

ARTICLE



Clinical Studies

Efficacy of front-line treatment for hormone receptor-positive HER2-negative metastatic breast cancer with germline *BRCA1/2* mutation

J.-S. Frenel¹✉, A. Lusque², S. Delaloue³, J.-M. Ferrero⁴, T. Bachelot⁵, I. Desmoulins⁶, C. Levy⁷, J.-C. Eymard⁸, A. Gonçalves⁹, A. Patsouris¹⁰, M. A. Mouret Reynier¹¹, M. J.-C. Thery¹², T. Petit¹³, L. Cabel¹⁴, L. Uwer¹⁵, M. Debled¹⁶, M. Chevrot¹⁷, A. Mailliez¹⁸, W. Jacot¹⁹ and T. de La Motte Rouge²⁰

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BACKGROUND: Efficacy of endocrine therapy in HR+/HER2– metastatic breast cancer could differ depending on the presence of *BRCA1/2* germline mutation.

METHODS: The ESME metastatic breast cancer platform (NCT03275311) is a French real world database. Multivariable models including a time-varying approach and landmark analyses assessed the association between time-dependent *gBRCA* status (categorised as *gBRCAm*, *gBRCAwt* (wild type), and untested), overall survival (OS), and first-line progression-free survival (PFS1).

RESULTS: A total of 170 patients were *gBRCAm* carriers, 676 *gBRCAwt*, and 12,930 were untested at baseline. In the multivariable analysis, *gBRCAm* carriers overall had a lower OS compared to *gBRCAwt* (adjusted HR [95% CI] 1.26 [1.03–1.55]). *gBRCAm* patients treated with front-line endocrine therapy had lower adjusted OS (adjusted HR [95% CI] = 1.54 [1.03–2.32]) and PFS1 (adjusted HR [95% CI] 1.58 [1.17–2.12]) compared to *gBRCAwt* patients. However, for patients who received frontline chemotherapy, neither OS nor PFS1 differed between *gBRCAm* carriers and the other groups (HR versus *gBRCAwt* for OS: 1.12 [0.88–1.41], $p = 0.350$; PFS1: 1.09 [0.90–1.31], $p = 0.379$).

CONCLUSION: In this large cohort of HR+/HER2– MBC patients treated in a pre-CDK4/6 inhibitors era, *gBRCAm* status was associated with a lower OS and lower PFS following first-line endocrine therapy, but not following first-line chemotherapy.

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INTRODUCTION

Approximately 20 and 77% of breast cancers occurring in germline *BRCA1* and *BRCA2* mutation carriers, respectively, are hormone receptor (HR)-positive [1]. HR-positive BC among *BRCA1/2* carriers is frequently characterised by a more aggressive phenotype with higher tumour grade and higher proliferation assessed by Ki67 level [1, 2]. In addition, higher recurrent score as assessed by Oncotype DX test are noted as compared to *BRCAwt* patients, with >80% of patient having intermediate or high-risk disease [3]. Conflicting results have been reported on the prognostic impact of *BRCA1/2* mutation in HR-positive breast cancer and data in the metastatic setting are very scarce [4, 5].

Specific therapeutic options for these patients have emerged with PARP inhibitors thanks to two pivotal randomised trials demonstrating the benefit of olaparib or talazoparib, compared with chemotherapy in the first- to third-line metastatic setting. The magnitude of the benefit was similar between triple-negative and HR-positive breast cancer subtypes [6, 7]. However, front-line endocrine-based treatment remains the preferred option in the guidelines for treating patients with HR-positive/HER2-negative metastatic breast cancer, regardless of *gBRCA* status [8]. This treatment includes now CDK4/6 inhibitors in combination with endocrine therapy.

The real efficacy of endocrine-based therapy among *gBRCA* carriers with HR-positive/HER2-negative MBC has not been well

¹Medical Oncology, ICO Institut de Cancerologie de l'Ouest René Gauducheau, Saint-Herblain, France. ²Biostatistics & Health Data Science Unit, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France. ³Department of Cancer Medicine, Institut Gustave Roussy, Villejuif, France. ⁴Medical Oncology, Centre Antoine Lacassagne, Nice, France. ⁵Medical Oncology Department, Centre Léon Bérard, Lyon, France. ⁶Medical Oncology, Centre Georges-François Leclerc (Dijon), Dijon, France. ⁷Medical Oncology, Centre François Baclesse, Caen, France. ⁸Medical Oncology, Institut Jean Godinot, Reims, France. ⁹Medical Oncology Department, Institute Paoli Calmettes, Marseille, France. ¹⁰Medical Oncology Department, ICO - Institut de cancerologie de l'Ouest - Site Paul Papin, Angers, France. ¹¹Medical Oncology, Jean Perrin Center, Clermont-Ferrand, France. ¹²Medical Oncology, Centre Henri Becquerel, Rouen, France. ¹³Bas-Rhin, Centre Paul Strauss Centre de Lutte contre le Cancer, Strasbourg, France. ¹⁴Medical Oncology, Hôpital René Huguenin - Institut Curie, Saint-Cloud, France. ¹⁵Medical Oncology, Institut de Cancerologie de Lorraine - Alexis Vautrin, Vandoeuvre Les Nancy, France. ¹⁶Medical Oncology, Institut Bergonié, Bordeaux, France. ¹⁷Department of Real World Data, UNICANCER, Paris, France. ¹⁸Medical Oncology, Centre Oscar Lambret, Lille, France. ¹⁹Medical Oncology Department, ICM Regional Cancer Institute of Montpellier, Montpellier University, INSERM U1194 Montpellier, France. ²⁰Medical Oncology, Centre Eugene - Marquis, Rennes, France.

