The Breast 65 (2022) 136–144

Contents lists available at ScienceDirect

The Breast

journal homepage: www.journals.elsevier.com/the-breast

Efficacy of taxanes rechallenge in first-line treatment of early metastatic relapse of patients with HER2-negative breast cancer previously treated with a (neo)adjuvant taxanes regimen: A multicentre retrospective observational study

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ARTICLE INFO

Keywords:
Metastatic breast cancer
Rechallenge
Taxanes
Early relapse

ABSTRACT

Background: Taxanes are one of the most effective chemotherapies (CT) in breast cancer (BC), but the efficacy of taxanes rechallenge in early metastatic relapse has been poorly studied in patients previously treated by taxanes in the (neo)adjuvant setting. Our study aimed to analyse the efficacy of taxane rechallenge in case of early metastatic relapse in a multicentre retrospective observational study compared with other chemotherapies.
Methods: We analysed the French national ESME metastatic BC (MBC) database and selected HER2- MBC patients who received CT in first-line treatment for a metastatic relapse occurring 3–24 months after previous (neo) adjuvant taxanes treatment.
Results: Of 23,501 female patients with MBC in ESME, 1057 met the selection criteria. 58.4% received a taxane-based regimen (75.4% concomitant bevacizumab) and 41.6% received other CT.

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https://doi.org/10.1016/j.breast.2022.07.014
Received 8 June 2022; Received in revised form 29 July 2022; Accepted 31 July 2022
Available online 4 August 2022

In hormone-receptor positive (HR+)/HER2- MBC, multivariate analysis showed no difference in OS between taxanes without bevacizumab compared to other CT (HZR = 1.3 [0.97; 1.74], but taxanes was significantly associated with worse PFS (HZR = 1.48 [1.14; 1.93]).
In TNBC, taxanes without bevacizumab and carboplatin/gemcitabine were not superior to other CT for OS (HZR = 1.07 [0.79; 1.44] and HZR = 0.81 [0.58; 1.13], respectively), while for PFS, taxanes was inferior (HZR = 1.33 [1.06–1.67]) and carboplatin plus gemcitabine was superior to other CT (HZR = 0.63 [0.46; 0.87]).
For both subtypes, the worse outcome observed with paclitaxel was no longer observed with the addition of bevacizumab.
Conclusions: With the limitation of retrospective design, taxanes rechallenge in early metastatic relapse of BC may result in a worse PFS in TNBC and HR+/HER2- MBC, which was not observed with the addition of bevacizumab.

1. Introduction

Breast cancer (BC) is the most common cancer and the leading cause of death in women [1]. Among patients treated for early BC, 8–20% will develop distant metastases [2,3]. Taxanes, paclitaxel and docetaxel, represent one of the most effective chemotherapies (CT) used in BC, in the three major subtypes – hormone receptor-positive and HER2--negative(HR+/HER2-), triple-negative breast cancer (TNBC) and HER2-positive (HER2+) BC [4–7]. Initially, efficacy was demonstrated in metastatic BC (MBC) [8–11], with an overall response rate (ORR) ranging from 25 to 69% when taxanes were used as a first-line treatment in taxane-naive MBC [12]. Taxanes then became a major agent in early BC in both neoadjuvant and adjuvant settings [4,13]. Thus, among patients with a metastatic relapse, a large proportion of patients have already been exposed to taxanes in the (neo)adjuvant setting, but the impact of taxanes-free period duration on efficacy has been poorly reported in the literature. Two retrospective studies with small numbers of patients evaluated the tumour response of taxanes rechallenge in metastatic relapse after (neo)adjuvant CT [14,15], and reported a tumour response rate ranging from 40 to 58.5%.

Currently, in first-line management of advanced setting, patients with TNBC should receive CT, and in case of PD-L1 positivity, the recommended standard regimen is nab-paclitaxel plus atezolizumab [16], or pembrolizumab plus (nab)paclitaxel, or carboplatin-gemcitabine [17]). Patients with HR+/HER2- MBC should receive endocrine therapy plus CDK4/6 inhibitor [18–20], with first-line CT restricted to "visceral crisis" [13].

In this context, current recommendations suggest a rechallenge by taxanes in metastatic relapse, particularly if there has been a disease-free interval (DFI) of at least 1 year [13]. However, few data are available to support the use of taxanes in early relapse (≤24 months), while tumour resistance might be possible. Other CT are available in first-line [13], such as capecitabine [21], anthracyclin-based regimen [22] and navelbine [23,24], and might be used instead of taxanes in early relapse. It should be noted that bevacizumab was used as a first line treatment in combination with CT after showing an improvement in response rate and progression-free survival (PFS) [25–27]. Based on the lack of overall survival (OS) benefit and increased toxicity, the FDA revoked approval of bevacizumab for BC in November 2011. However, in Europe, the European Medicines Agency has maintained its indication. Since 2016, bevacizumab is only reimbursed in France for TNBC.

The purpose of this study was to evaluate in first line of metastatic treatment the efficacy of taxanes rechallenge in early metastatic relapse of patients with HER2- MBC who had previously received (neo)adjuvant taxanes in a large, nationwide, multi-centre real-world database of patients with MBC.

2. Materials and methods

2.1. Study design

Study design is based on the large Epidemiological Strategy and Medical Economics (ESME) MBC database, (NCT03275311), a national multicentre retrospective observational programme. It collects individual data from all consecutive patients, aged ≥18 years, who have started treatment for MBC at one of the 18 French Comprehensive Cancer Centres that are part of the UNICANCER network, between January 1, 2008 and December 31, 2017. Data are updated annually and include primary patient and tumour characteristics, outcome and treatment patterns.

