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Original Research

Assessment of the efficacy of successive endocrine therapies in hormone receptor–positive and HER2-negative metastatic breast cancer: a real-life multicentre national study

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Exceptional response

Abstract ***Background:*** For luminal metastatic breast cancer (MBC), endocrine therapy (ET) is the recommended initial treatment before chemotherapy. Our objective was to evaluate the efficacy of multiple ET lines in a real-life study.
Methods: The Breast Cancer Epidemiological Strategy and Medical Economics (ESME) project analysed data from all patients with systemic treatment for MBC initiated between 2008 and 2014 in one of the 18 French Comprehensive Cancer Centres. The primary end-point was the successive progression-free survival (PFS) evaluation.
Results: The ESME research programme included 9921 patients with hormone receptor −positive (HR+)/human epidermal growth factor receptor 2 (HER2) negative (HER2-) MBC. Before any chemotherapy, 4195 (43.4%), 1252 (29.8%) and 279 (6.6%) patients received one, two or three ET ± targeted therapy, respectively. The median PFS for first-, second- and third-line ET ± targeted therapy was 11.5 (95% confidence interval [CI], 10.8−12.1), 5.8 (95% CI, 5.3−6.1) and 5.5 (95% CI, 4.6−6.3) months, respectively. In a multivariate analysis, time from diagnosis to metastatic recurrence ($P < 0.0001$), presence of symptoms at metastatic relapse ($P = 0.01$), number of metastatic sites ($P = 0.0003$) and their localisation ($P < 0.0001$) were prognostic factors for PFS1. Duration of previous PFS was the only prognostic factor for subsequent PFS (10% threshold). Ten percent of the patients showed long-term response to ET, with a total treatment duration before chemotherapy ≥43.6 months.
Conclusions: Median PFS in our HR+/HER2- real-life cohort is similar to median first-line PFS reported in clinical trials, regardless of ET used as second- and third-line treatment. Despite the international consensus on early initiation of ET, the latter is not prescribed in most of the cases. Patients with a low tumour burden may achieve prolonged response on ET.

1. Introduction

About 70% of breast cancers are hormone receptor positive (HR+) and HER2 negative (HER2-). International guidelines recommend initial endocrine therapy (ET) as the treatment of choice for HR+/HER2- metastatic breast cancer (MBC) unless there is a 'visceral crisis' or concern or proof of endocrine resistance [1,2]. The Epidemiological Strategy and Medical Economics (ESME) research programme is an academic initiative launched in 2014 by the French network of cancer centres UNICANCER. The ESME programme provides access to exhaustive, high-quality and centralised real-life data on different solid tumours including MBC. This database gathers more than 16000 MBC cases with complete characteristics from pathology to the outcome from 18 academic cancer centres managing together more than one-third of all breast cancer cases nationwide (NCT03275311). A previous analysis conducted on the ESME database, based on a propensity score, showed similar overall survival (OS) for patients with HR+/HER2- MBC, whether treatment began with ET or chemotherapy, subsequently favouring ET, a lighter and less toxic therapy [3]. Sequential ET regimens are recommended until endocrine resistance development, before switching to chemotherapy in the absence of life-threatening visceral disease [1]. Recently, the ET landscape has been expanded with the advent of mammalian target of rapamycin inhibitors such as everolimus and cyclin-dependent kinase (CDK) 4/6 inhibitors. However, unlike aromatase inhibitors (AIs) or tamoxifen [4–6] that showed similar efficacy and a favourable safety profile compared with chemotherapy in a systematic review [7,8], no OS advantage was shown in the pivotal phase III clinical trial assessing the combination of everolimus and AIs compared with AIs [8]. CDK4/6 inhibitors are a new promising class of drugs. OS data are not yet available for CDK4/6 inhibitors and ET combination in first-line therapy [9–11], and physicians should be aware of the specific toxicity profile of each drug. Moreover, palbociclib combined with fulvestrant in endocrine-resistant patients failed to show a significant gain in OS in the intent-to-treat population (hazard ratio [HR] for death, 0.81; 95% confidence interval [CI], 0.64−1.03; $P = 0.09$) [12]. Finally, some patients do present long response to ET alone as shown in the FALCON trial, with 30−40% and 20% of the patients still receiving fulvestrant alone at 2 years and 3 years, respectively [13].

Systemic treatments for metastatic disease are not curative. The use of minimally toxic drugs such as ET is therefore preferred in this setting without jeopardising the efficacy. Real-world data in oncology provides the opportunity to assess the activity of specific products outside the framework of clinical trials. The objective of this study was to evaluate the efficacy of multiple ET lines in a real-life study through the ESME programme, according to clinical and biological characteristics and the type of ET.