✉email: Jean-sebastien.frenel@ico.unicancer.fr

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documented. Outcomes from combined endocrine and CDK4/6 inhibitor therapy may be less favourable among *gBRCA* carriers compared with their wild-type counterparts, although conflicting results have been reported [9–12]. Given the lack of evidence regarding outcome and first-line endocrine treatment efficacy in patients with HR-positive/HER2-negative MBC harbouring a *gBRCA1/2* mutation, we collected and analysed this data from a large, real-world database (ESME).

METHODS

Study design

This non-interventional, retrospective, comparative study was performed to determine the outcome of selected MBC patients from the ESME MBC database (NCT03275311). This database is an ongoing unique national cohort that gathers real-world individual, retrospective data from all consenting consecutive patients, male or female, ≥ 18 years, having started a first-line anti-cancer treatment for MBC in any of the 18 cancer centres that participate in the ESME Research Programme. We included for the present study patients initiating a treatment from January 01, 2008 to December 31, 2016. Patient-, hospitalisation-, and pharmacy-related data are collected, including patient demographic characteristics, pathology, and outcomes. Treatment protocols are recorded, which include chemotherapy, targeted agents, endocrine therapy (ET), radiotherapy (RT), or other local treatments, as well as supportive therapy. In the present study, we specifically selected MBC patients with HR+/HER2– status and the available information on germline *BRCA1/2* status. The data were compiled until the cut-off date (October 15, 2018), death, or date of last contact (if lost to follow-up). The 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; however, all patients had approved the re-use 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 the applicable European regulations, a complementary authorisation was obtained on October 14, 2019 regarding the ESME Research Data Warehouse.

Objectives and endpoints

The primary objective of the present study was to compare the OS of *gBRCAm* HR+/HER2– MBC patients to that of *gBRCAwt* and untested patients. The secondary objectives were to compare first-line PFS (PFS1) between these groups of HR+/HER2– MBC patients and to compare OS and PFS1 between these groups in patients treated with first-line endocrine-based (in the absence of chemotherapy) or chemotherapy-based (+/– ET) treatment.

OS was the primary endpoint and was defined as the time between the starting date of first-line treatment (baseline) and the date of death from any cause or the date of last contact (censored data). PFS1 was defined as the time between the starting date of first-line treatment and the date of first disease progression or date of death. Patients that were still alive and without progression at the time of the analysis were censored at their last follow-up. A treatment line was defined as a given therapeutic strategy set up until disease progression or death; therefore, it may involve multiple treatments including chemotherapy, targeted agents, or ET. De novo metastatic disease was defined as the presence of metastasis at the time or within six months (180 days) from primary tumour diagnosis.

Tumour subtype assessment and evaluation

HER2 and hormone receptor status were performed locally and derived from the existing results of metastatic tissue sampling if available, or from the last sampling of early disease if not available. Breast cancer was classified as hormone receptor-positive if the estrogen receptor or progesterone receptor expression was $\geq 10\%$ as determined by immunohistochemistry following the European guidelines. Subtypes (and the use of metastatic versus primary sample data) have been uniformly defined for the ESME database and were described previously [13].

Germline BRCA testing

gBRCA1/2 status was used to define three groups of patients: *gBRCAm* (presence of a demonstrated germline deleterious alteration of either

BRCA1 or *BRCA2*), *BRCAwt* (patient was tested and no *gBRCA* alteration was identified, although the patient could carry another germline alteration), and untested. Only pathogenic *BRCA* alterations (i.e., variant class 4 or 5) were considered to define *gBRCAm*. The mutational status was defined, according to different analyses, either at baseline, or at any time during the disease course using a time-varying approach and at different time points using a landmark approach: within the first three months or within the first six months of treatment initiation.

First-line systemic treatment

Systemic therapies were classified into the following four groups: ET, chemotherapy, immunotherapy, and targeted therapy (CDK4/6 inhibitors, mTOR inhibitors, PARP inhibitors). Patients who received ET as maintenance after chemotherapy were included with the chemotherapy group.

Statistical analyses

Quantitative variables are presented as the median and range (minimum–maximum), whereas qualitative variables are summarised by frequency and percentage. Comparisons between groups were assessed using the Kruskal–Wallis test for quantitative variables and the Chi-squared or Fisher exact test for qualitative variables. The Kaplan–Meier method and log-rank test were used to estimate and compare time-to-event endpoints (PFS1 and OS). Hazard ratios and 95% confidence intervals (95% CI) were calculated using the Cox proportional hazards model. Multivariable Cox proportional hazard models were performed to evaluate the association between time-to-event endpoint and *BRCA* status adjusted on the main known prognostic factors such as age at metastatic diagnosis, metastatic free interval (<6 months versus [6–24] months versus >24 months), number of metastatic sites (<3 versus ≥ 3), presence of visceral metastases (yes versus no).

