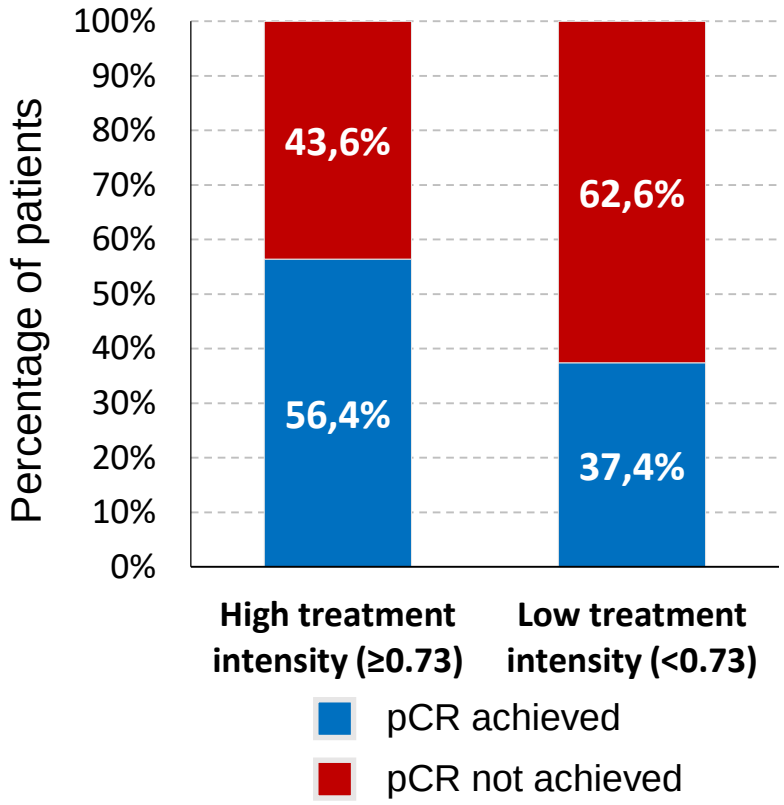


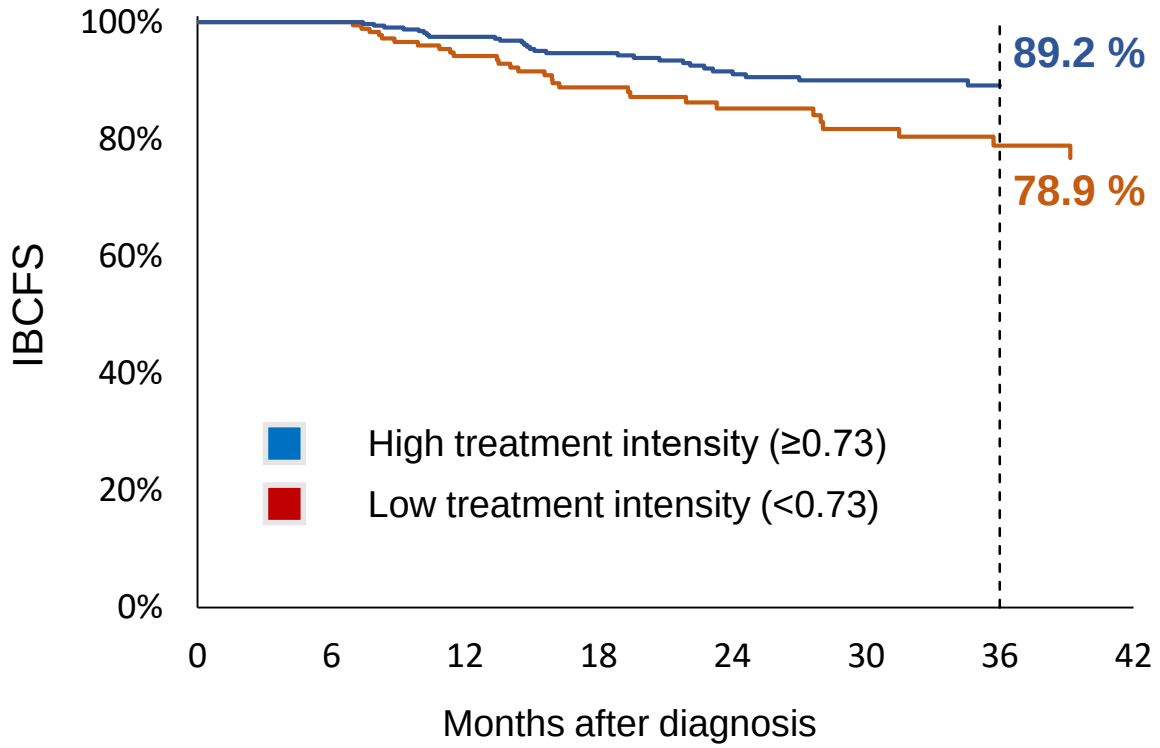
Multivariate analysis of IBCFS

		n	Hazard Ratio and 95% CI (0,0 1,0 2,0 3,0 4,0 5,0)	Multivariate Cox regression model HR (95% CI)	p-value
ECOG Performance Status	0	662			
	≥1	101		**2.66** (1.60; 4.41)	<**0.001**
Clinical T Stage	T1	130			
	T2	486		**0.97** (0.59; 1.59)	0.914
	T3/4	146		**1.96** (1.21; 3.19)	**0.007**
Clinical N Stage	N0	369			
	N1/2/3	392		**1.88** (1.11; 3.20)	**0.019**
Inflammatory Breast Cancer	No	729			
	Yes	34		**3.68** (2.12; 6.39)	<**0.001**
Biological Subtype	TNBC	514			
	Luminal HER2+	147		**0.49** (0.24; 1.00)	**0.050**
	Non luminal HER2+	102		**0.37** (0.16; 0.87)	**0.022**
Paclitaxel	High intensity (≥0.73)	528			

