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Original article

Outcome beyond third-line chemotherapy for metastatic triple-negative breast cancer in the French ESME program

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ABSTRACT

Purpose: Among metastatic breast cancer (MBC) patients, those with a triple-negative breast cancer phenotype (mTNBC) have the worst prognosis, but the benefit of chemotherapy beyond second line on outcome remains uncertain. The purpose of this study was to identify predictive factors of outcome after third- or fourth-line chemotherapy.

Methods: The ESME-MBC database is a French prospective real-life cohort with homogeneous data collection, including patients who initiated first-line treatment for MBC (2008–2016) in 18 cancer centers. After selection of mTNBC cases, we searched for independent predictive factors (Cox proportional-hazards regression models) for overall survival (OS) on third- and fourth-line chemotherapy (OS3, OS4). We built prognostic nomograms based on the main prognostic factors identified.

Results: Of the 22,266 MBC cases in the ESME cohort, 2903 were mTNBC, 1074 (37%) and 598 (20%) of which had received at least 3 or 4 lines of chemotherapy. PFS after first- and second-line chemotherapy (PFS1, PFS2) and number of metastatic sites $\geq$3 at baseline were identified by multivariate analysis as prognostic factors for both OS3 (HR = 0.76 95%CI[0.66–0.88], HR = 0.55 95%CI[0.46–0.65], HR = 1.36 95% CI[1.14–1.62], respectively), and OS4 (HR = 0.76 95%CI[0.63–0.91], HR = 0.56 95%CI[0.45–0.7], HR = 1.37 95%CI[1.07–1.74]), respectively. In addition, metastasis-free interval was identified as a prognostic factor for OS3 (p = 0.01), while PFS3 influenced OS4 (HR = 0.75 95%CI[0.57–0.98]). Nomograms predicting OS3 and OS4 achieved a C-index of 0.62 and 0.61, respectively.

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Conclusion: The duration of each previous PFS is a major prognostic factor for OS in mTNBC patients receiving third- or fourth-line chemotherapy. The clinical utility of nomograms including this information was not demonstrated.

1. Introduction

Metastatic breast cancer (MBC) is the leading cause of cancer death among women worldwide [1]. Women with a triple-negative breast cancer phenotype (mTNBC) have a very poor prognosis, with a median overall survival (OS) of 14.5 months compared to 42 months in women with hormone receptor-positive disease, as shown in the ESME (Epidemiological Strategy and Medical Economics) MBC database, a large real-life French Cohort [2].

Although combination chemotherapy increases response rate, a single-agent strategy is the standard of care in MBC, especially in later lines, to avoid impairing quality of life [3]. However, the real benefit derived from consecutive lines of treatment remains debated and has never been adequately addressed [4]. Several studies have suggested a benefit of subsequent lines, reporting an increased overall survival (OS) for patients treated beyond second- or third-line chemotherapy, but stressing the need for better patient selection to avoid unacceptable adverse effects and impaired quality of life [5,6]. Identifying factors predictive of outcome at different time points during consecutive lines of therapy may therefore help to guide the treatment strategy in daily practice, especially in the absence of robust data derived from clinical trials [5,7].

Although previous progression-free survival (PFS) and chemosensitivity are usually both recognized as prognostic factors for breast cancer management [8,9], the magnitude of their effect has been poorly studied or reported. The purpose of this study was to search for potential factors predicting OS following third- or fourth-line chemotherapy for mTNBC, based on the French national multicenter ESME cohort, designed to construct a nomogram to guide clinical practice.

2. Patients and methods

2.1. ESME database

The ESME MBC database (NCT03275311) is a unique French national cohort built from existing information systems, pharmacy records and patient electronic medical records (EMR), with homogeneous on-site data collection. The structure of the ESME MBC database has been previously reported in detail [10]. The global aim of the ESME research program is to ensure centralization of real-life data on cancer care for epidemiological research purposes. The primary objective is to describe clinical features, treatment patterns and outcomes over a period of several years. This population-based prospective cohort is designed to select all consecutive patients who initiated anticancer therapy for MBC in 1 of the 18 cancer centers participating in the ESME program. Currently available data cover the period from January 1st, 2008 to December 31st, 2016 with more than 22,463 cases. Diagnosis, treatment and follow-up data (demographics, primary tumor, metastatic disease, treatment patterns and vital status) are collected throughout the course of the disease.

2.2. Cohort selection and statistical analysis in the ESME database

Our study population included all women with mTNBC who received at least 3 lines of chemotherapy for metastatic disease. The main patient characteristics were compared with those of the cohort of patients who received less than 3 lines of chemotherapy, using Chi-square or Fisher's exact test.