The establishment of a *gBRCA* group was done according to *gBRCA* status, which was defined at baseline (first-line initiation). Associations between *gBRCA* status and time-to-event endpoints were assessed using a Cox proportional hazards model including *gBRCA* status as a time-dependent variable to avoid immortal-time biases related to the time between treatment initiation and knowledge of *gBRCAm* or *gBRCAwt* status, which may occur after baseline. Thus, *gBRCA* status can change over time. A patient may be switched from untested status to *gBRCAm* or *gBRCAwt* status. In addition, sensitivity analyses were performed by defining *gBRCA* status at different time points to prevent immortal-time biases: at first-line initiation (baseline) or using a landmark approach at three or six months after first-line initiation. For each of these sensitivity analyses, *gBRCA* status was defined on the basis of genetic testing, which was performed before the time point, and for patients who died, progressed, or were lost of follow-up before the time point, were excluded. All statistical tests were two-sided, and a *p*-value <0.05 was considered statistically significant. Statistical analyses were carried out using STATA software version 16 (StataCorp LLC, College Station, TX).

RESULTS

Patients, tumour characteristics, and initial treatments according to *gBRCA* mutational status

A total of 13,776 patients in the ESME database matched the inclusion criteria. The flow chart is shown in Fig. 1. The *gBRCA* status at baseline was identified as “mutated” (presence of a deleterious alteration of *gBRCAm*), negative (*gBRCAwt*) or untested for 170 (1.2%), 676 (4.9%), and 12,930 (93.9%) patients, respectively. The median time (range) from diagnosis of metastatic disease to *BRCA* testing (months) ($n = 226$) was -16.4 (-171.5 : 67.7) months. Indeed, 75% (170/226) of *BRCA* carriers were known to bear a mutation prior to be diagnosed with mBC. Patient characteristics according to baseline *gBRCA* status are shown in Table 1. Out of 170 baseline *gBRCAm* patients, 51 (30.0%) harboured a *BRCA1* alteration, 117 (68.8%) a *BRCA2* alteration, and two (1.2%) had both. Characteristics of patients with *BRCA1* versus *BRCA2* alterations are shown on Supplementary Table 1. As expected, *gBRCAm* patients were young, with a median age of 47 years (range 26–82), primary histological tumour grade of 2 or 3 (95.1%), and de novo metastases accounted for 5.9% of the cases. Visceral metastases were more frequent at initial presentation in

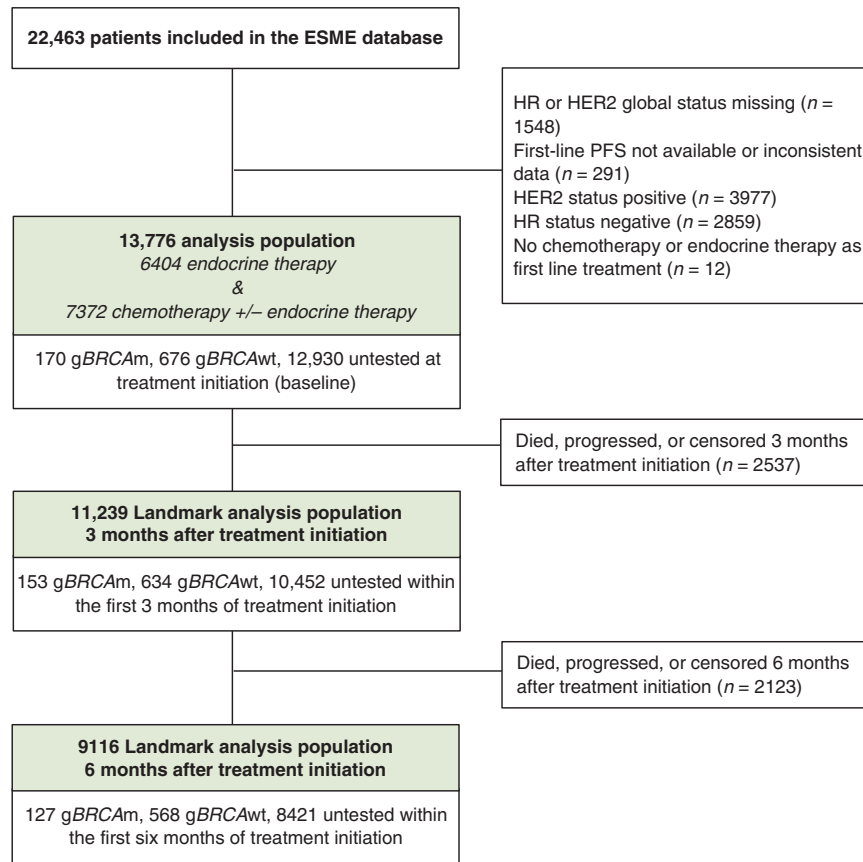


Fig. 1 Flow Chart.

gBRCAm patients (67.6%) compared with the *gBRCAwt* population (56.7%). Bone-only metastases were present in 20% of the *gBRCAm* patients, which was significantly less frequent, compared with the remaining patients. Regarding systemic front-line treatment, *gBRCAm* patients more frequently received first-line chemotherapy (72.9%) compared with *gBRCAwt* (60.7%) and non-tested patients (52.9%) ($p < 0.0001$). Characteristics of patients who received frontline endocrine therapy versus chemotherapy are shown on Supplementary Table 2. Only ten patients from the entire cohort received PARP inhibitors alone or in combination as front-line treatment, including seven with *gBRCAm*.