2. Patients and methods

2.1. Overall study design

We conducted a non-interventional, retrospective study to describe the outcome of patients with MBC selected in the ESME MBC database. This database collects individual data from all patients, male or female, aged ≥18 years, having started an anticancer treatment for MBC in 1 of the 18 cancer centres participating in the ESME research programme, from January 2008 to December 2014. The ESME MBC database was built from existing information systems, treatment databases and patients' electronic medical records, with homogenous on-site collected information and high-level quality control [14].

Following a data management plan, all centralised data were controlled and homogenised before importation into the final database. On-site quality control of the patient selection process and data collection (key parameters) were performed randomly. Data collection and project management processes were internally audited.

The ESME research programme centralised all existing data using retrospective data collection. The present 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 use of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorised by the French data protection authority (authorisation no. 1704113, NCT03275311) and managed by R&D UNICANCER in accordance with the current best practice guidelines [15,16].

2.2. Study population

Our population included all patients with HR+/HER2- MBC confirmed on primary tumour or, if unavailable, on metastasis. Data on adjuvant ET should be specified.

2.3. Evaluation criteria

The primary end-point was progression-free survival (PFS) on successive ET lines for patients treated with ET ± targeted therapy. The secondary end-point was to explore prognostic factors for longer sequential ET lines that are prognostic factors for PFS1, PFS2 and PFS3 and for a subsequent line of ET.

Ten percent of the patients who were treated with an ET, whatever the line, for the longest time were defined as exceptional ET responders (National Cancer Institute's definition). We evaluated the predictive factors for being an exceptional ET responder.

2.4. Statistical analysis

Descriptive statistics were used to summarise patients' initial characteristics at diagnosis of metastatic disease. Comparisons between groups were performed using a chi-square or Fisher's exact test for categorical data and t-test or non-parametric Wilcoxon test for continuous data; a p value < 0.05 was considered statistically significant.

OS was defined as the time between the diagnosis of metastatic disease and the date of death (from any cause) or censored to the date of latest news. PFS1 was defined as the time from the starting date of first-line treatment until the first disease progression or death or the date of latest news. PFS2 was defined as the time from the second strategy implemented within the 12 months following the first progression until the second disease progression or death or the date of latest news. PFS3 was defined as the time from the strategy implemented within the 12 months following the second progression until the third disease progression or death or the date of latest news. Both OS and PFS were estimated using the Kaplan–Meier method. The reverse Kaplan–Meier method was used to estimate the median follow-up durations.

The Cox proportional hazards model was used to investigate prespecified factors for PFS1, PFS2 and PFS3. The prespecified factors were as follows: age at metastatic diagnosis (≤45, >45 years), time between diagnosis and metastatic disease (≤2 years, >2 years, MBC at diagnosis), presence of symptoms at diagnosis (yes, no), number of metastatic sites (≤3, >3), localisation of metastatic sites (bone-only, no visceral [skin and lymph node], brain, visceral excluding brain), length of PFS1 (≤12 months, >12 months; only for PFS2 prognosis factors) and length of PFS1+PFS2 (≤18 months, >18 months; when studying PFS3 prognosis factors). Variables judged as sufficiently informative (less than 10% missing value in univariate analyses) and significant at a 10% level were included in a backward selection procedure to keep factors significant at a 5% level in the final multivariate model. HRs are presented with 95% CI.

A subgroup analysis of predictive factors of a subsequent line of ET was performed by selecting patients under ET in the first line who began a second ET line. The prespecified factors were age at the end of the first line (≤45, >45), time between diagnosis and metastatic disease (≤2 years, >2 years, MBC at diagnosis), number and localisation of metastatic sites at the end of the first line (≤3, >3) and duration of PFS1 (cut-off, 6 months).

Logistic regression was performed to search for predictive factors of exceptional ET responders. The prespecified factors were the same as those used in the Cox proportional hazards model for PFS1.

For these two logistic analyses, variables judged as sufficiently informative (less than 10% missing value in

univariate analyses) and significant at a 10% level were included in a backward selection procedure to keep factors significant at a 5% level in the final multivariate model. Odds ratios (ORs) are presented with 95% CI.

SAS version 9.4 was used for all statistical analyses.

3. Results

3.1. Patient characteristics and follow-up

The ESME programme enrolled a total of 16702 patients including 9921 patients with HR+/HER2- MBC, 9677 of whom were receiving at least one line of therapy for MBC (Fig. 1). The median follow-up was 48.6 (range, 0–104.5) months. The patients' characteristics are shown in Table 1.