The primary endpoints were OS following third-line (OS3) and fourth-line chemotherapy (OS4), defined as the time between initiation of third- or fourth-line chemotherapy, respectively, and the date of death from any cause or last news. Secondary endpoints were PFS on third-line (PFS3) and fourth-line chemotherapy (PFS4), defined as the time between initiation of third- or fourth-line chemotherapy, respectively, and the date of first new progression or death, or date of last news. OS and PFS were both estimated using the Kaplan-Meier method. Median follow-up was estimated using the reverse Kaplan-Meier method.

For each endpoint, Cox proportional hazards models were used to identify independent prognostic factors including: age at metastatic onset (<55, ≥55 years), metastatic sites at the time of MBC diagnosis (liver, bone, brain, skin, lymph node, lung), number of metastatic sites (<3, ≥3), metastasis-free survival (time between primary diagnosis and MBC, with different cutoffs, 6, 24, and 60 months), and PFS on previous lines of therapy (PFS1, PFS2 and PFS3, with a 6-month cutoff). The final selection of prognostic factors was based on both clinical relevance and statistical significance. The significance level was set at p=.15. All variables found to be statistically significant on univariate analyses were included in multivariate analyses.

We evaluated the performance of predictive models by considering discrimination and calibration. Discrimination was quantified using the c-index [11]. Calibration was quantified using an estimate of slope shrinkage (Harrell, 1999), based on 300 bootstrap samples, and evaluated by plotting calibration curves (at 3, 6 and 12 months for PFS3, 3 and 6 months for PFS4 and 6, 12 and 24 months for OS3 and OS4).

All *P* values were 2-tailed, with 5% significance levels. All statistical analyses were performed using R software, version 3.4.2 [12].

3. Results

3.1. Patient characteristics

Of the 22,463 patients included in the ESME database, 22,266 patients were women in the ESME MBC cohort and 2903 had mTNBC. Of these 2903 mTNBC patients, 1792 (61%), 1074 (37%) and 598 (20%) had received at least 2, 3 or 4 lines of chemotherapy, respectively. Median follow-up was 53.3 months (range 4.6–103) (Fig. 1 flow chart). Patient characteristics are shown in Table 1, and compared to patients who had received fewer than 3 lines, these patients had better baseline prognostic factors: more cases without visceral metastasis (41.7% versus 29.1%) or with less than 3 metastatic sites (80.9% versus 73.1%), all $p < 0.01$.

The main chemotherapy regimens administered as third- and fourth-line (>2% of patients) were capecitabine (31.7%, 25.6%),

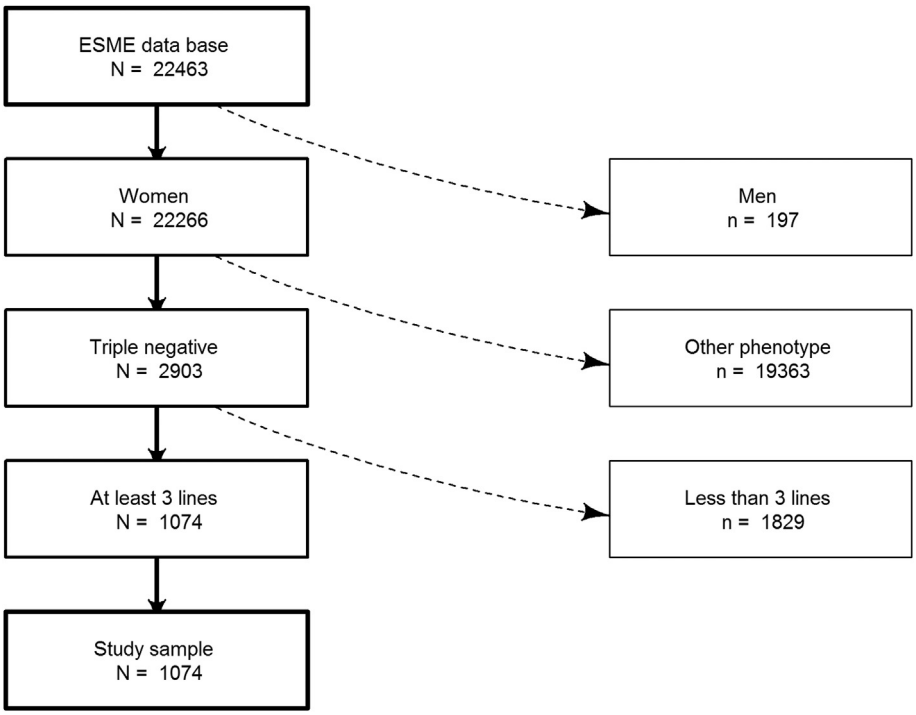

Fig. 1. Flow diagram of patients selected from the ESME database.