Favors longer IBCFS Favors shorter IBCFS

pCR rate and IBCFS by paclitaxel dose intensity : TNBC cohort

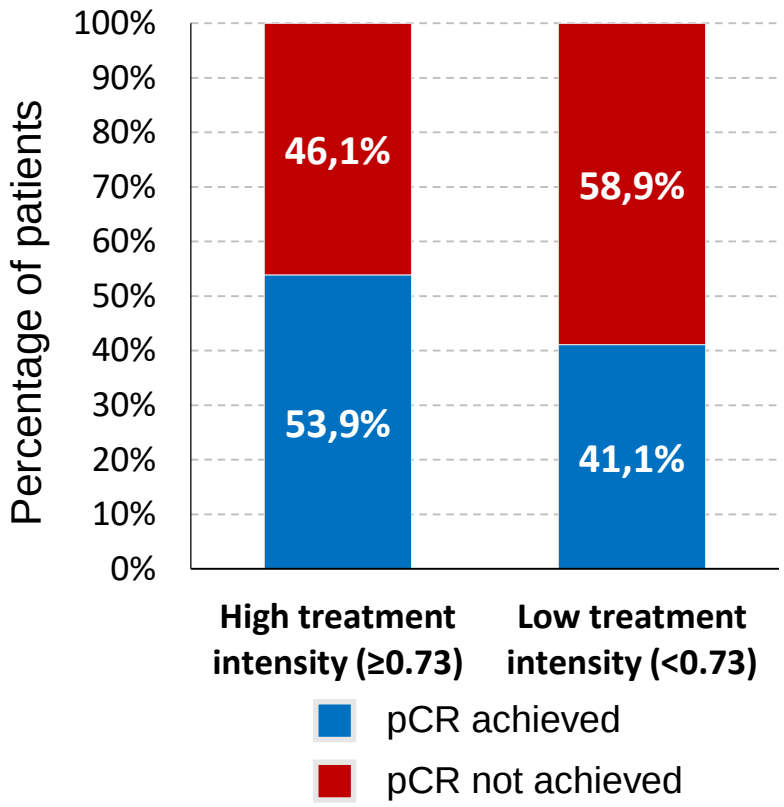


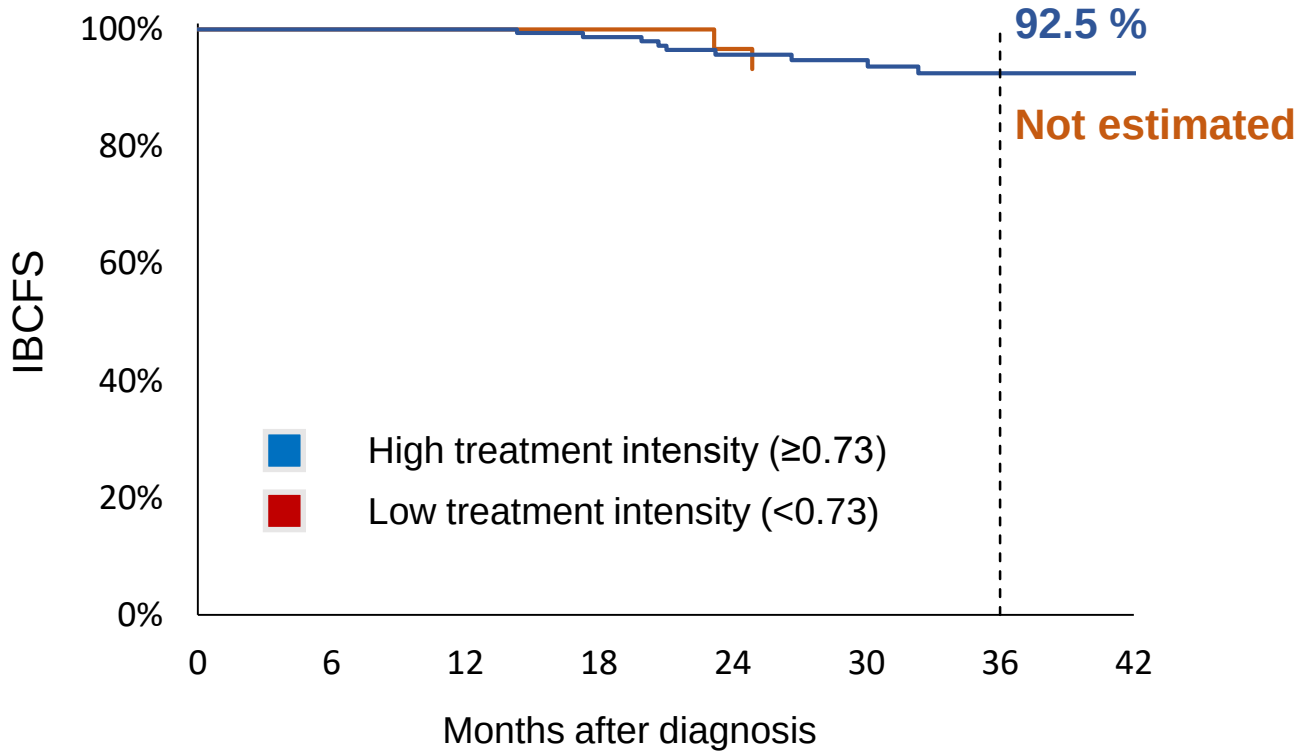


Paclitaxel	n	OR (95% CI)	p-value
High intensity (≥ 0.73)	335		
Low intensity (< 0.73)	179	**0.46** (0.32 ; 0.67)	**<0.001**

Paclitaxel	n	HR (95% CI)	p-value
High intensity (≥ 0.73)	335		
Low intensity (< 0.73)	179	**2.12** (1.25 ; 3.60)	**0.005**

pCR rate and IBCFS by paclitaxel dose intensity : HER2+ cohort





Paclitaxel	n	OR (95% CI)	p-value
High intensity (≥ 0.73)	193		
Low intensity (< 0.73)	56	0.60 (0.33 ; 1.09)	0.093