Outcomes of *gBRCAm* patients versus others (Table 2 and Fig. 2)

The median follow-up for the entire population was 50.6 months (95% CI: 49.7–51.7) and the median OS was 42.6 months (41.9–43.6). Survival analyses were performed for the three groups (*gBRCAm*/*BRCAwt*/untested) with respect to different time points: at treatment initiation (baseline), with landmark analysis at three and six months, or at any time (time-varying analysis). The median OS for the three groups was 36.5 (33.4–42.9), 40.6 (37.8–44.1), and 42.8 (42.0–44.0) months, respectively, considering baseline *BRCA* status ($p = 0.1351$; log-rank test) (Fig. 2). For the multivariable analysis using *gBRCA* status as a time-dependent variable and adjusted for age, visceral metastases, the number of metastatic sites, and metastasis-free interval, *gBRCAm* patients exhibited a lower OS compared with *gBRCAwt* patients (adjusted HR [95% CI] = 1.26 [1.03–1.55]). The sensitivity analyses defining *gBRCA* status at different time points to prevent immortal-time biases revealed a similar trend in terms of OS, which was, however, not statistically significant (Supplementary Table 3).

Outcomes of patients treated with first-line endocrine-based therapy by *gBRCA* status

A total of 6404 patients (46.5%) received front-line ET alone or in combination with targeted treatment (but no chemotherapy) (46,266, and 6092 patients in the *gBRCAm*, *gBRCAwt*, and untested groups, respectively). These patients were treated between 2008 and 2016, thus only a few received a combination of ET plus targeted therapy ($n = 381$; 5.9%) including 201 patients with everolimus and 113 patients with a CDK4/6 inhibitor. The characteristics of these patients are shown in Supplementary Table 4. Briefly, *gBRCAm* patients were younger and had more visceral disease compared with *gBRCAwt* patients. The univariable analysis indicated that *gBRCAm* patients had a significantly lower PFS1 (median PFS1 [95% CI]: 6.9 [3.4–12.7], 10.3 [7.8–13.4], and 11.4 [10.8–11.9] months in patients with *gBRCAm*, *gBRCAwt*, and untested patients, respectively; log-rank test $p = 0.0403$) (Fig. 2). In a multivariable analysis using *gBRCA* status as a time-dependent variable and adjusted for age, visceral metastasis, number of metastatic sites, and metastasis-free interval, PFS1 remained significantly lower for *gBRCAm* patients who received first-line ET compared with the *gBRCAwt* group (adjusted HR [95% CI]: 1.58 [1.17–2.12]) (Table 2). Sensitivity analysis using the landmark approach confirmed this trend (Supplementary Table 3). Additional analyses adjusting for endocrine sensitivity or resistance revealed similar results (Supplementary Table 4). OS analyses revealed similar results: median OS was 38.7 (35.1–46.2), 51.3 (42.8–65.7), and 48.1 (46.7–49.5) months in the *gBRCAm*, *BRCAwt*, and untested groups at baseline, respectively ($p = 0.0391$; log-rank test). In a multivariable analysis (Cox model with time-dependent variable adjusted on age, visceral metastases, number of metastatic sites, and metastasis-free interval), *gBRCA* mutation remained a pejorative prognostic factor for OS (adjusted HR 1.54

Table 1. Patient characteristics and treatment according to *gBRCA1/2* mutation status defined at baseline (treatment initiation).