Table 1
Patient baseline characteristics.

Characteristics (%)	Included in the cohort (n = 1074)	Not included (n = 1829)	P-value
Age, Median (range)	50 (22–93)	54(22–93)	<0.001
Performance status (at metastatic relapse)			<0.01
0	shifted		
1	**315 (29.3)**	**308 (16.8)**	
2	239 (22.3)	356 (19.5)	
Missing data	40 (3.7)	286 (15.6)	
this row need to be removed due to shift	480 (44.7)	879 (48%)	
SBR grade			
I/II	227 (29.5) =>> above	325 (25.1)=>> above	
III	448 (58.3)=>> above	782 (60.3)=>> above	0.05
Missing data	94 (12.2)=>> above	190 (14.6)=>> above	
Metastasis-free interval			0.003
De novo or <6 months	299 (27.9)	521 (28.5)	
6–24 months	374 (34.9)	696 (38.1)	
>24–60 months	263 (24.5)	344 (18.8)	
Missing data	137 (12.8)	266 (14.6)	
Number of metastatic sites (at metastatic relapse)			
<3	shifted		<0.01
≥3	869 (80.9)=> above	1337 (73.1)=>> above	
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Visceral sites (at metastatic relapse)	**626 (58.3) =>> below**	1296 (70.9) 533 (29.1)	<0.01
Yes	**448 (41.7) =>> below**		
No			
Prior (neo)adjuvant chemotherapy			
Yes	722 (93.3)	1133 (86.8)	<0.01
No	52 (6.7)	173 (13.2)	

SBR: Scarff-Bloom-Richardson.

carboplatin or cisplatin (17.9%, 15.8%), vinorelbine (15.4%, 16.1%), eribulin (5.7%, 18.5%), gemcitabine (15.8%, 15%), anthracycline-based chemotherapy (12.6%, 16%), paclitaxel (13.8%, 8.9%) or docetaxel (2.6%, 3.4%), and oral etoposide (3.4%, 5.9%). Some patients may have received different chemotherapy agents as part of the same line, as the adverse effects observed with a first drug may require switching to another drug.

3.2. OS and PFS of mTNBC patients on third- or fourth-line chemotherapy according to previous PFS

Median PFS3, PFS4, OS3 and OS4 were 2.3 months (95%CI [2.3–2.5]), 2.1 months (95%CI [1.9–2.3]), 6.6 months (95%CI [6.3–7.2]) and 5.9 months (95%CI [5.2–6.4]), respectively (Fig. 2). When starting third-line therapy, 59.1% of patients had PFS1 < 6