3.2. First-line ET

As first-line therapy, 4195 (43.4%) patients received ET ± targeted therapy, and 5482 (56.6%) patients received chemotherapy ± ET ± targeted therapy. Among the patients who received first-line ET, 134 (3.2%) received a targeted therapy in combination. Non-steroidal AIs were the most frequent ET prescribed in first-line treatment, prescribed in at least 63.8% of cases. Tamoxifen alone or tamoxifen as associated treatment was prescribed to 18.7% of the patients (n = 784). Everolimus was the most frequently associated targeted therapy in first-line treatment (n = 83/134, 61.9%) (Table 2). The median PFS for the first-line ET was 11.5 months (95% CI, 10.8–12.1) (Fig. 2). The PFS rate at 1 year was 48.7% (95% CI, 47.1–50.2). The univariate Cox regression analysis identified the following factors

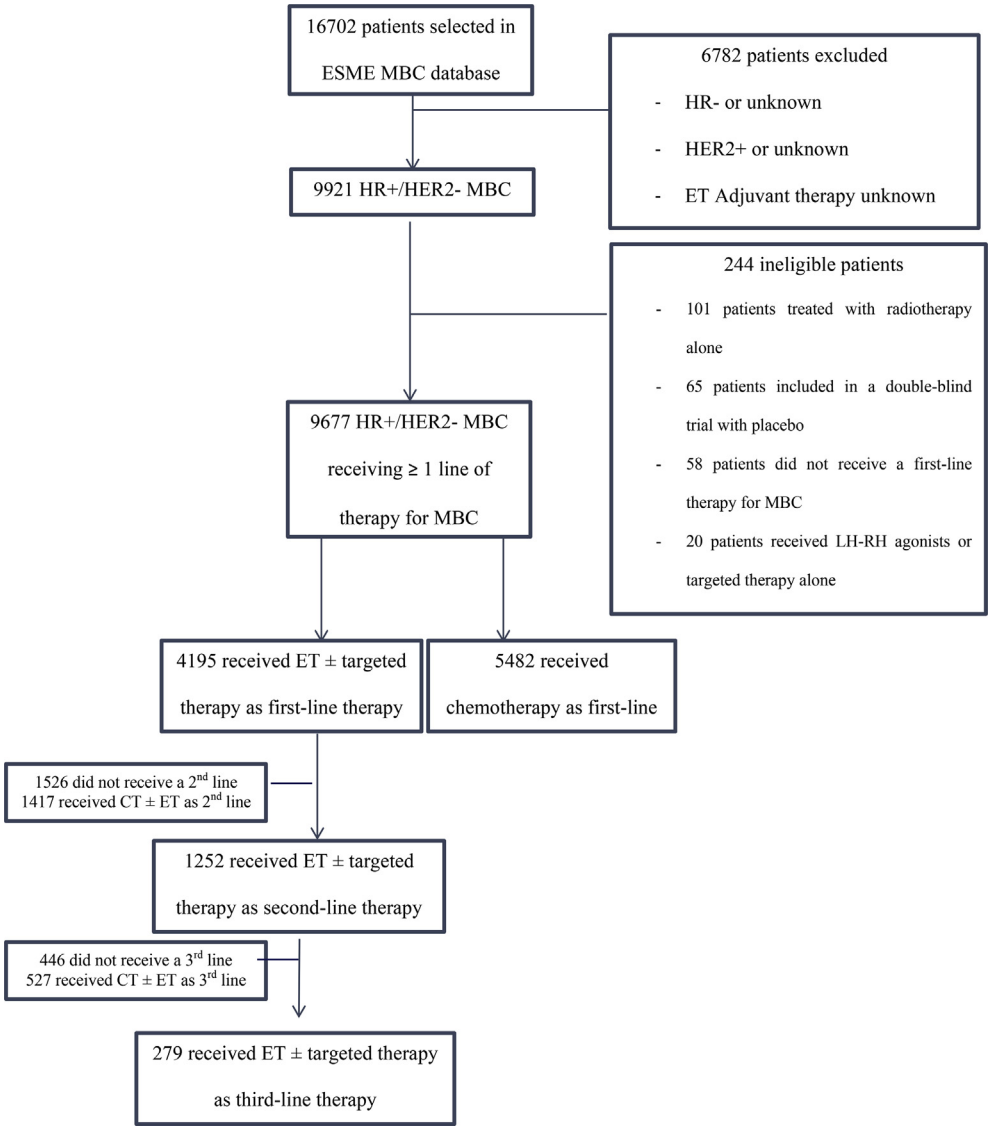

Fig. 1. Study flow chart. ESME, Epidemiological Strategy and Medical Economics; MBC, metastatic breast cancer; HR+, hormone receptor positive; ET, endocrine therapy; LH-RH, Luteinizing hormone-releasing hormone; CT, chemotherapy.