This analysis was approved by an independent ethics committee (Comité De Protection Des Personnes Sud-Est II- 2015-79). No formal dedicated informed consent was required, but all patients had approved the reuse of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorised by the French data protection authority (Registration ID 1704113 and authorisation N°DE-2013.-117). Moreover, in compliance with applicable European regulations, additional authorisation was obtained on 14-Oct-2019 regarding the ESME research Data Warehouse.

2.2. Study objectives

The primary objective was to describe the impact of rechallenge with taxanes in metastatic first line with relapse between 3 and 24 months after (neo)adjuvant treatment including taxanes, using median OS and PFS as primary endpoints.

Secondary objectives were to describe the impact of rechallenge with taxanes in metastatic first line (PFS and OS) according to DFI (between 3 and 12 months, and 12 and 24 months) and according to administration of bevacizumab for both HR+/HER2-and TNBC and carboplatin plus gemcitabine for TNBC.

2.3. Study population and data collected

Demographic characteristics, tumour characteristics, treatment patterns, and outcomes were obtained from the patients' electronic medical records, in patient hospitalisation records and pharmacy records using a retrospective data collection process which is updated annually. A quality control process was carried out for all data, which were harmonised and anonymised within each centre before transmission [28]. Demographic and tumour characteristics were compiled for all female patients both in early-stage and metastatic disease.

Our population included all female patients with HER2- MBC, who received a first-line CT for metastatic relapse between 3 and 24 months after (neo)adjuvant CT including taxanes. Two groups were defined for first-line CT: "taxanes rechallenge" (including paclitaxel and docetaxel) and "other CT". For the survival analysis, in HR+/HER2- MBC we defined 3 variables: taxanes only, taxanes plus bevacizumab (with no other CT in induction) and other CT only. For TNBC, we defined 4 variables: taxanes only, taxanes plus bevacizumab, other CT only and carboplatin plus gemcitabine. To ensure a more homogeneous population, patients treated with polyCT were excluded, except for carboplatin gemcitabine in TNBC because it is a recommended treatment.

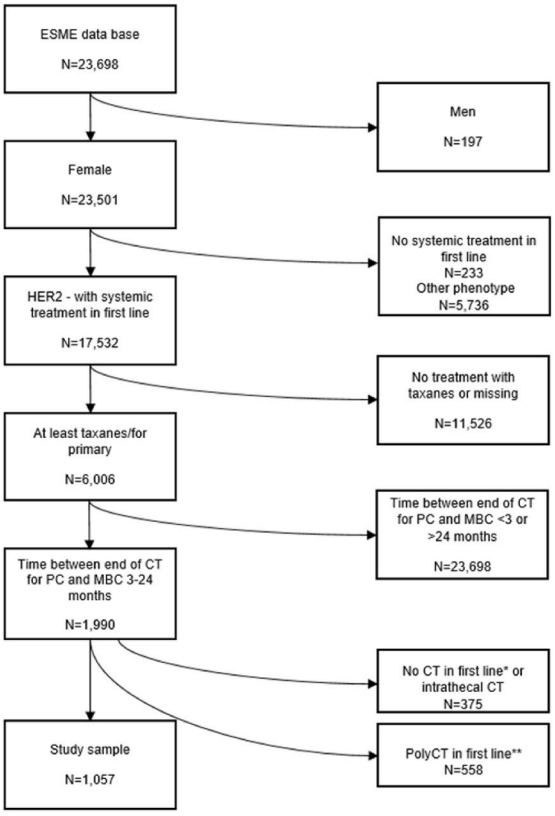


Fig. 1. Flow chart. *Including endocrine therapy and CDK4/6 inhibitors. Twenty of these patients were excluded because they received anti-HER-2 therapy. ** Including the combination of taxanes and platinum (carboplatin or cisplatin), CT other than taxanes plus bevacizumab. However, carboplatin plus gemcitabine combination was included in TNBC.

2.4. Statistical analysis

Clinicopathological characteristics and demographics were assessed using descriptive statistics. Qualitative variables were expressed as counts and percentages and compared using Pearson's Chi-squared or Fisher tests, while quantitative variables were expressed as mean and standard deviation or median and interquartile range (IQR) and compared by Student's test.

OS was defined as the time (in months) from date of MBC to the date of death for any cause. Patients alive at last contact were censored at the last news date. PFS1 was defined as the time from the start date of first-line treatment to disease progression or death from any cause.

Median follow-up (from MBC to death or last follow-up) with its 95% confidence interval (95%CI) were described according to the reverse Kaplan-Meier method [29].

Survival curves were plotted according to the Kaplan-Meier method and the difference between survival was assessed using the log-rank test. Univariate and multivariate hazard-ratios (HZR) with their 95% confidence interval were estimated using Cox proportional hazards model.

All analyses were performed separately in patients with TNBC and HR+/HER2- MBC. All analyses were carried out using R software (version 3.3.2). The significance level alpha was fixed at 5%. As these were exploratory analyses, no adjustments were made for multiple comparisons.

Table 1
Patient characteristics.

Primary tumour	Other CT		Taxanes rechallenge		
	N = 420	%	N = 637	%	
Primary tumour grade					
Grade I/II	156	37.1	244	38.4	p = 0.56
Grade III	210	50	324	50.9	
NA	54	12.9	69	10.7	
Histological type					
Ductal	365	87.1	535	84.3	p = 0.38
Lobular	28	6.7	41	6.5	
Other	26	6.1	59	8.9	
NA	1	0.1	2	0.3	
(Neo-)adjuvant CT					
Neoadjuvant	163	38.8	251	39.4	p = 0.92
Adjuvant	214	51	325	51	
NA	43	10.2	61	9.6	
CT regimen in (neo)-adjuvant treatment					
Taxanes only	32	7.6	15	2.4	p = 0.001
Anthracycline and taxanes	388	92.4	622	97.6	
Metastatic breast cancer (all patients)					
Age at MBC (years)					
<55	215	51.2	376	59	p = 0.012
≥55	205	48.8	261	41	
BC subtype (latest)					
HR+/HER2-	199	47.4	308	48.4	p = 0.76
TN	221	52.6	329	51.6	
Time to relapse (months)					
3–12	220	52.4	228	35.8	p = 0.001
12–24	200	47.6	409	64.2	
Performance status					
PS 0	77	18.3	167	26.2	p = 0.018
PS 1	99	23.6	152	23.9	
PS 2-4	57	13.6	77	12.1	
NA	187	44.5	241	37.8	
Visceral metastases					
No	156	37.1	234	30.2	p = 0.011
Yes	264	62.9	541	69.8	
Number of metastatic site					
<3	311	74	453	71.1	p = 0.3
≥3	109	26	184	28.9	