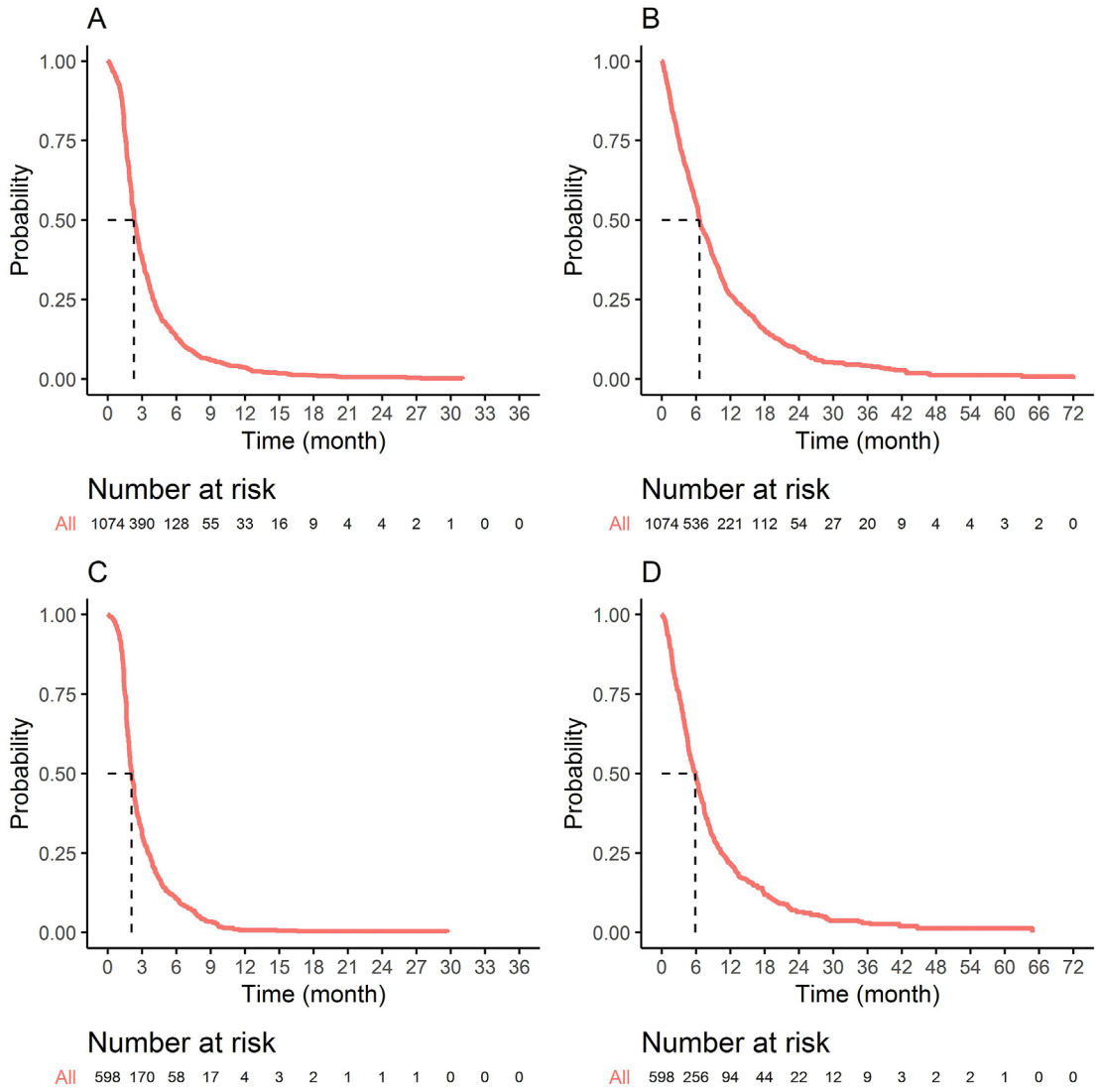


Fig. 2. Progression-free survival (PFS) and overall survival (OS) for patients receiving third-line (PFS3/OS3) and fourth-line (PFS4/OS4) chemotherapy for mTNBC. PFS3 (A), OS3 (B), PFS4 (C), OS4 (D).

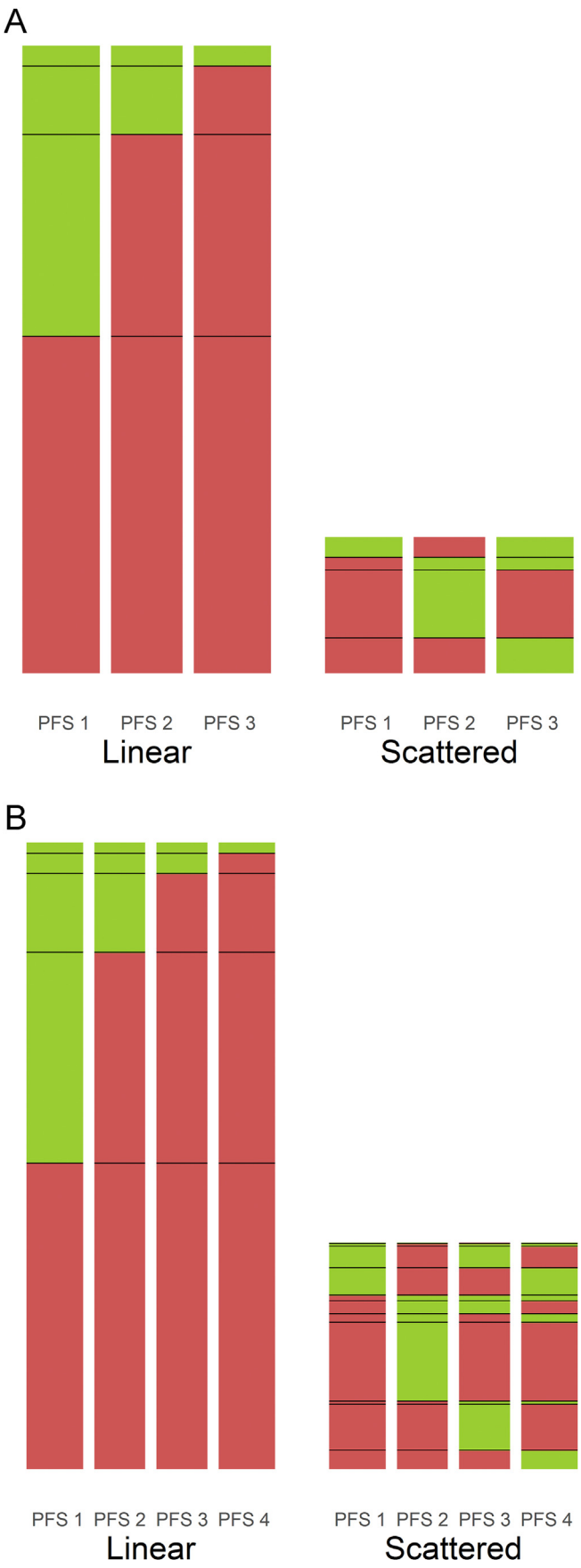
months and 77.7% had PFS2 < 6 months. As shown in Fig. 3, most patients had a linear evolution of PFS during treatment, defined as the absence of further benefit following a PFS less than 6 months, which was observed in 82% and 74% of women on third- and fourth-line. therapy, respectively. Patient characteristics and chemotherapy regimens were not different between the subgroups with linear or non-linear PFS (not shown), except for the number of metastatic sites (less than 3 in 79.3% of patients with linear PFS versus 88.5% with non-linear PFS, p = 0.003). Patients who had received 4 or more lines of chemotherapy had a longer overall survival from metastatic relapse than patients who had received 3 or more lines (26.1 months 95%CI [24.6–27.5] versus 21.2 months 95%CI [20.1–22.3] (no p-value due to the overlap between these two cohorts).