Table 1
Patients' initial characteristics at baseline.

HR+/HER2-	Endocrine therapy ± targeted therapy in first-line treatment N = 4195	Chemotherapy ± endocrine therapy ± targeted therapy in first-line treatment N = 5482	At least one first-line therapy N = 9677	*P*-value
Sex				0.965
Male	44 (1.0)	58 (1.1)	102 (1.1)	
Female	4151 (99.0)	5424 (98.9)	9575 (98.9)	
Age at MBC diagnosis				<0.001
Median (range)	66.0 (26–96)	58.0 (23–96)	62.0 (23–96)	
Time between initial diagnosis and MBC diagnosis (years)[a]				<0.001
Median (minimum–maximum)	7.40 (0.50–47.94)	5.56 (0.50–44.37)	6.37 (0.50–47.94)	
Primary tumour histological type				<0.001
Invasive ductal carcinoma	2534 (73.9)	3603 (78.4)	6137 (76.5)	
Invasive lobular carcinoma	703 (20.5)	784 (17.1)	1487 (18.5)	
Both	66 (1.9)	77 (1.7)	143 (1.8)	
Other	127 (3.7)	131 (2.9)	258 (3.2)	
Missing data	765	887	1652	
Grade of the primary tumour				<0.001
I	523 (16.5)	425 (9.9)	948 (12.7)	
II	1943 (61.3)	2400 (56.0)	4343 (58.2)	
III	642 (20.2)	1399 (32.6)	2041 (27.4)	
Missing data	1087	1258	2345	
MBC at diagnosis				<0.001
Yes	1098 (26.2)	1661 (30.3)	2759 (28.5)	
No	3097 (73.8)	3821 (69.7)	6918 (71.5)	
Type of metastases				<0.001
Bone-only disease	1865 (44.5)	1169 (21.3)	3034 (31.4)	
Visceral metastases (excluding brain metastases)	1551 (37.0)	3278 (59.8)	4829 (49.9)	
Non-visceral metastases (skin and lymph nodes)	654 (15.6)	772 (14.1)	1426 (14.7)	
Brain visceral metastases	125 (3.0)	263 (4.8)	388 (4.0)	
Number of metastatic sites				<0.001
Median (minimum–maximum)	1.0 (1–6)	2.0 (1–8)	1.0 (1–8)	
Presentation				<0.001
Asymptomatic disease	1970 (48.8)	2994 (57.1)	4964 (53.5)	
Symptomatic disease	2063 (51.2)	2246 (42.9)	4309 (46.5)	
Missing data	162	242	404	
Adjuvant chemotherapy				<0.001
Yes	1842 (43.9)	2899 (52.9)	4741 (49.0)	
No	2353 (56.1)	2583 (47.1)	4936 (51.0)	
Adjuvant endocrine therapy				0.002
Yes	2619 (62.4)	3250 (59.3)	5869 (60.6)	
No	1576 (37.6)	2232 (40.7)	3808 (39.4)	
Adjuvant radiotherapy				0.028
Yes	2728 (65.1)	3447 (62.9)	6175 (63.9)	
No	1464 (34.9)	2032 (37.1)	3496 (36.1)	
Missing data	3	3	6	

HER2-, HER2 negative; HR+, hormone receptor positive; MBC, metastatic breast cancer; HER, human epidermal growth factor receptor.
Values are numbers (percentages) unless otherwise specified.
[a] Patients with metastatic disease at presentation excluded.

Table 2
Type of endocrine therapy prescribed in each line.

Endocrine therapy (ET)	First line N = 4195	Second line N = 1252	Third line N = 279
Non-steroidal aromatase inhibitors (AIs)	2678 (63.8)	668 (53.4)	56 (20.1)
Steroidal AI	785 (18.7)	443 (35.4)	156 (55.9)
Tamoxifen	784 (18.7)	346 (27.6)	63 (22.6)
Fulvestrant	581 (13.8)	549 (43.8)	161 (57.7)
LHRH analogues	337 (8.0)	87 (6.9)	23 (8.2)
Other	31 (0.7)	25 (2.0)	9 (3.2)

Values are numbers (%) unless otherwise specified. A patient may have received multiple treatments at the same time. A patient can therefore be counted several times, and percentages may total higher values than 100%. LHRH, luteinizing hormone-releasing hormone.