	gBRCAm (N = 170)	gBRCAwt (N = 676)	Not Tested (N = 12,930)	p-value
Age at metastatic disease diagnosis (years)				<0.0001
Median	47.0	51.0	62.0	
(Range)	(26.0;82.0)	(26.0;88.0)	(22.0;103.0)	
Age at metastatic disease diagnosis				<0.0001
<50 years	101 (59.4%)	314 (46.4%)	2358 (18.2%)	
50–70 years	57 (33.5%)	306 (45.3%)	6947 (53.7%)	
>70 years	12 (7.1%)	56 (8.3%)	3625 (28.0%)	
Gender				0.0163
Female	166 (97.6%)	663 (98.1%)	12,801 (99.0%)	
Male	4 (2.4%)	13 (1.9%)	129 (1.0%)	
Germline BRCA mutation — no. (%)				
BRCA1	51 (30.0%)	NR	NR	
BRCA2	117 (68.8%)	NR	NR	
BRCA1 and BRCA2	2 (1.2%)	NR	NR	
Histological grade of primary tumour				<0.0001
Grade I	7 (4.9%)	74 (13.1%)	1541 (14.4%)	
Grade II	74 (51.4%)	319 (56.6%)	6532 (60.9%)	
Grade III	63 (43.8%)	171 (30.3%)	2661 (24.8%)	
Missing	26	112	2196	
Histological type of primary tumour				<0.0001
Invasive ductal carcinoma	134 (79.3%)	505 (75.3%)	9146 (72.2%)	
Invasive lobular carcinoma	13 (7.7%)	76 (11.3%)	2177 (17.2%)	
Other	22 (13.0%)	90 (13.4%)	1351 (10.7%)	
Missing	1	5	256	
Primary tumour surgery				<0.0001
No	18 (10.7%)	55 (8.1%)	3214 (25.3%)	
Yes	151 (89.3%)	620 (91.9%)	9484 (74.7%)	
Missing	1	1	232	
Metastasis-free interval (months)				<0.0001
<6 months	10 (5.9%)	26 (3.8%)	3904 (30.3%)	
[6–24] months	21 (12.4%)	72 (10.7%)	1002 (7.8%)	
>24 months	139 (81.8%)	578 (85.5%)	7991 (62.0%)	
Missing	0	0	33	
De novo metastatic disease				<0.0001
No	160 (94.1%)	650 (96.2%)	8997 (69.8%)	
Yes	10 (5.9%)	26 (3.8%)	3900 (30.2%)	
Missing	0	0	33	
Number of metastatic sites at MBC diagnosis				0.0034
1 site	78 (45.9%)	366 (54.1%)	7252 (56.1%)	
2 sites	37 (21.8%)	165 (24.4%)	3036 (23.5%)	
≥3 sites	55 (32.4%)	145 (21.4%)	2642 (20.4%)	
Type of Metastases at MBC diagnosis				0.0003
Visceral	115 (67.6%)	383 (56.7%)	6910 (53.4%)	
Non-visceral	55 (32.4%)	293 (43.3%)	6020 (46.6%)	
Bone metastases only				<0.0001
No	136 (80.0%)	507 (75.0%)	8898 (68.8%)	
Yes	34 (20.0%)	169 (25.0%)	4032 (31.2%)	
Adjuvant endocrine therapy				<0.0001
No	40 (23.0%)	115 (17%)	5356 (41.5%)	
Yes	130 (76.5%)	561 (83.0%)	7543 (58.5%)	

Table 1. continued

	gBRCAm (N = 170)	gBRCAwt (N = 676)	Not Tested (N = 12,930)	p-value
Aromatase inhibitor	56	240	4343	
Tamoxifen	100	434	4006	
LHRH analogues	11	89	369	
Others	1	2	63	
Missing	3	11	628	
Chemotherapy or Endocrine therapy within first treatment line				<0.0001
Chemotherapy alone	55 (32.4%)	153 (22.6%)	2463 (19.0%)	
Endocrine therapy alone	46 (27.1%)	266 (39.3%)	6092 (47.1%)	
Chemotherapy + Endocrine therapy	69 (40.6%)	257 (38.0%)	4375 (33.8%)	
HR status derived from a metastasis biopsy by subgroup of treatment				
Endocrine therapy alone (subgroup n = 6404)				
Yes	24 (52.2%)	125 (47.0%)	2111 (34.7%)	
No	22 (47.8%)	141 (53.0%)	3981 (65.3%)	
Chemotherapy +/- Endocrine therapy (subgroup n = 7372)				
Yes	27 (21.8%)	135 (32.9%)	2010 (29.4%)	
No	97 (78.2%)	275 (67.1%)	4828 (70.6%)	
CDK4-6 inhibitors within first treatment line				
No	170 (100.0%)	667 (98.7%)	12,808 (99.1%)	0.2858
Yes	0 (0.0%)	9 (1.3%)	122 (0.9%)	
PARP inhibitor within first treatment line				
No	163 (95.9%)	676 (100.0%)	12,927 (100.0%)	
Yes	7 (4.1%)	0 (0.0%)	3 (0.0%)	

Statistically significant p-values are in bold.

[1.03–2.32]) compared with the gBRCAwt group. Sensitivity analyses using the landmark approach confirmed this trend (Supplementary Table 3). Descriptive analyses by type of BRCA alteration (BRCA1 versus BRCA2) showed a median PFS of 5.9 months (95% CI [2.9; 14.5]) and 6.9 months (95% CI [3.4; 12.9]) for BRCA1 and BRCA2, respectively. The median OS was 37.5 months (95% CI [9.9; NR]) and 38.7 months (95% CI [35.1; NR]) for BRCA1 and BRCA2, respectively.

Outcome of patients treated with first-line chemotherapy by gBRCA status

A total of 7372 patients (53.5%) received front-line chemotherapy as part of first-line MBC treatment (+/- ET and +/- targeted therapy) with 124, 410 and 6838 patients in the gBRCAm, gBRCAwt, and untested groups at baseline, respectively. Bevacizumab was associated with chemotherapy in 2194 (29.8%) patients. Maintenance ET was proposed for 69 (55.6%), 257 (62.7%), and 4375 (64%) patients in the gBRCAm, gBRCAwt, and untested groups, respectively. Anthracycline and/or taxane-based chemotherapy accounted for 83.5% of the chemotherapy regimens. The characteristics of the patients are listed in Supplementary Table 6. Median PFS1 and OS were 9.5 (7.6–10.7) and 34.9 (26.7–44.1) months, respectively, in the gBRCAm patients receiving front-line chemotherapy. In a multivariable analysis using gBRCA status as a time-dependent variable and adjusted for age, visceral metastasis, number of metastatic sites, and metastasis-free interval, outcomes were similar for gBRCAm patients who received first-line chemotherapy compared with the gBRCAwt group (OS: adjusted HR [95% CI]: 1.12 [0.88–1.41]) and (PFS1: adjusted HR [95% CI]: 1.09 [0.90–1.31]). (Table 2, Fig. 2, and Supplementary Table 3). Only descriptive analyses were performed for type of BRCA alteration (1 versus 2) given the small numbers of patients. The median PFS was 5.4 months (95% CI [3.8; 7.4]) and

10.7 months (95% CI [9.4; 14.3]) for BRCA1 and BRCA2 altered groups, respectively. The median OS was 21.2 months (95% CI [9.5; 34.9]) and 43.4 months (95% CI [31.4; 51.4]) for BRCA1 and BRCA2 altered groups, respectively.