Median PFS3, PFS4, OS3 and OS4 according to previous duration of PFS are shown in Table 2 and in Fig. 4. The worst prognosis (OS3 and OS4) was observed in patients with all previous PFS <6 months versus those with all previous PFS ≥ 6 months: 5.2 months (95%CI [4.7–5.9]) and 4.5 months (95%CI [3.9–5.4]) versus 11.9 months 95%CI [9.9–15.2] (HR = 0.43 95%CI [0.34–0.54]) and 10.7 months [8.5-non-evaluable] (HR = 0.25 95%CI [0.14–0.45]). When starting third-line chemotherapy, PFS2 was a better predictor for OS3 than PFS1 (HR = 0.55 [0.46–0.65] vs HR = 0.76 [0.66–0.88]) (Table 3). When starting fourth-line chemotherapy, PFS2 and PFS3 exceeding 6 months was rare (6% of patients), not related to PFS1, and associated with a high median OS4 (16.7 months [9.8–28.7] (HR = 0.27 95%CI [0.18–0.42]).

3.3. Predictive factors for PFS3, OS3, PFS4 and OS4 on multivariate analysis

Significant predictive factors for PFS3, OS3, PFS4 and OS4 on multivariate analysis are shown in Table 3.

PFS1 and PFS2 exceeding 6 months and fewer than 3 metastatic sites at baseline were identified as prognostic factors by multivariate analysis for both OS3 (HR 0.76 95%CI [0.66–0.88], HR 0.55 95% CI [0.46–0.65], HR 0.74 95%CI [0.62–0.88]) and OS4 (HR 0.76 95%CI [0.63–0.91], HR 0.56 95%CI [0.45–0.7], HR 0.73 95%CI [0.57–0.93]). In addition, metastasis-free interval and PFS3 were identified on multivariate analysis as independent factors for OS3 (p = 0.01) and



OS4 (HR 0.75 95%CI [0.57–0.98], p = 0.03), respectively (Table 3).

Nomograms predictive of OS3 and OS4 were construction on the basis of the results of multivariate analysis, including PFS1, PFS2 and number of metastatic sites at baseline. Age, liver metastasis at baseline and metastasis-free interval were added to the OS3 nomogram, while PFS3 was added to the OS4 nomogram. Nomograms predictive of OS3 and OS4 achieved a C-index of 0.62 and 0.61, respectively (and corrected shrinkage slopes of 0.92, 0.95, 0.93 and 0.91, respectively).

4. Discussion

Based on the large ESME program (>20,000 MBC cases), we searched for prognostic factors that could guide treatment decision-making for subsequent lines of treatment of MBC, as very few data are available in this setting, with the exception of eribulin or sacituzumab-govitecan that have been shown to improve OS beyond second-line chemotherapy [4,13,14].