CT: chemotherapy; NA: not available; MBC: metastatic breast cancer; BC: breast cancer; HR+/HER2-: hormone receptor; HER2: human epidermal growth factor receptor 2; TN: triple-negative; PS: performance status.

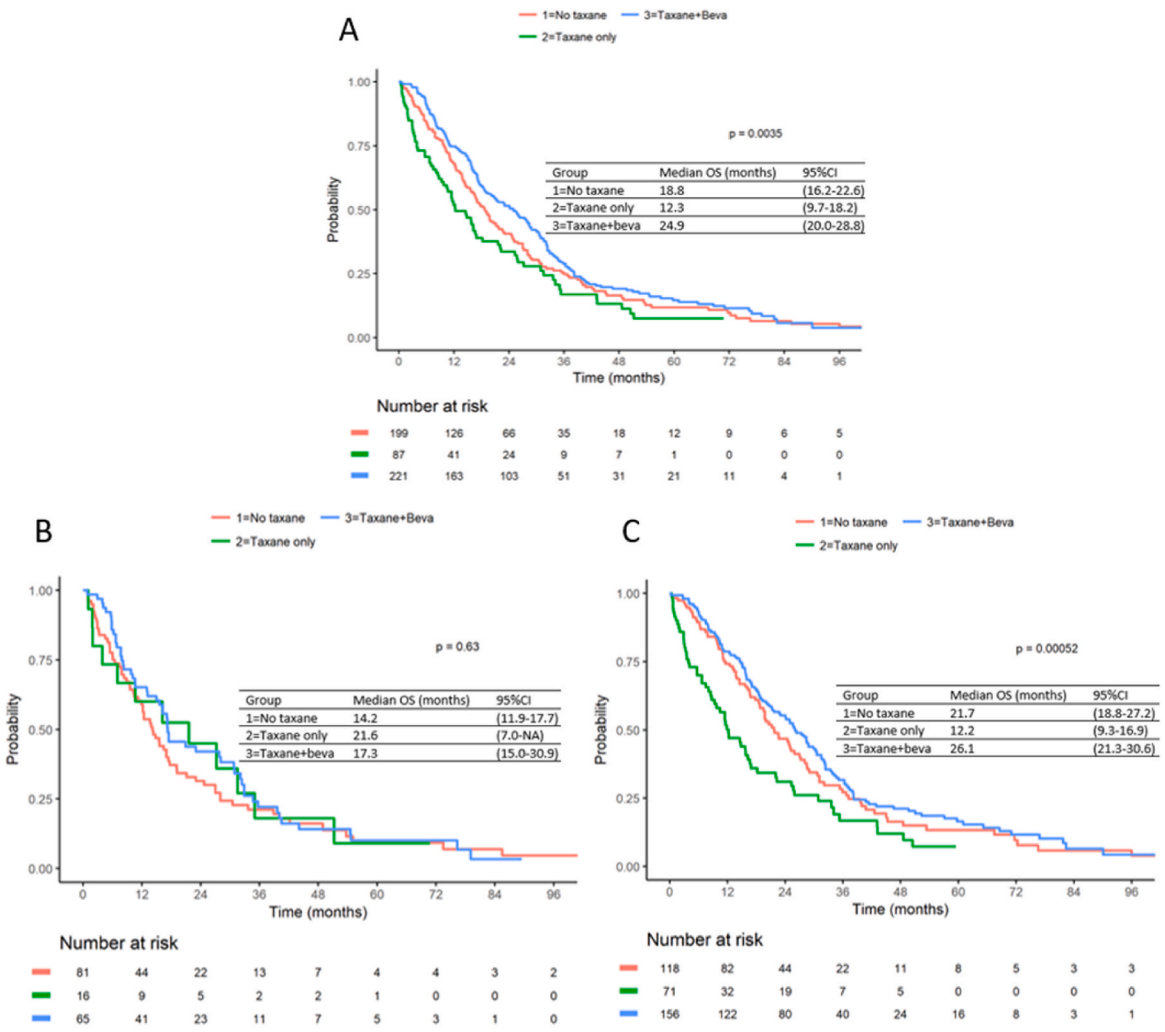
3. Results

3.1. Patient characteristics

Of 23,501 BC female patients included in the ESME database between 2008 and 2017, 17,532 had an overall HER2-status and 1990 patients had a metastatic relapse with HER2- MBC 3–24 months after last taxanes administration therapy. After excluding patients who did not receive first-line CT (including endocrine therapy and CDK4/6 inhibitors) or received a polyCT regimen (except for carboplatin gemcitabine in TNBC), 1057 patients were analysed. (Fig. 1).

The median follow-up of the patient sample was 68.1 months, 95% CI [58.6–76.1]).