DISCUSSION

This large unique real-world dataset enables a comprehensive analysis of the prognostic impact of gBRCA status in patients with hormone receptor-positive, HER2-negative MBC. We found that these patients have a median OS of 36.5 months (33.4–42.9), which is less than would have been expected in this setting, despite a pre-CDK4/6 inhibition era [14]. Of note, a recent study using the Flatiron Health electronic health record database identified 165 gBRCAm patients with HR-positive/HER2-negative metastatic disease [15]. Their median OS was 38 months (30.8–42.9), which appears similar to our population and confirms the representation of our data. Our data strongly suggest an independent detrimental effect of gBRCA mutations on both PFS1 and OS in the overall population, as well as among patients who received first-line endocrine treatment. However, this negative effect disappeared in patients who received front-line chemotherapy.

The prognostic impact of gBRCA status has been widely reported in early settings with discordant results with respect to the impact of gBRCAm [4, 16–23]. In the metastatic setting, data are very scarce, though we confirmed a more aggressive tumour phenotype for gBRCAm patients versus gBRCAwt patients with primarily grade 3 tumours, which reflects an over-representation of the luminal B-like HR+ breast cancer phenotype [24, 25]. However, the detrimental OS impact of gBRCA mutations in the present study remained after adjusting for different classical prognostic factors. In contrast, a recent study which included 2595

Table 2. Survival analysis for the overall population and according to first-line therapy (endocrine therapy or chemotherapy).

	Overall population		Patients treated with first line endocrine therapy		Patients treated with 1st line chemotherapy (+/- endocrine therapy)	
	Adjusted HR [95% CI]	<i>p</i>	Adjusted HR [95% CI]	<i>p</i>	Adjusted HR [95% CI]	<i>p</i>
Overall survival						
<i>gBRCAwt</i>	1		1		1	
<i>gBRCAm</i>	1.26 [1.03–1.55]	0.024	1.54 [1.03–2.32]	0.037	1.12 [0.88–1.41]	0.350
<i>gBRCA</i> untested	1.13 [1.03–1.25]	0.010	1.25 [1.05–1.49]	0.012	1.09 [0.98–1.23]	0.125
1st line Progression-free survival						
<i>gBRCAwt</i>	1		1		1	
<i>gBRCAm</i>	1.21 [1.03–1.41]	0.017	1.58 [1.17–2.12]	0.003	1.09 [0.90–1.31]	0.379
<i>gBRCA</i> untested	1.02 [0.95–1.10]	0.551	1.09 [0.97–1.24]	0.149	0.98 [0.90–1.07]	0.698

Statistically significant *p*-values are in bold.

The adjusted Hazard Ratios were estimated using a multivariable Cox model including *gBRCA* status as a time-varying variable.

MBC patients with 129 *gBRCAm*, did not shown an effect of *gBRCA* mutation on patient outcome [26]. This small cohort, however, included both HR-positive and HR-negative MBC patients and no subgroup analysis was performed.

The inferior OS observed among *gBRCAm* patients is remarkable for patients receiving first-line ET, with a hazard ratio of 1.54 [1.03–2.32] compared with *gBRCAwt* patients in multivariable analyses. In addition, *gBRCAm* patients had a significantly lower PFS1 with front-line ET compared with *gBRCAwt* patients, with a median PFS1 of 6.9 months for the front-line ET group. Although this number appears very low, it is concordant with that of a small study showing a median PFS of 7.8 months in the same context [27]. Similar lower PFS in *gBRCAm* patients are reported with ET combined with CDK4/6 inhibitors which is now a standard front-line treatment for HR+/HER2– MBC [8]. The registration trials for CDK4/6 inhibitors lacked pre-specified subgroup analysis plans for *gBRCA1/2m* carriers. However, in a pooled analysis of the MonALEEsa two, three, and seven trials, ctDNA *BRCA1/2m* patients had a median PFS of 7.06 months with ET alone, whereas median PFS was not reached with ribociclib (HR 0.3 95% CI [0.15–0.61]) [9]. In the PADA-1 trial, our group reported that *gBRCAm* or *gPALB2m* patients tended to have a shorter PFS with first-line aromatase inhibitor plus palbociclib compared with that of *gBRCAwt* patients (14.3 m (CI95% [10.4; NR]) versus 26.7 m (95% CI [24.1; 29.4]); HR 0.58 (CI95%[0.2–1.02]), *p* = 0.056) [10]. This observation was supported by two recent studies [12, 28]. In a MSKCC patient cohort, *gBRCA2* alterations were significantly associated with inferior PFS (HR 2.17, 95% CI 1.46–3.22, *p* < 0.001) for first-line treatment with CDK4/6 inhibitor plus ET [28]. In this study, the 24 *gBRCA2m* patients exhibited a median PFS of seven months [4.0–10.0] with front-line CDK4-6 inhibitor. The median PFS was very similar to that observed in our study population.