To our knowledge, this is the largest study ever conducted with this aim in mTNBC, showing that the duration of previous PFS is an important prognostic factor, especially beyond second-line therapy.

As shown in other reports [15,16], patients with mTNBC in our series had a poor prognosis, as only 37% and 20% received third- and fourth-line treatment, respectively. Of note, Dufresne et al. showed that a significant subgroup could derive clinical benefit from later lines: disease control >6 months in 50.5%, 40%, 36%, and 23.5% of patients receiving second-, third-, fourth-, and fifth-line therapy, respectively [15]. This potential benefit from late lines is also suggested by other small, retrospective series [5,6,16]. Not surprisingly, patients had a longer survival from metastatic relapse when they had received at least four rather than three lines of chemotherapy.

Interestingly, Dufresne et al. also showed that the only factor that influenced the duration of disease control was the duration of disease control observed in the previous line, for each line of treatment [15]. In another retrospective study of 980 MBC patients (any phenotype), time to treatment failure on previous treatment was the only prognostic factor identified by multivariate analysis to be predictive of the benefit of subsequent lines of treatment, compared to other factors such as hormone receptor status, liver metastasis, or adjuvant chemotherapy [16]. Similarly, Bonotto et al. showed that PFS less than 6 months with first-line therapy was predictive of limited benefit of subsequent lines [9]. In our series, we chose the same 6-month cutoff for PFS, corresponding to a widely accepted and relevant value for clinical benefit in the metastatic setting. Of note, the impact of the duration of PFS on previous treatments on OS when initiating third-line therapy has also been reported in other studies, suggesting that this information may be clinically relevant [17–19]. However, these studies did not focus on mTNBC, and were underpowered to adequately address the question of the clinical benefit beyond second-line chemotherapy.

In this study, we show that each previous duration of PFS had an impact on the OS associated with subsequent lines, with variations of magnitude according to treatment line, PFS2 was more strongly predictive of outcome than PFS1 for third-line therapy, while PFS2 and PFS3 with a 6-month cutoff had an impact on outcome irrespective of PFS1 for fourth-line therapy. While PFS1 has been previously shown to be associated with OS [8], our series shows, for the first time, that PFS on subsequent lines of treatment has a greater

Fig. 3. Duration of PFS on third-line (A) or fourth-line (B) chemotherapy, red: PFS < 6 months and green: PFS > 6 months. The height of each column is proportional to the number of patients of each profile.

Table 2
OS and PFS according to previous PFS (<6 or ≥ 6 months) NR: not reached.

Previous PFS 1/2 (months)	N = 1074	PFS3 Months [95%CI]	HR [95%CI]	p	OS3 months [95%CI]	HR [95%CI]	p
<6/<6	524 (48.8)	2.1 [1.9–2.2]	1	<0.001	5.2 [4.7–5.9]	1	<0.001
≥6/<6	312 (29.1)	2.4 [2.2–2.6]	0.86 [0.75–1]		7.3 [6.4–8.7]	0.71 [0.58–0.87]	
<6/≥6	112 (10.4)	2.7 [2.3–3.5]	0.69 [0.56–0.85]		11.3 [8.1–13.4]	0.44 [0.32–0.59]	
≥6/≥ 6	126 (11.7)	3.5 [3.2–4.1]	0.52 [0.42–0.64]		11.9 [9.9–15.2]	0.41 [0.31–0.56]	
X/≥6	**238 (22.2)**	**3.2 [2.8–3.7]**	**0.59 [0.5–0.69]**		**11.3 [10.3–13.2]**	**0.45 [0.38–0.54]**	
Previous PFS1/2/3 (months)	**N= 598**	**PFS4 months [95%CI]**	**HR [95%CI]**		**OS4 months [95%CI]**	**HR [95%CI]**	**p**
<6/<6/<6	228 (38.1)	1.8 [1.6–1.9]	1	<0.001	4.5 [3.9–5.4]	1	<0.001
<6/<6/≥6	35 (5.9)	2.1 [1.8–2.8]	0.83 [0.57–1.2]		7.0 [4.1–10.9]	0.7 [0.47–1.04]	
≥6/<6/≥6	17 (2.8)	3.0 [1.6-NR]	0.54 [0.31–0.94]		6.9 [4.3-NR]	0.7 [0.4–1.22]	
≥6/<6/<6	166 (27.8)	2.3 [1.9–2.7]	0.66 [0.54–0.81]		5.6 [4.7–6.7]	0.65 [0.52–0.8]	
≥6/≥6/<6	56 (9.4)	2.1 [1.8–2.4]	0.87 [0.64–1.18]		7.8 [4.9–11.1]	0.54 [0.38–0.75]	
<6/≥6/<6	60 (10)	2.4 [1.9–3.0]	0.65 [0.49–0.88]		8.1 [6.7–12.7]	0.45 [0.33–0.63]	
<6/≥6/≥6	13 (2.2)	4.2 [2.3-NR]	0.32 [0.17–0.59]		16.7 [5.9-NR]	0.3 [0.16–0.57]	
≥6/≥6/≥6	23 (3.8)	4.8 [3.4–8.0]	0.33 [0.21–0.51]		10.7 [8.5-NR]	0.25 [0.14–0.45]	
At least one PFS ≥ 6	**334 (55.9)**	**2.3 [2.1–2.4]**	**0.7 [0.58–0.83]**	<0.001	**6.5 [5.5–7.4]**	**0.59 [0.49–0.72]**	<0.001
X/≥6/≥6	**36 (6)**	**4.8 [3.4–7.8]**	**0.33 [0.23–0.48]**		**16.7 [9.8–28.7]**	**0.27 [0.18–0.42]**	