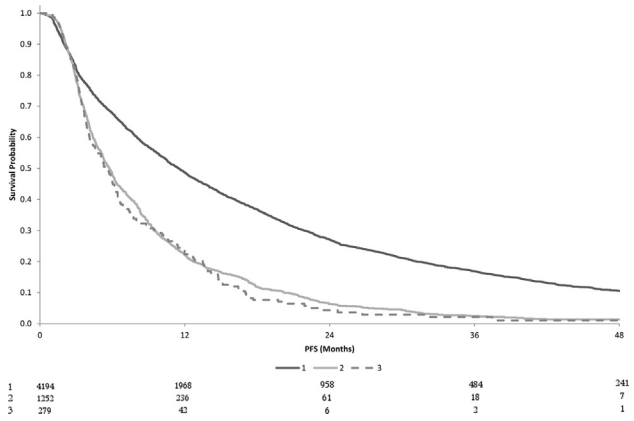

Fig. 2. Successive median PFS on successive ET ± targeted therapy lines. PFS, progression-free survival; ET, endocrine therapy.

as significant for PFS1: age at diagnosis of MBC, time from diagnosis to metastatic disease, presence of symptoms and number and localisation of metastatic sites (Table 3). The multivariate analysis indicated factors significantly associated with a longer PFS1 time from initial diagnosis to metastatic disease for MBC at diagnosis (HR = 0.60 [95% CI, 0.52–0.69] and for MBC >2 years after diagnosis, HR = 0.65 [95% CI, 0.57–0.73] compared with MBC <2 years after diagnosis, $P < 0.0001$); asymptomatic disease (HR = 0.92 [95% CI, 0.85–0.98], $P = 0.0127$); less than 4 metastatic sites (HR = 0.7 [95% CI, 0.58–0.85], $P = 0.0003$) and involvement sites (no visceral metastasis HR = 0.71 [95% CI, 0.58–0.88] or bone-only metastases HR = 0.8 [95% CI, 0.65–0.97]) (Table 3).

3.3. Second-line therapy

Before any chemotherapy, only 1252 (29.8%) patients who had received ET as first-line treatment received a second-line ET ± targeted therapy (Fig. 1). Combined to second-line ET, 14.8% of the patients received a targeted therapy (n = 185). Non-steroidal AIs were prescribed in second-line treatment in 53.4% of cases (n = 668/1252) (Table 2). The median PFS for second-line therapy was 5.8 months (95% CI, 5.3–6.1) (Fig. 2). The PFS rate at 1 year was 22.1% (95% CI, 19.7–24.6). The univariate Cox analysis showed duration of PFS1 (cut-off, 12 months) as the only significant prognostic factor for PFS2 (>12 months HR = 0.89 [95% CI, 0.79–1], $P = 0.0672$) (Table 3).

3.4. Third-line therapy

Before any chemotherapy, only 279 received a third line of ET ± targeted therapy, which represents 22.3% of the patients who had received two lines of ET and 6.6% of

Table 3
Prognostic factors of PFS1, PFS2 and PFS3 in univariate and multivariate analyses.

Prognostic factors of PFS	Univariate analysis			Multivariate analysis		
	Hazard ratio	[95% CI]	*P*	Hazard ratio	[95% CI]	*P*
Prognostic factors of PFS1						
Age at diagnosis of MBC			0.0199			
0–45 years						
>45 years	0.85	[0.73–0.97]				
Time between initial diagnosis and MBC diagnosis (years)			<0.0001			<0.0001
0–2						
Metastatic at presentation	0.61	[0.53–0.70]		0.59	[0.52–0.68]	
>2 years	0.67	[0.59–0.75]		0.65	[0.57–0.73]	
Presentation			0.0036			0.01
Symptomatic disease						
Asymptomatic disease	0.91	[0.85–0.97]		0.92	[0.86–0.98]	
Number of metastatic sites			<0.0001			0.0003
>3						
0–3	0.66	[0.55–0.79]		0.70	[0.58–0.85]	
Metastatic sites			<0.0001			<0.0001
Brain visceral metastasis						
No visceral metastasis	0.64	[0.52–0.79]		0.71	[0.58–0.88]	
Bone-only disease	0.71	[0.58–0.86]		0.80	[0.65–0.97]	
Visceral metastasis (excluding brain metastasis)	0.85	[0.7–1.04]		0.94	[0.77–1.16]	
Prognostic factors of PFS2						
Duration of PFS1			0.0672			
≤12 months						
>12 months	0.89	[0.79–1.01]				
Prognostic factors of PFS3						
Duration of PFS1/PFS2			0.0008			
≤18 months						
>18 months	0.59	[0.44–0.80]				

CI, confidence interval; MBC, metastatic breast cancer.

the patients who had received ET as first-line therapy (Fig. 1). A total of 28.7% of the patients received targeted therapy (n = 80) combined with ET in third-line treatment. Fulvestrant and steroidal AIs were the most frequently prescribed therapy, with 57.7% and 55.9% of patients treated, respectively (Table 2). The median PFS for third-line therapy was 5.5 months (95% CI, 4.6–6.3) (Fig. 2). The PFS rate at 1 year was 22.4% (95% CI, 16.9–28.3). The univariate Cox analysis showed that cumulative duration of previous lines (PFS1+PFS2; cut-off, 18 months) was the only significant factor that remained significant in the multivariate model for PFS3 (>18 months HR = 0.59 [95% CI, 0.44–0.8], $P < 0.001$) (Table 3).