One potential explanation is that *BRCA* deficiency and the subsequent defect in homologous repair (HRD) remains a key driver for HR+ tumours arising in *gBRCAm* patients. PARP inhibitors are effective in the metastatic setting irrespective of HR status, which highlights the importance of HRD, even in the context of HR + MBC [6, 7]. Genomic analysis revealed a specific mutational signature (signature 3) for HR+/HER2– MBC harbouring HRD [29]. Most *BRCA1m* HR + tumours exhibit a BRCAness copy number profile and LOH, indicating that a loss of functional *BRCA1* protein plays a central role in tumorigenesis [30]. Meanwhile, evidence of endocrine resistance in patients with HRD dominant HR+/HER2– is increasing. In a study based on the MSK-IMPACT cohort, patients with HRD HR+/HER2– MBC experienced shorter PFS on ET +/- CDK4/6i (7.6 m [5.3–12.3]; HR = 1.71 [1.2–2.5]; *p* = 0.006) suggesting that the genomic instability

conferred by HRD results in early resistance [31]. Similarly, patients with tumours harbouring HRD-related genomic scars at the initiation of palbociclib had a significantly worse PFS in a recent study and, as expected, *BRCA1/2* mutations were significantly associated with the HRD index [32]. The link between HRD and endocrine resistance is still to be investigated. The occurrence rate of *ESR1* mutation under endocrine therapy was not more predominant in *BRCA1/2m* compared to *BRCAwt* MBC patients in a sub study of the PADA1 trial but additional data are necessary [10].

These data suggest that HR + BC in *gBRCAm* carriers are unique at the molecular level and early introduction of a PARP inhibitor may be effective for HR + *gBRCAm* patients. Combination trials of ET, CDK4/6 inhibitors, and PARP inhibitors in *gBRCAm* patients are ongoing and may answer this important question. These findings may be relevant to determine the choice of adjuvant treatment in the context of high clinical risk disease in *gBRCAm* HR + patients. Indeed, there are currently two options that should be discussed in this setting: either one year of olaparib or 2 years of abemaciclib combined with ET.

In addition, we would point out that in *gBRCAm* patients, higher recurrent score as assessed by Oncotype DX test are noted as compared to *BRCAwt* patients [3]. This finding may reflect that the biology of *gBRCAm* HR + BC is biased toward a more aggressive behaviour. Moreover, higher RS is associated with increased sensitivity to chemotherapy. These findings may show that chemotherapy plays a more important role for *gBRCAm* HR + BC than endocrine treatment, and provide additional arguments to explain our results.

Several limitations of our study should be considered. First, the study was retrospective, even though the data was collected with a clinical trial-like methodology. PFS assessment is a major challenge in RWD studies. In ESME, data are collected in a clinical trial-like fashion, through an independent assessment of patients' files. This ensures that the strict definition of PFS we use is homogeneously applied throughout the dataset. Second, the very poor OS observed in patients who received endocrine treatment first could be linked to biased baseline characteristics leading to this choice, such as a poorer general condition. Propensity score weighting could help clarify this issue but the limited number of patients precludes this approach. Third, the management of patients was done before CDK4/6 and PARP inhibitors became available era and chemotherapy was commonly used as first line in the early years of the cohort. This limits the interpretation of some data given the current importance of these drugs in current treatment protocols. Indeed, the combination of CDK4/6 inhibitors with ET should still be offered to every eligible patients as stated