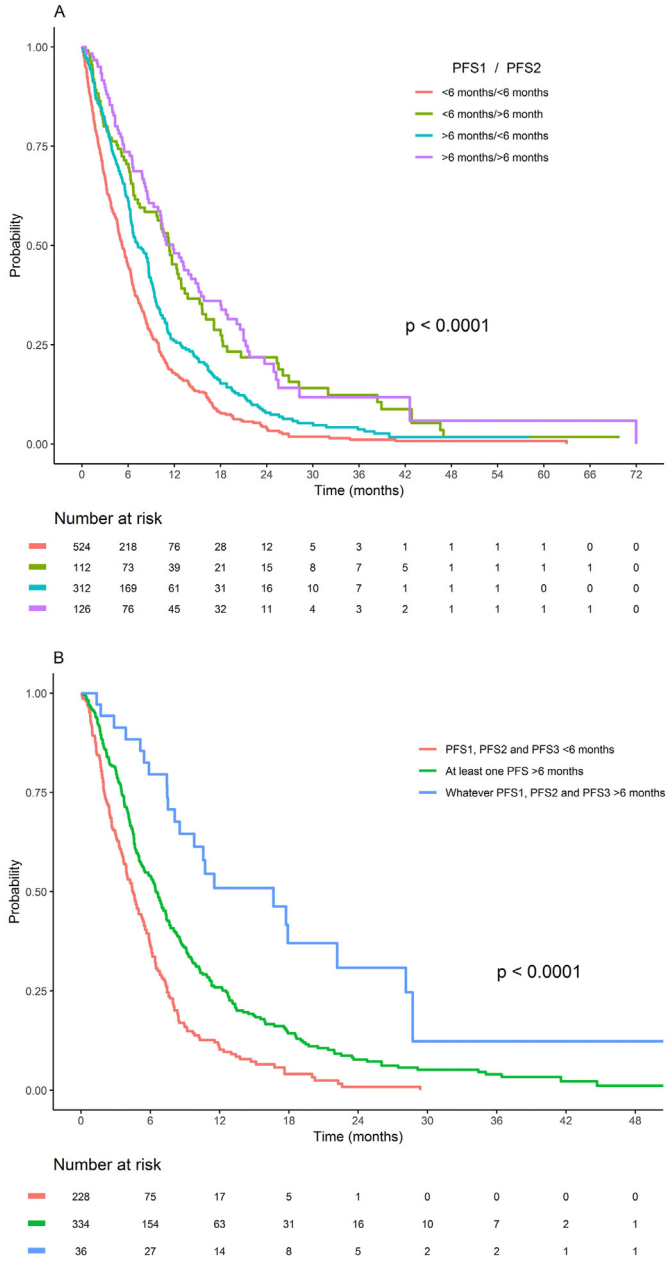


Fig. 4. OS according to previous PFS duration (< 6 or ≥ 6 months). OS3 (A). OS4 (B).

impact. We suggest that the duration of PFS on the immediately preceding line of treatment should be included as an important prognostic factor in clinical studies on treatments beyond first line, and as a tool for treatment decision-making in clinical practice.

However, before such information can be implemented in routine clinical practice, algorithms or nomograms need to be developed and validated to select appropriate candidates for subsequent lines of chemotherapy. Unfortunately, the nomograms developed to predict OS with third- or fourth-line chemotherapy did not achieve sufficient clinical utility (i.e. C-index<0.65). Therefore, although these factors provide important prognostic information, they are not sufficiently reliable to guide treatment decisions.