3.5. Predictors of subsequent lines of ET

Among the subgroup of patients starting a second line of treatment following an ET ± targeted therapy in first-line treatment (2669 patients), 1252 (47%) patients began a second line of ET ± targeted therapy, whereas the other 1417 (53%) patients switched to chemotherapy ± targeted therapy. The univariate logistic analysis revealed as time from diagnosis to metastatic disease, age at the end of first-line therapy, number and localisation of metastatic sites at the end of first-line therapy and duration of PFS1 (cut-off 6 months) as factors significantly linked to a subsequent line of ET. Multivariate analysis identified time from diagnosis to metastatic disease (>2 years OR = 1.23 [95% CI, 0.90–1.70] or MBC at diagnosis (OR = 1.85 [95% CI, 1.30–2.61], $P \leq 0.0001$), age at the end of first-line therapy (>45 years old, OR = 2.11 [95% CI, 1.42–3.12], $P = 0.0002$), metastatic sites at the end of first-line therapy (bone-only metastases, OR = 2.2 [95% CI, 1.41–3.43]) and duration of PFS1 (>6 months, OR = 3.01 [95% CI, 2.53–3.6], $P < 0.0001$) were predictive factors for prescribing a 2nd line of ET at the time of progressive disease (Table 4).

3.6. Predicting long-term time under ET

By focussing on the 10% of patients with the longest ET treatment regardless of the lines, we reported a duration of ET superior or equal to 43.6 months. The patient characteristics are presented in Table 5. The logistic univariate analysis identified time from diagnosis to metastatic disease and localisation and a lower number of metastatic sites as factors significantly associated with long-term time under ET. Multivariate analysis revealed that time from diagnosis to metastatic disease (>2 years, OR = 2.74 [95% CI, 1.58–4.75]) or MBC at diagnosis (OR = 2.43 [95% CI, 1.37–4.32], $P = 0.0013$), less than 4 metastatic sites (OR = 3.12 [95% CI, 1.13–8.6], $P = 0.0276$) and localisation of metastatic sites (presence of metastases other than visceral or brain, OR = 1.73, [95% CI, 1.29–2.32] or bone-only metastases, OR = 1.37 [95% CI = 1.08–1.74] compared with visceral/non-brain metastases, $P = 0.0025$) were predictive factors of a prolonged benefit of ET treatment (Table 6).

3.7. Overall survival

The median OS for patients receiving ET ± targeted therapy in the first line was 49.6 months (95% CI, 48.1–51.2).

4. Discussion

The ESME programme represents the first large-scale European real-life initiative on MBC, involving more than 16 000 patients. In this analysis, we showed, contrary to published guidelines [1,17], that ET was prescribed to less than 50% of the patients with HR+/HER2- MBC in first-line therapy and only to a small

Table 4
Predictive factors of subsequent lines of ET.

Predictive factors		Univariate analysis			Multivariate analysis		
		OR	95% CI	*P-value*	OR	95% CI	*P-value*
Time between initial diagnosis and MBC diagnosis (years)	0–2	1.00		<0.0001	1.00		<0.0001
	>2	1.43	1.06–1.94		1.23	0.90–1.69	
	Metastatic at presentation	2.58	1.86–3.57		1.85	1.30–2.61	
Age at the end of first-line therapy	0–45 years	1.00		<0.0001	1.00		0.0002
	>45 years	2.44	1.69–3.52		2.11	1.43–3.12]	
Metastatic sites at the end of first-line therapy	Brain metastasis	1.00		<0.0001	1.00		<0.0001
	Visceral metastasis (excluding brain metastasis)	1.19	0.79–1.79		0.98	0.63–1.51	
	No visceral metastasis	1.64	1.05–2.56		1.38	0.86–2.21	
	Bone-only disease	2.78	1.82–4.24		2.20	1.41–3.43	
Number of metastatic sites at the end of first-line therapy	>3	1.00		0.0097			
	0–3	1.43	1.09–1.88				
Duration of PFS1	0–6 months	1.00		<0.0001	1.00		<0.0001
	>6 months	3.40	2.86–4.03		3.01	2.53–3.60	

CI, confidence interval; OR, odds ratio; MBC, metastatic breast cancer.