Patient characteristics in the "taxanes rechallenge" or "other CT" are shown in Table 1. The major clinical difference between these 2 groups was the time between the end of (neo)adjuvant CT and the relapse (median time of 14.1 months versus 11.8 months, respectively, $p < 0.001$). In the "taxanes rechallenge" group, slightly more patients received anthracycline plus taxanes CT during the (neo)adjuvant setting (97.6% vs 92.4% $p < 0.001$), had visceral metastasis (70.3% vs 62.9%, $p = 0.011$), were under 55 years old at MBC (59% vs 51.2%, $p = 0.012$), and had a lower performance status (PS) ($p = 0.018$), while the other characteristics such as tumour grade, histology, number of metastatic sites, (neo)adjuvant administration of taxane-based CT were similar in the two groups. In the first-line MBC of the 637 patients who received



OS: overall survival; NA: not available; beva: bevacizumab; CI: confidence interval

Fig. 2. OS in patients with HR+/HER2- MBC according to CT regimen: relapse between 3 and 24 months (A), relapse between 3 and 12 months (B), relapse between 12 and 24 months (C).

taxanes, 617 (96.9%) received paclitaxel and 480 (75.4%) received concomitant bevacizumab (Table 1).

Of the patients who did not receive taxanes as first-line therapy, 60.2% received at least capecitabine, carboplatin (15.2%), gemcitabine (12.9%), intravenous 5-fluorouracil (8.6%), eribulin (6.4%), anthracycline-based CT (4.8%), vinorelbine (2.1%) and in TNBC 12.4% received a combination of carboplatin plus gemcitabine (the total is more than 100% as some patients may have changed treatment for reasons of toxicity).

3.2. Outcome of patients with HR+/HER2- MBC

In univariate analysis among patients with HR+/HER2- MBC, taxanes rechallenge without bevacizumab led to inferior OS and PFS compared to other CT (median OS: 12.3 months [9.7; 18.2] versus 18.8 months [16.2; 22.6], respectively, HZR = 1.34 [1.01; 1.79]; median PFS: 3.4 months [2.7; 4.9] versus 5.3 months [4.1; 6.3], respectively, HZR = 1.52 [1.17; 1.96]), while the addition of bevacizumab improved PFS but no OS (median PFS: 7.4 months [6.6; 8.2], HZR = 0.77 [0.63; 0.94] and median OS: 24.9 months [20.0; 28.8], HZR = 0.84 [0.68; 1.04]) (Figs. 2–3).

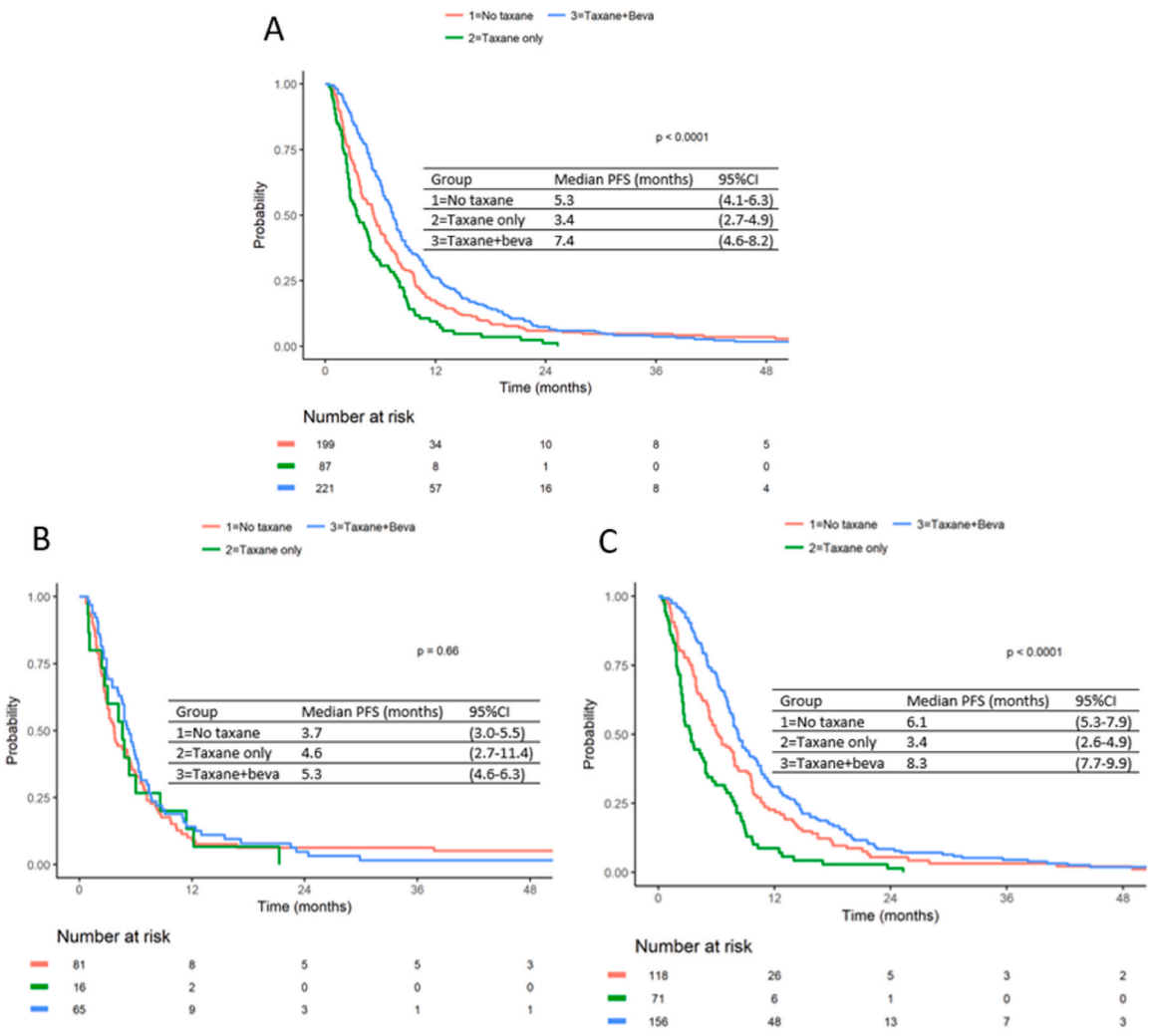
Interestingly, this deleterious effect of taxanes without bevacizumab on OS and PFS was mainly observed at 12–24 months (OS: HZR = 1.62 [1.16; 2.26] and PFS: HZR = 1.83 [1.35; 2.47]) but not at 3–12 months (OS: HZR = 0.9 [0.49; 1.67], PFS: HZR = 1.04 [0.6; 1.81]) (Fig. 2B and C, Fig. 3B and C). However, interaction test between taxanes rechallenge and time to rechallenge was not significant for both OS and PFS (p = 0.43 and p = 0.19, respectively).