This study has several limitations. First, some prognostic factors were not available or were underreported in this large cohort, such as LDH or performance status [20–22], Second, some other factors were only available at baseline, but not at each subsequent line of chemotherapy, such as the presence of liver metastasis or the number of metastatic sites. Finally, the high frequency (about 18% in third line and 26% in fourth line) of a non-linear course of PFS at each line (expected: declining PFS over time) may have limited the treatment decision-making process at the individual level. The prognostic factors observed in this study will have to be re-evaluated with the arrival of new therapies that improve the prognosis of metastatic TNBC, such as immune checkpoint inhibitors [23,24] and sacituzumab-govitecan [14].

The ongoing prospective study (METAL3 METAstatic Line 3 NCT01574170) is a multicenter trial designed to prospectively construct a prognostic score, including selected clinicopathological factors, circulating tumor cells and baseline quality of life, in order to identify MBC patients who are candidates for third-line chemotherapy [22]. A prospective trial randomizing chemotherapy versus best supportive care at third- or fourth-line chemotherapy in MBC patients could possibly address the issue of the survival benefit provided by subsequent lines of chemotherapy.

5. Conclusion

PFS on each previous line of treatment is a major prognostic factor in mTNBC to guide the decision to administer third- or fourth-line chemotherapy. It can help to classify patients into different risk categories, but further work is needed to build clinically relevant nomograms.

Table 3
Predictive factors for PFS3 and OS3 at third-line chemotherapy and predictive factors for PFS4 and OS4 at fourth-line chemotherapy on multivariate analysis with $p < 0.1$

Third-line chemotherapy					
Factors		PFS3		OS3	
	N = 1074 (%)	HR [95%CI]	P value	HR [95%CI]	P value
PFS1 (months)					
<6	635 (59.1)	1	0.03	1	<0.001
≥6	439 (40.9)	0.86 [0.76–0.98]		0.76 [0.66–0.88]	
PFS2 (months)					
<6	835 (77.7)	1	<0.001	1	<0.001
≥6	239 (22.3)	0.67 [0.58–0.79]		0.55 [0.46–0.65]	
Liver metastasis					
No	831 (77.4)	1	0.01	1	0.07
Yes	243 (22.6)	1.24 [1.06–1.44]		1.16 [0.99–1.37]	
Age at MBC					
<55 yrs	568 (52.9)	1	0.09	1	0.2
≥55 yrs	506 (47.1)	0.9 [0.79–1.02]		0.92 [0.8–1.05]	
Baseline number of metastatic sites					
<3	868 (80.8)	1	0.08	1	<0.001
≥3	206 (19.2)	1.16 [0.98–1.37]		1.36 [1.14–1.62]	
Metastasis-free interval (months)					
≤6	299 (27.8)	1	0.07	1 0.98 [0.82–1.16]	0.01
>6-≤24	374 (34.8)	1.04 [0.88–1.22]			
>24-≤60	263 (24.5)	0.92 [0.77–1.09]		0.79 [0.66–0.95]	
>60	138 (12.8)	0.8 [0.65–0.99]		0.73 [0.58–0.92]	
Fourth-line chemotherapy					
Factors		PFS4		OS4	
	N = 598	HR [95%CI]	P value	HR [95%CI]	P value
PFS1 (months)					
<6	336 (56.2)	1	0	1	<0.001
≥6	262 (43.8)	0.77 [0.65–0.91]		0.76 [0.63–0.91]	
PFS2 (months)					
<6	446 (74.6)	1	0.02	1	<0.001
≥6	152 (25.4)	0.79 [0.65–0.97]		0.56 [0.45–0.7]	
PFS3 (months)					
<6	510 (85.3)	1	0	1	0.03
≥6	88 (14.7)	0.68 [0.53–0.87]		0.75 [0.57–0.98]	
Baseline number of metastatic sites					
<3	497 (83.1)	1	0.01	1	0.01
≥3	101 (16.9)	1.32 [1.06–1.64]		1.37 [1.07–1.74]	

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Ethical approval

The present analysis was approved by an independent ethics committee (Comité de Protection des Personnes Sud-Est II-2015–79). No specific informed consent was required, but all patients had approved the re-use of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorized by the French data protection authority (Authorization No. 1704113).

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Contribution

Luc Cabel and Florence Lerebours: study concept and design, data analysis, manuscript preparation.

Matthieu Carton

Statistical analysis.

All authors except Luc Cabel, Matthieu Carton and Matthieu Robain: data acquisition.

All authors: manuscript review and editing.

Declaration of competing interest

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