Table 5
Outlier characteristics.

Characteristics	Short responders		Outliers		All		Test
	N = 3773		N = 421		N = 4194		
Age at the time of metastatic diagnosis							Wilcoxon P = 0.685
N	3773		421		4194		
Median (minimum; maximum)	66.8 (26; 97)		67.2 (34; 96)		66.8 (26; 97)		
Age at diagnosis							Chi-square P = 0.549
0–45 years	215	(5.7%)	21	(5.0%)	236	(5.6%)	
>45 years	3558	(94.3%)	400	(95.0%)	3958	(94.4%)	
Number of ET lines							Chi-square P= <0.001
1	2706	(71.7%)	236	(56.1%)	2942	(70.1%)	
2	867	(23.0%)	106	(25.2%)	973	(23.2%)	
3	185	(4.9%)	63	(15.0%)	248	(5.9%)	
4+	15	(0.4%)	16	(3.8%)	31	(0.7%)	
Time between initial diagnosis and MBC diagnosis (years)							Chi-square P= <0.001
Metastatic at presentation	994	(26.3%)	104	(24.7%)	1098	(26.2%)	
0–2	306	(8.1%)	14	(3.3%)	320	(7.6%)	
>2 years	2473	(65.5%)	303	(72.0%)	2776	(66.2%)	
Presentation							Chi-2 P = 0.101
Missing data	145		17		162		
Asymptomatic disease	1757	(48.4%)	213	(52.7%)	1970	(48.9%)	
Symptomatic disease	1871	(51.6%)	191	(47.3%)	2062	(51.1%)	
Relapse							Chi-square P = 0.121
Missing data	10		1		11		
None	3509	(93.3%)	396	(94.3%)	3905	(93.4%)	
Local	76	(2.0%)	12	(2.9%)	88	(2.1%)	
Locoregional	178	(4.7%)	12	(2.9%)	190	(4.5%)	
Metastatic sites							Chi-square P= < 0.001
Bone-only metastasis	1663	(44.1%)	202	(48.0%)	1865	(44.5%)	
Visceral metastasis (excluding brain metastasis)	1428	(37.8%)	122	(29.0%)	1550	(37.0%)	
No visceral metastasis	566	(15.0%)	88	(20.9%)	654	(15.6%)	
Brain metastasis	116	(3.1%)	9	(2.1%)	125	(3.0%)	
Number of metastatic sites							Fisher's Exact P = 0.002
0–3	3636	(96.4%)	417	(99.0%)	4053	(96.6%)	
>3	137	(3.6%)	4	(1.0%)	141	(3.4%)	

ET, endocrine therapy; MBC, metastatic breast cancer.

minority of patients in subsequent lines. Surprisingly, although lobular carcinomas present limited chemosensitivity, more than half of the patients with lobular carcinoma (52.7%, n = 784/1487) were treated with chemotherapy as first-line therapy. These results are consistent with previous descriptive studies reporting that only 51–54% of European patients received ET in first-line treatment. This proportion seems higher in the United States of America (53–60%) [18,19]. In second- and third-line treatment, the results were consistent with our study, and other authors reported that less than 10% of the patients received three lines of ET [18–22] before initiation of chemotherapy for metastatic disease. As previously reported in the ESME breast cohort, chemotherapy was preferentially prescribed to younger patients with visceral or brain metastases [3].

Table 6
Predictive factors of long-term time under ET.

Predictive factors		Univariate analysis			Multivariate analysis		
		OR	95% CI	*P-value*	OR	95% CI	*P-value*
Time between initial diagnosis and MBC diagnosis (years)	0–2	1.00		0.0013			0.0013
	Metastatic at presentation	2.29	1.29–4.05		2.43	1.37–4.32	
	>2	2.68	1.55–4.63		2.74	1.58–4.75	
Metastatic sites	Visceral metastasis (excluding brain metastasis)	1.00		0.0003			0.0025
	No visceral metastasis	1.82	1.36–2.43		1.73	1.29–2.32	
	Brain metastasis	0.91	0.45–1.83		1.07	0.52–2.17	
	Bone-only metastasis	1.42	1.12–1.8		1.37	1.08–1.74	
Number of metastatic sites	>3	1.00		0.0073			0.0276
	0–3	3.93	1.45–10.67		3.12	1.13–8.60	

ET, endocrine therapy; OR, odds ratio; CI, confidence interval; MBC, metastatic breast cancer.