In multivariate analysis for patients with HR+/HER2- MBC, no difference in OS was found between taxanes or taxanes plus bevacizumab compared to other CT (Table 2) (HZR = 1.3 [0.97; 1.74] and HZR = 0.91 [0.73; 1.14], respectively). However, taxanes without bevacizumab was significantly associated with worse PFS compared to other CT (HZR = 1.48 [1.14; 1.93]), which was no longer observed with the addition of bevacizumab (HZR = 0.82 [0.67; 1.01]) (Table 2).

3.3. Outcome of patients with TNBC

In univariate analysis, the OS of patients with TNBC was significantly improved by the addition of bevacizumab to taxanes compared to other CT (median OS: 14.6 months [12.4; 17.5] and 11.5 months [8.7; 13.5], respectively, HZR = 0.71 [0.57; 0.87]), while no difference was found between taxanes alone and carboplatin plus gemcitabine compared to other CT (HZR = 1.21 [0.9; 1.62] and HZR = 1.07 [0.77; 1.49], respectively) (Fig. 4).

PFS was also improved by the addition of bevacizumab to taxanes



PFS: progression-free survival; beva: bevacizumab; CI: confidence interval

Fig. 3. PFS in patients with HR+/HER2- MBC according to CT regimen: relapse between 3 and 24 months (A), relapse between 3 and 12 months (B), relapse between 12 and 24 months (C).

compared to other CT (5.1 months [4.6; 5.4], 2.6 months [2.3; 3.0], respectively, HZR = 0.6 [0.49; 0.73]), while taxanes without bevacizumab was significantly associated with worse PFS than other CT (HZR = 1.44 [95%CI 1.09; 1.91]), (Fig. 5). No significant difference was found between carboplatin plus gemcitabine and other CT (HZR = 0.74 [0.54; 1.02]).

By contrast to the HR+/HER2-subtype, at the 12–24 months period, the deleterious effect of taxanes without bevacizumab was only observed for PFS (HZR = 1.64 [1.09; 2.46]). No significant differences were found at the 3–12 months period, with a non-significant interaction test between taxanes rechallenge and time to rechallenge for both OS/PFS (p = 0.59 and p = 0.49, respectively) (Fig. 4B and C, Fig. 5B and C).

In multivariate analysis for patients with TNBC, taxanes alone and carboplatin plus gemcitabine were not superior to other CT for OS (HZR = 1.07 [0.79; 1.44], HZR = 0.81 [0.58; 1.13], respectively), while for PFS, taxanes alone was inferior (HZR = 1.33 [1.06–1.67]) and carboplatin plus gemcitabine was superior (HZR = 0.63 [0.46; 0.87]) (Table 2). The benefit of bevacizumab administration compared to other CT was confirmed for both OS and PFS (HZR = 0.74 [95%CI 0.6–0.92], HZR = 0.63 [95%CI 0.52–0.78], respectively).

4. Discussion

To the best of our knowledge, this is the largest retrospective study of rechallenge by taxanes in first-line metastatic CT in patients treated for HER2- MBC in early relapse after (neo)adjuvant treatment including taxanes.

In metastatic settings, taxanes rechallenge with another taxanes molecule has been reported (docetaxel/paclitaxel). In one phase II study, the efficacy of paclitaxel in docetaxel-resistant patients (n = 46), who had received mostly 2 or more CT regimens, showed a median time to progression (TTP) of 11 weeks (range 1–104 weeks) and ORR of 17.4% [30]. In a similar population, a retrospective study (n = 82 patients) found a median TTP and median OS of 3.7 months and 9.4 months with paclitaxel [31]. Toulmonde et al. evaluated the rechallenge with the same taxane (docetaxel) in metastatic setting and reported a median TTP and OS of 5.7 months and 10.2 months, respectively. They also suggested that patients should be retreated with docetaxel notably after previous response or if docetaxel was stopped for causes other than progression [32]. Thus, the impact on outcome of previous taxanes administration and free-time interval remains a relevant question. A DFI of one year is generally recommended in current guidelines for taxanes rechallenge in first-line metastatic disease, but this is not based on

Table 2
Prognostic factors of taxanes rechallenge in early relapsed patients with HER2- MBC for OS and PFS according to subtype in multivariate analysis.