Paclitaxel	n	HR (95% CI)	p-value
High intensity (≥ 0.73)	193		
Low intensity (< 0.73)	56	0.75 (0.17 ; 3.44)	0.715

Causes of reduced paclitaxel dose intensity

	Any treatment modification (n=585)	**Dose reduction** (n=184)	**Early cessation** (n=281)	**Interval prolongation** (n=454)
Neuropathy	105 (17.9 %)	56 (30.4 %)	66 (23.5 %)	15 (3.3 %)
Neutropenia	198 (33.8 %)	50 (27.2 %)	44 (15.7 %)	176 (38.8 %)
Liver toxicity	13 (2.2 %)	9 (4.9 %)	1 (0.4 %)	10 (2.2 %)
Allergy	19 (3.2 %)	3 (1.6 %)	15 (5.3 %)	3 (0.7 %)
Disease progression	6 (1.0 %)	0 (0.0 %)	6 (2.1 %)	0 (0.0 %)
Other medical reason	222 (37.9 %)	46 (25.0 %)	76 (27.0 %)	158 (34.8 %)
Non-medical or unknown reason	357 (61.0 %)	38 (20.7 %)	100 (35.6 %)	277 (61.0 %)

Conclusions

- In this multi-centric cohort of TNBC and HER2-positive BC treated with NAT, 67% of patients had a paclitaxel dose-intensity modification, whereas 31% even had a high dose reduction (> 27% of intended intensity).
- Paclitaxel dose-intensity reduction had a clinically meaningful and statistically significant negative impact on pCR rate, IBCFS and OS.
- These findings appear mainly driven by the TNBC cohort, but statistical power could limit the analysis of HER2-positive BC.
- Reason for treatment adaptation is frequently missing in real-world data, questioning the existence of a medically relevant and meticulously assessed underlying cause.
- Paclitaxel dose-intensity reduction, through dose delay, dose reduction or treatment interruption, should not be proposed without a relevant medical reason.
- Studies regarding prevention and early treatment of paclitaxel-induced peripheral neuropathy could empower higher treatment dose-intensity and reduce the risk of relapse of BC.

Acknowledgements

- We would like to generously thank the medical and paramedical staff in our institutions that daily take care of our patients.

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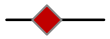
- We are very grateful to the enthusiastic work of James Anderson, Will Sopwith and their team who connected us all together.

Sensitivity analysis of pCR rate using the leave-one-out method

Effect of individual centres on the resulting estimate of the odds ratio of achieving pCR at low treatment intensity.

Excluded participating centres (anonymised)	**Odds Ratio and 95% CI**	**Multivariate logistic regression model estimates**	
	0,0 0,5 1,0 1,5 2,0	**OR** (95% CI)	**p-value**
A		**0.50** (0.35; 0.71)	**<0.001**
B		**0.50** (0.35; 0.71)	**<0.001**
C		**0.50** (0.35; 0.72)	**<0.001**
D		**0.54** (0.38; 0.76)	**<0.001**
All 8 centers included		**0.55** (0.39; 0.77)	**<0.001**
E		**0.57** (0.39; 0.84)	**0.004**
F		**0.58** (0.40; 0.84)	**0.004**
G		**0.59** (0.42; 0.84)	**0.003**
H	Favors no pCR Favors pCR	**0.65** (0.44; 0.96)	**0.031**

Difference in unknown reasons for treatment intensity reduction between centres

Participating centres (anonymised)	**Dose reduction**	**Early cessation**	**Interval prolongation**
	% of unknown reasons 0% 50% 100%	% of unknown reasons 0% 50% 100%	% of unknown reasons 0% 50% 100%
A	1 57%	1 69%	1 71%
B	2 28%	2 54%	2 63%
C	3 25%	3 63%	3 21%
D	4 17%	4 50%	4 21%
All 8 centers combined	5 **20%**	5 **31%**	5 **21%**
E	6 12%	6 23%	6 24%
F	7 31%	7 0%	7 13%
G	8 0%	8 13%	8 20%
H	9 6%	9 13%	9 3%