The reasons for not adhering to the international guidelines in the real life, outside of clinical trials, are multiple. Physicians may think that clinical trials are strictly selecting patients who are in better physical condition and are not representative of daily practice. The real-life median PFS for first-line ET in the present study was consistent with the median PFS reported in clinical trials [4,5]. The ESME analysis based on a propensity score showed that, whatever the first-line treatment, chemotherapy or ET, for HR+/HER2- MBC was, OS was similar. This should further stimulate the choice of a regimen such as ET lighter and safer [3]. In subsequent lines, the median PFS from our analysis compared favourably with the clinical trial results of ET alone, with PFS ranging from 2.8 months for exemestane in the BOLERO-2 trial [8] to 4.6 months with fulvestrant in the PALOMA-3 trial [23]. We also showed that more than 20% of patients in second- and third-line treatment still benefited from ET, with no progression at one year. This should be an argument for prescribing more than one line of ET as some patients will benefit from another ET line with a favourable profile and for a long time. Interestingly, in the present study, the duration of PFS of the previous line significantly correlated with the duration of disease control for every successive line of ET, pointing out the interest of an additional ET line in long responders.

Whether we should prescribe CDK4/6 inhibitors in combination with ET to all patients in first-line ET is still debatable. The present study showed some patients with long-term disease control with monotherapy (ET), especially patients with MBC at diagnosis, or prolonged time from diagnosis to metastatic disease (more than 2 years), patients with few metastatic sites and patients without visceral or bone-only metastases, thus highlighting that, in some cases, new therapies such as CDK4/6 inhibitors (CDKI) may not be essential. Indeed, CDK4/6 inhibitors raise several issues. First, OS data from studies combining ET and CDK inhibitors in first-line treatment for MBC are not yet mature. As shown by Grossmann et al [24], most European Medicines Agency–approved cancer drugs do not meet the threshold for 'meaningful clinical benefit (MCB)' especially because end-points such as PFS are not correlated with MCB. Secondly, in the MONARCH-3 trial, subgroup analysis showed that the benefit of CDK4/6 inhibitors was less meaningful for patients presenting a treatment-free interval of $\geq$36 months [10]. Fulvestrant monotherapy could be an option for patients with low- or intermediate-risk disease with good prognosis (e.g. non-visceral disease) and patients with high-risk disease who have comorbidities restricting the use of combination targeted therapy as shown in the FALCON trial [25]. Third, although quality of life is reported to be similar for patients receiving the combination of ET + targeted therapy, methodology regarding quality of life in clinical trials is often hazardous [26], and serious adverse events (AEs) are still more frequent when a combination is used compared with ET alone [8,11]. Finally, in pivotal trials for targeted therapy, older patients with comorbidities, multiple treatments or poor performance status were underrepresented. Indeed, even in older and fit patients, the rate of AEs such as diarrhoea was more frequent with CDK4/6 inhibitors combination therapy: as an example, the increasing rate of diarrhoea (any grade) from 26% up to 41% in patients aged $\geq$65 years when combining CDKI to ET [11]. As shown here, some patients benefit from ET alone and may not need the addition of targeted therapies with its potential associated risk of toxicity that can impair quality of life. For these patients, a first-line ET alone might be considered for a better efficacy/toxicity ratio, the combination of ET and CDK inhibitors being still available in second-line ET. With no demonstrated OS benefit in first-line treatment and considering specific toxicity risk of targeted agents, it is essential to identify and characterise patients who will benefit from ET alone in first-line treatment, and further research is needed to better understand how to optimise the sequencing of the available treatment options in this setting.

An important limitation of this study is the selection of patients from academic comprehensive cancer centres, which may not reflect the real life of other clinical institutions. Other limitations are inherent in the retrospective and observational nature of the study design. For the analysis, the 'progression' outcome was derived based on several data sources, according to their availability (physician claims, pathological report, other report...). The frequency of information on the progression depended on the patient follow-up time points and the recurrence of clinical examination and imaging assessment. An underestimation of the progression rate might have happened.

However, the present work has several major strengths. First, rigorous standard screening procedures across all 18 cancer centres and a statistical methodology were applied to minimise selection bias. Second, the analysis was based on a large number of well-documented cases, with a high level of quality control and exhaustive patient selection across participating centres.

To conclude, we found that patients received more chemotherapy in first-line treatment than what the international guidelines recommended, although similar PFS was reported in this real-life study compared with clinical trial results. We also identified a subpopulation of patients with exceptional response and with very good prognosis. The results of this retrospective analysis emphasise the need for physicians to stick to their daily practice as close as possible to the evidence-based medicine and to the international recommendations.

Conflict of interest statement

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