Cox multivariate analysis							
Variables	N	OS			PFS		
		HZR	95%CI	*p* value	HZR	95%CI	*p* value
HR+/HER2- MBC							
Age at primary cancer(years)							
≤45	183	1		0.001			
45–60	212	1.43	[1.14; 1.79]	0.002			
>60	112	1.06	[0.80; 1.41]	0.69			
Time to relapse (months)							
3–12	162	1		0.001	1		0.001
12–24	345	0.79	[0.64; 0.98]		0.74	[0.61; 0.90]	
Number of metastatic sites							
<3	383	1		0.001	1		0.001
≥3	124	2.13	[1.68; 2.69]		1.56	[1.26; 1.94]	
Performance status							
PS 0	121	1		0.001	1		0.001
PS 1	109	1.65	[1.22; 2.24]	0.001	1.42	[1.08; 1.87]	0.01
PS 2-4	66	3.29	[2.33; 4.64]	<0.0001	1.89	[1.38; 2.58]	<0.0001
PS NA	211	1.42	[1.09; 1.85]	0.009	1.27	[1.01; 1.61]	0.04
Taxanes CT							
No taxanes	199	1		0.1	1		0.1
Only taxanes	87	1.3	[0.97; 1.74]	0.07	1.48	[1.14; 1.93]	0.004
Taxanes + Bev	221	0.91	[0.73; 1.14]	0.42	0.82	[0.67; 1.01]	0.06
TNBC							
Time to relapse (months)							
3–12	286	1		0.001	1		0.001
12–24	264	0.74	[0.61; 0.89]		0.73	[0.61; 0.87]	
Number of metastatic sites							
<3	381	1		0.001	1		0.001
≥3	169	1.97	[1.57; 2.47]		1.54	[1.26; 1.87]	
Performance status							
PS 0	123	1		0.001	1		0.001
PS 1	142	1.59	[1.22; 2.07]	0.001	1.19	[0.93; 1.53]	0.14
PS 2-4	68	2.55	[1.82; 3.58]	<0.0001	1.86	[1.35; 2.56]	<0.0001
PS NA	217	1.17	[0.92; 1.5]	0.19	1.05	[0.84; 1.32]	0.75
Taxanes CT							
No taxanes	169	1		0.001	1		0.001
Only taxanes	70	1.07	[0.83; 1.34]	0.69	1.43	[1.07; 1.90]	0.017
Taxanes + bev	259	0.74	[0.67; 0.94]	0.01	0.63	[0.52; 0.78]	<0.0001
Carboplatin + gemcitabine	52	0.81	[0.58; 1.13]	0.25	0.63	[0.46; 0.87]	0.004
Visceral metastases							
No	175	1		0.001			
Yes	375	1.31	[1.05; 1.63]				

MBC: metastatic breast cancer; HZR: hazard ratio; CI: confidence interval; OS: overall survival; PFS: progression-free survival; HR: hormone receptor; HER2: human epidermal growth factor receptor 2; PC: primary cancer; TN: triple-negative; bev: bevacizumab; PS: performance status; NA: not available.

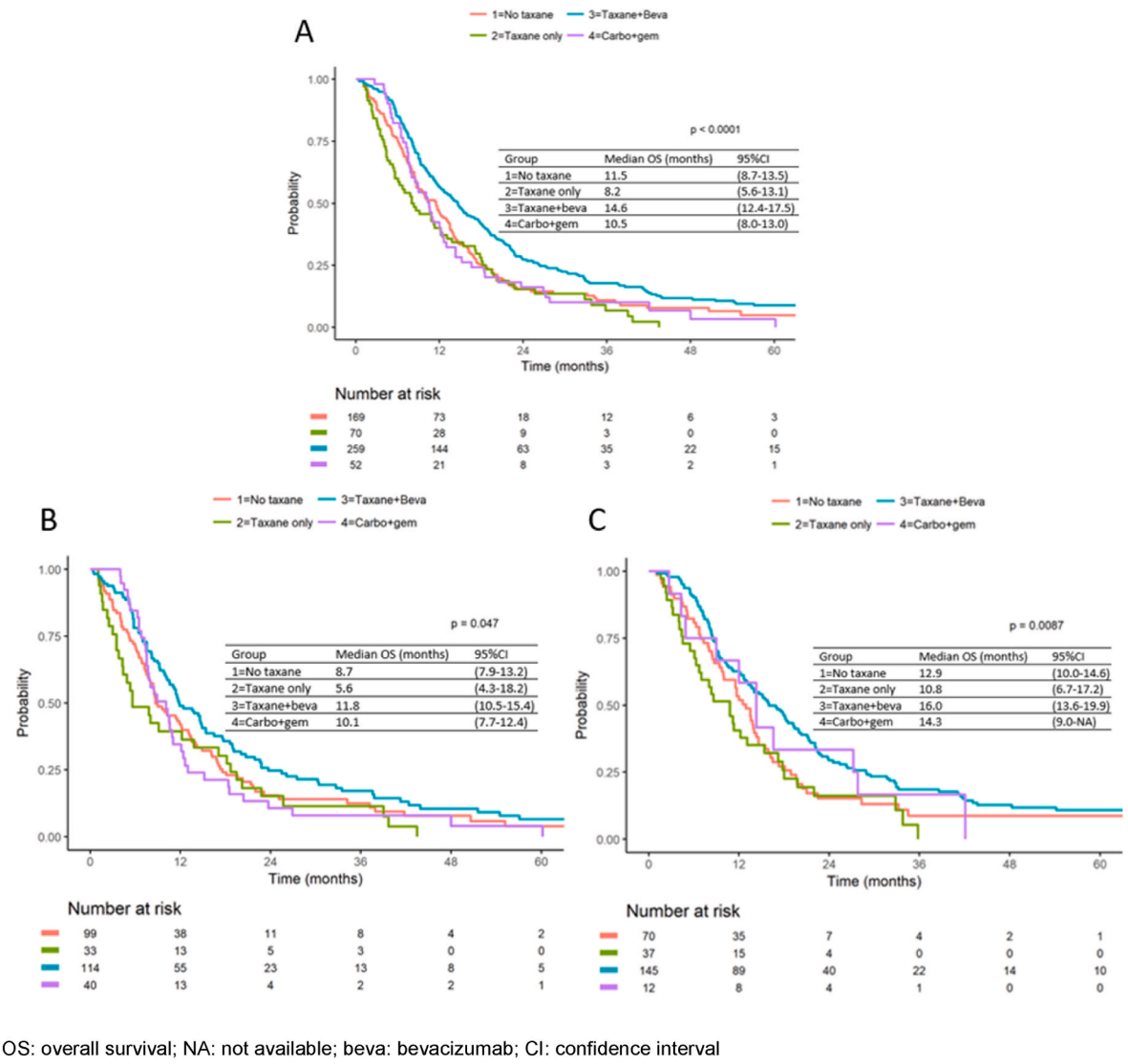
robust data. This cut-off of one year is often required in studies evaluating taxanes in the metastatic setting [13,25,33].