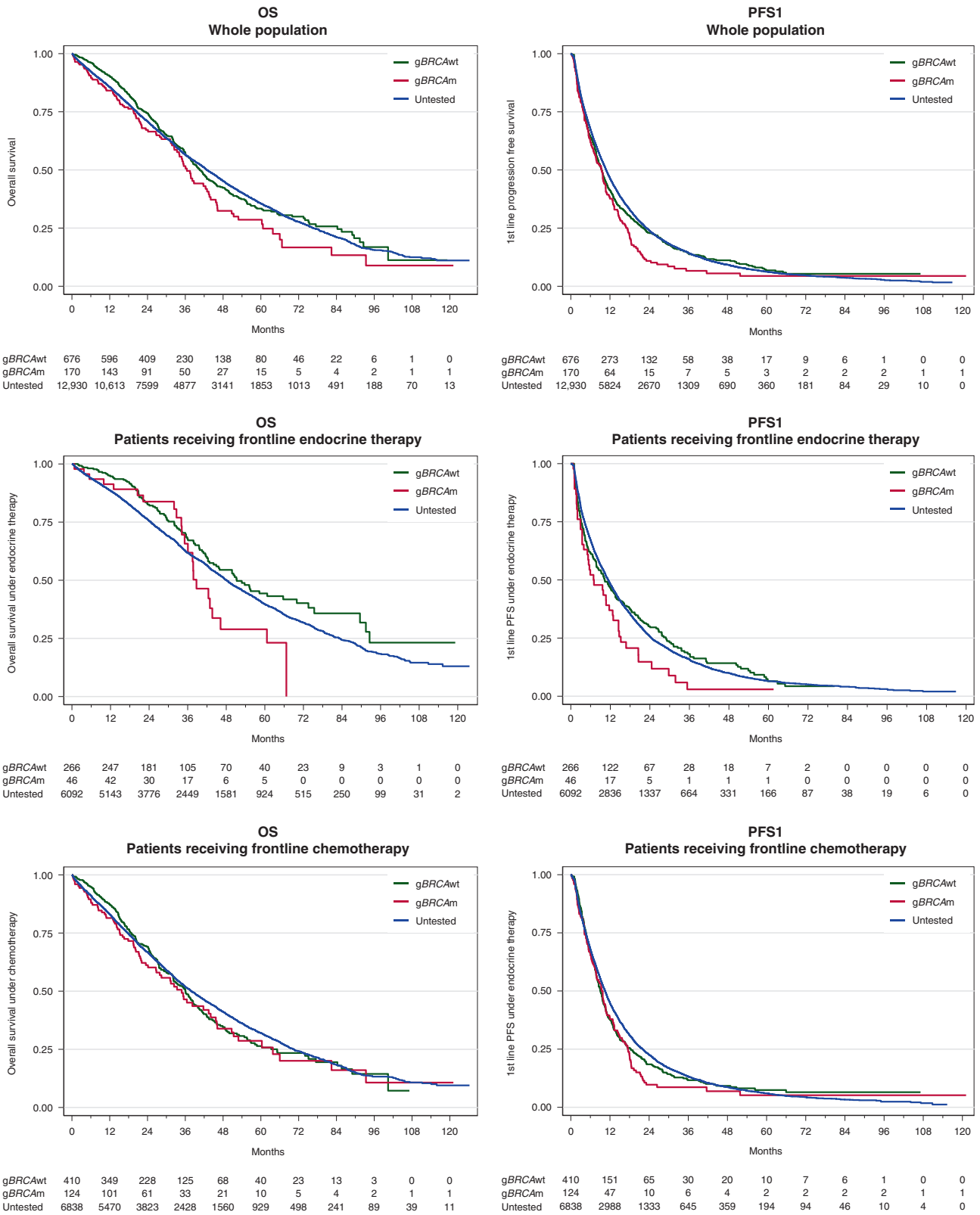


Fig. 2 Overall survival and first-line progression-free survival according to gBRCA groups at treatment initiation and type of first-line treatment. gBRCAwt, gBRCAm and untested patients are pictures in green, red and blue respectively.

in the guidelines. Finally, a limited portion of the population was tested for gBRCA status, and indications were primarily based on non-theranostic approaches at that time. We could not completely rule out biases linked to the setting of gBRCA testing and its

potential association with specific tumour features and behaviours, as well as survivors' biases. This has been widely described in retrospective studies assessing the prognosis of localised breast cancer patients according to gBRCA status. In the present study,

the setting was metastatic disease. Prognosis is assessed according to baseline status, which avoids most of these biases. Furthermore, time-varying analyses include both the onset of new mutant or wild type status. Several sensitivity analyses as well as landmark analyses were implemented to limit these potential biases.

CONCLUSION

In a large, real-world cohort of HR-positive/HER2-negative MBC patients treated in the pre-CDK4/6 inhibitor era, *gBRCAm* status was associated with a lower OS mostly driven by a lower progression-free and OS in patients who received first-line ET. However, eligible HR-positive/HER2-negative MBC patients with *gBRCAm* should receive first-line ET combined with CDK4-6 inhibitors as stated in guideline. Future clinical trials combining ET, CDK4-6 inhibitors, and new PARP inhibitors may significantly improve the management of this disease

DATA AVAILABILITY

All data are contained in the ESME database, which is managed by Unicancer (<http://www.unicancer.fr/>). However, the ESME database is not publicly available for the following reason: in the ESME Research programme, public data sharing is not automatic in order to ensure that only trained users can analyse the ESME datasets. The analysis datasets will be made available only under data transfer and use agreements executed between Unicancer and the potential licensee. Interested parties should contact the corresponding author. Amélie Lusque had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data supporting the findings of this study are available from UNICANCER but restrictions apply to the availability of these data, which was used under licence for this study and is therefore not publicly available. However, the data are available from the authors upon reasonable request and with permission from UNICANCER.

CODE AVAILABILITY

Codes used to generate the data are available upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualisation JSF, AL, SD, AMa, WJ, TDLM. Formal analysis JSF, AL, SD, AMa, WJ, TDLM. Project administration MC. Investigation JSF, AL, SD, JMF, TB, ID, CL, JCE, AG, AP, MAM, JCT, TP, LC, LU, MD, MC, WJ, TDLM. Writing original draught JSF, AL, SD, AMa, WJ, TDLM. Writing review and editing JSF, AL, SD, JMF, TB, ID, CL, JCE, AG, AP, MAM, JCT, TP, LC, LU, MD, MC, WJ, TDLM

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COMPETING INTERESTS

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

ESME MBC database was authorised by the French data protection authority (Registration ID 1704113 and authorisation N°DE-2013-117).

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to J.-S. Frenel.

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