In this study, we found that rechallenge with taxanes without bevacizumab in patients with a short taxanes free-interval (≤24 months) was inferior to other CT in terms of PFS in both HR+/HER2-and TNBC MBC. However, the addition of bevacizumab to taxanes led to a better outcome, especially in TNBC, both in terms of PFS and OS, while the carboplatin plus gemcitabine combination improved PFS. According to the time to relapse, at 12–24 months for patients with HR+/HER2- MBC, we observed a deleterious effect of taxanes without bevacizumab on OS and PFS, while for patients with TNBC this deleterious effect was observed only for PFS. No significant differences were found at the 3–12 months' period for both patients with HR+/HER2-and TNBC MBC, with a poor prognosis observed in this setting. Few studies have focused on the question of rechallenge in case of early relapse. For example two studies, of small size, investigated taxanes rechallenge after (neo)adjuvant CT in patients with all BC subtypes [14,15]. Guo et al. found, in 74 patients, a median OS of 1.3 years and reported that a better outcome was associated with a metastasis-free interval >2 years. More recently, Kucukoztas et al. found, in 41 patients, a median PFS of 8.7 months and a median OS of 28.5 months, with no difference between taxanes rechallenge and capecitabine, but there were very few patients with early relapse in this study.

Regarding the observed benefit of bevacizumab addition, a previous study demonstrated that the addition of bevacizumab to paclitaxel [26], docetaxel [25] or other CT [27] significantly prolonged PFS compared to CT alone. These studies failed to show an improvement in OS. Note that the addition of bevacizumab was beneficial for patients with prior taxanes exposure and early relapse. Our results for TNBC are in accordance with our previous large-scale, real-world evaluation, in the ESME MBC database, of patients with HER2- MBC who received paclitaxel plus bevacizumab as first-line CT, showing a significantly better OS and PFS than those receiving paclitaxel alone [34]. We may also observe a prescription bias with taxanes±bevacizumab, that may not be fully corrected in the multivariate analysis.

Currently, CT in first line of HR+/HER2- MBC is restricted to "visceral crisis", limiting the indication of taxanes rechallenge. However, in this setting with a poor prognosis, the choice of the best CT regimen is crucial.

The choice of taxanes backbone recently appeared to be important in TNBC, as the addition of atezolizumab (antibody anti-PD-L1) to paclitaxel [35] or nab-paclitaxel [16] led to different results. Both trials

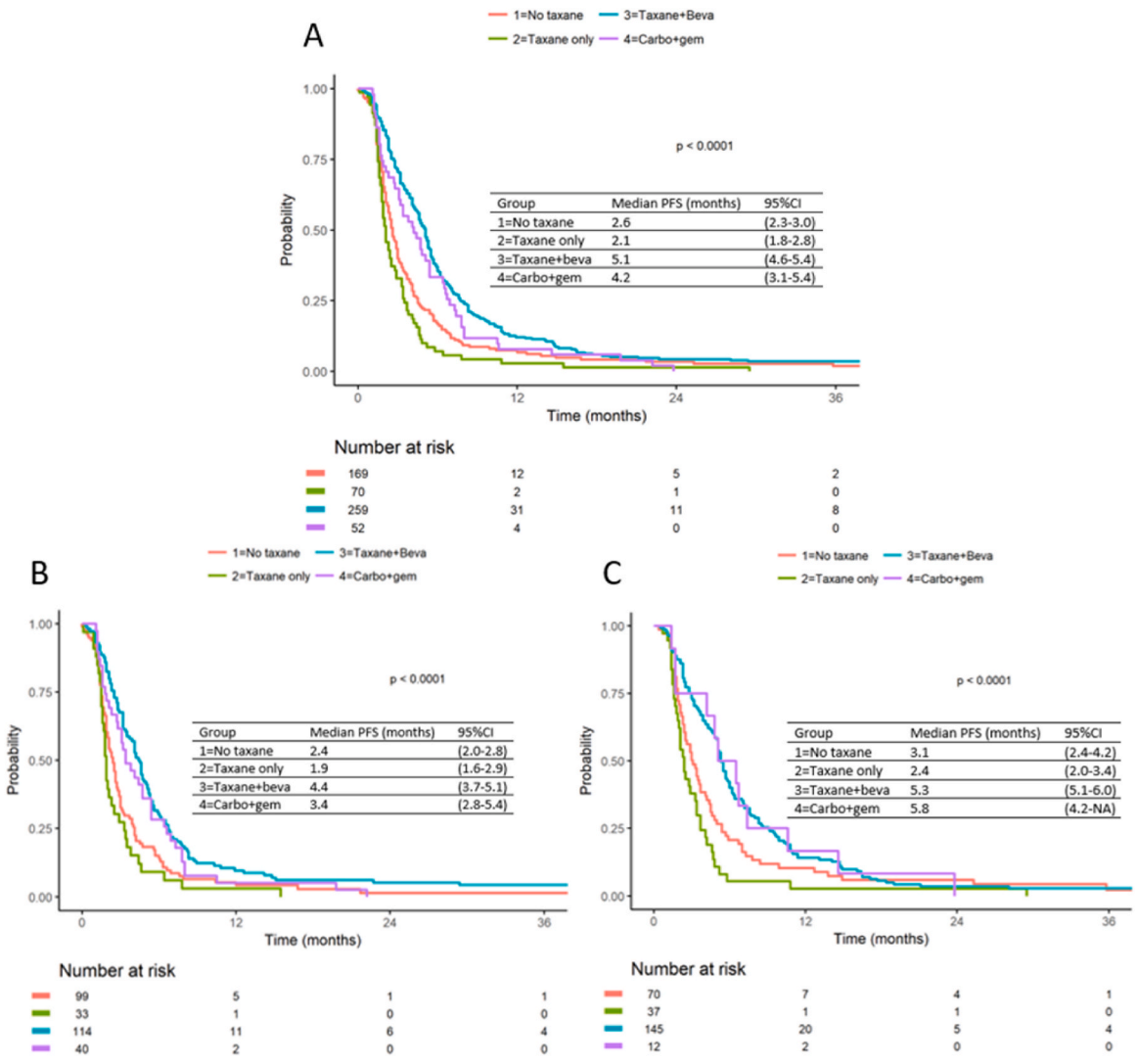


OS: overall survival; NA: not available; beva: bevacizumab; CI: confidence interval

Fig. 4. OS in patients with TNBC according to CT regimen: relapse between 3 and 24 months (A), relapse between 3 and 12 months (B), relapse between 12 and 24 months (C).

enrolled a very similar study population with respect to line of treatment, age, PS, metastatic sites, PD-L1 expression, prior CT with taxanes as well as the proportion of *de novo* MBC. Patients who received CT (including taxanes) in (neo)adjuvant setting were included only if treatment was completed ≥12 months before randomization. The difference in results is not well-explained and the possible causes are discussed elsewhere [36]. It should be noted that in the Impassion 130 study (nab-paclitaxel ± atezolizumab trial), the benefit appears to be less in patients pre-treated with taxanes than in others. Interestingly, the Keynote-355 study showed a significant improvement in PFS with pembrolizumab plus CT versus CT alone, including taxanes (paclitaxel and nab-paclitaxel) and a non-taxanes platinum-based regimen (carboplatin plus gemcitabine) [17]. The population of Keynote-355 was similar to the Impassion130 and 131 studies, except that patients with stage I–III BC were eligible only if the relapse occurred at least 6 months after the end of the last treatment in the curative setting. In the subgroup analysis, better survival was reported in patients who received paclitaxel in combination with pembrolizumab, but there were no data regarding the DFI. This raises the question of which CT backbone should be used in combination with immunotherapy depending on the (neo)adjuvant CT and the DFI. Based on the results of our study, we suggest that taxanes might not be used alone in TNBC if relapse occurs within 2 years after (neo)adjuvant CT, while carboplatin plus gemcitabine seems to improve PFS, but further studies are needed in this immunotherapy combination setting. The phase III IMpassion132 (NCT03371017) trial is ongoing, evaluating atezolizumab with first-line CT (capecitabine or gemcitabine/carboplatin) for metastatic TNBC recurring ≤12 months after (neo) adjuvant anthracycline and taxanes CT.

The main limitations of our study are inherent to its retrospective and observational design. It is not possible to retrospectively define treatment indications, and treatment choices were made by physicians, especially whether bevacizumab was prescribed or not. Patients are recruited by French Comprehensive Cancer Centres (FCCCs), which may not fully represent the general French or European population. Among patients who received taxanes, fewer patients received taxanes alone compared with the combination of taxanes plus bevacizumab (respectively 25% versus 75%), and this bias may have affected the results observed between these 2 groups. In patients with HR+/HER2-subtype, the question of taxane rechallenge in case of early relapse is currently less relevant, as most of these patients will now receive endocrine therapy plus CDK 4/6 inhibitors. Nevertheless, our results provide information for patients who will be in visceral crisis and a phase III study is ongoing (NCT04158362) to compare the efficacy of standard endocrine therapy plus abemaciclib combination versus standard CT in



PFS: progression-free survival; NA: not available; beva: bevacizumab; CI: confidence interval

Fig. 5. PFS in patients with TNBC according to CT regimen: relapse between 3 and 24 months (A), relapse between 3 and 12 months (B), relapse between 12 and 24 months (C).

patients with visceral metastases of HR+/HER2- MBC and high tumour burden.

In conclusion, in early metastatic relapse of taxanes-pre-exposed HER2- MBC, taxanes without bevacizumab may be inferior to other CT, which was not more observed with the addition of bevacizumab.

Funding

The ESME MBC database receives financial support from an industrial consortium (Roche, Pfizer, AstraZeneca, MSD, Eisai and Daiichi Sankyo). Data collection, analysis and publication were managed entirely by UNICANCER independently of the industrial consortium.

Declaration of competing interest

Marie Robert reports grants from Amgen, Merck, Novartis (travel fees) and Eisai (board member). No other potential conflicts of interest were reported.

Acknowledgements

We wish to thank the 18 French Comprehensive Cancer Centres (FCCCs) for providing the data and each ESME local coordinator for managing the project at the local level. Moreover, we would like to thank the ESME Scientific Group and Strategic Committee for their ongoing support.

18 Participating French Comprehensive Cancer Centres: I. Curie, Paris/Saint-Cloud, G. Roussy, Villejuif, I. Cancérologie de l'Ouest, Angers/Nantes, C. F. Baclesse, Caen, ICM Montpellier, C. L. Bérard, Lyon, C. G-F Leclerc, Dijon, C. H. Becquerel, Rouen; I. C. Regaud, Toulouse; C. A. Lacassagne, Nice; Institut de Cancérologie de Lorraine, Nancy; C. E. Marquis, Rennes; I. Paoli-Calmettes, Marseille; C. J. Perrin, Clermont Ferrand; I. Bergonié, Bordeaux; C. P. Strauss, Strasbourg; I. J. Godinot, Reims; C. O. Lambret, Lille.

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