Prognosis and efficacy of frontline treatment for HR+ HER2- metastatic breast cancer occurring in gBRCA1/2 carriers

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Background

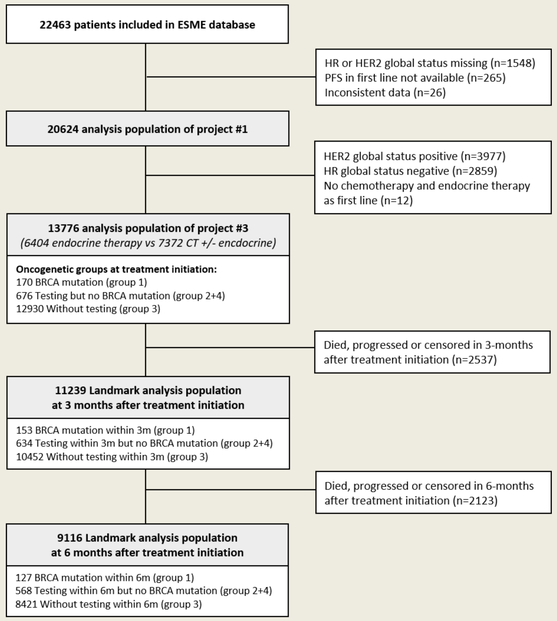
HR+/HER2- subtype accounts for a significant proportion of breast cancers occurring in germline BRCA1/2 mutation (gBRCAm) carriers.

The prognosis and the best management of these patients compared to HR+/HER2- BRCA1/2 wild type (gBRCAwt) patients is largely unknown.

We evaluated overall survival (OS) and progression-free survival (PFS) under first-line endocrine therapy (ET) or chemotherapy (CT) +/- ET among gBRCAm and gBRCAwt patients (pts) using the ESME database

ESME database and Flowchart

ESME is a unique French national multicenter cohort, collecting retrospectively data using clinical trial-like methodology.



Population characteristics according to BRCA1/2 status defined at treatment initiation

	BRCA status			
	Wild Type (N = 676)	Not Tested (N = 12930)	gBRCAm (N = 170)	p-value
Age at metastatic disease diagnosis				<0.0001
Median (years)	51.0	62.0	47.0	
(Range)	(26.0;88.0)	(22.0;103.0)	(26.0;82.0)	
Age at metastatic disease diagnosis				<0.0001
< 50 years	314 (46.4%)	2358 (18.2%)	101 (59.4%)	
50-70 years	306 (45.3%)	6947 (53.7%)	57 (33.5%)	
> 70 years	56 (8.3%)	3625 (28.0%)	12 (7.1%)	
Gender				0.0163
Female	663 (98.1%)	12801 (99.0%)	166 (97.6%)	
Male	13 (1.9%)	129 (1.0%)	4 (2.4%)	
Histological grade				<0.0001
Grade I	74 (13.1%)	1541 (14.4%)	7 (4.9%)	
Grade II	319 (56.6%)	6532 (60.9%)	74 (51.4%)	
Grade III	171 (30.3%)	2661 (24.8%)	63 (43.8%)	
Missing	112	2196	26	
Histological type				<0.0001
Invasive ductal carcinoma	505 (75.3%)	9146 (72.2%)	134 (79.3%)	
Invasive lobular carcinoma	76 (11.3%)	2177 (17.2%)	13 (7.7%)	
Other	90 (13.4%)	1351 (10.7%)	22 (13.0%)	
Missing	5	256	1	
De novo metastatic disease				<0.0001
No	650 (96.2%)	8997 (69.8%)	160 (94.1%)	
Yes	26 (3.8%)	3900 (30.2%)	10 (5.9%)	
Missing	0	33	0	
Number of metastatic sites				0.0034
1 site	366 (54.1%)	7252 (56.1%)	78 (45.9%)	
2 sites	165 (24.4%)	3036 (23.5%)	37 (21.8%)	
>=3 sites	145 (21.4%)	2642 (20.4%)	55 (32.4%)	
Type of Metastases				<0.0001
Central nervous system	32 (4.7%)	507 (3.9%)	24 (14.1%)	
Visceral non-CNS	351 (51.9%)	6403 (49.5%)	91 (53.5%)	
Non Visceral	293 (43.3%)	6020 (46.6%)	55 (32.4%)	
Bone only metastases				<0.0001
No	507 (75.0%)	8898 (68.8%)	136 (80.0%)	
Yes	169 (25.0%)	4032 (31.2%)	34 (20.0%)	
Endocrine therapy (first line or maintenance)				<0.0001
No	153 (22.6%)	2463 (19.0%)	55 (32.4%)	
Yes	523 (77.4%)	10467 (81.0%)	115 (67.6%)	
CDK4-6 (first line or maintenance)				
No	667 (98.7%)	12808 (99.1%)	170 (100.0%)	0.2858
Yes	9 (1.3%)	122 (0.9%)	0 (0.0%)	
Chemotherapy (first line)				<0.0001
No	266 (39.3%)	6092 (47.1%)	46 (27.1%)	
Yes	410 (60.7%)	6838 (52.9%)	124 (72.9%)	
Bevacizumab (first line)				<0.0001
No	483 (71.4%)	10962 (84.8%)	132 (77.6%)	
Yes	193 (28.6%)	1968 (15.2%)	38 (22.4%)	
Parp inhibitor (first line)				
No	676 (100.0%)	12927 (100.0%)	163 (95.9%)	
Yes	0 (0.0%)	3 (0.0%)	7 (4.1%)	

Methods

- **gBRCA1/2 status** was defined in three groups (**gBRCAm /BRCAwt /untested**) at any time during disease course using a time-varying approach and at different time points using a landmark approach: at 1st treatment initiation (baseline status), within the first three months of starting treatment or within the first six months.
- **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 the immortal-time bias. Thus, gBRCA status changes over time. A patient can switch from untested status to gBRCAm or BRCAwt status.**
- **Sensitivity analyses were carried out by defining gBRCA status at different time points to prevent immortal-time bias**

Survival analysis in the overall population and according to first line treatment

Overall population

	Median (months) [95%CI]	Time-varying analysis Adjusted HR [95%CI]	p-value
Progression free survival			
gBRCA m	9.4 [7.0-10.7]	1	
gBRCA wt	9.5 [8.5-10.3]	0.83 [0.71-0.97]	**0.017**
gBRCA untested	10.8 [10.6-11.1]	0.85 [0.73-0.98]	**0.021**
Overall survival			
gBRCA m	36.5 [33.4-42.9]	1	
gBRCA wt	40.6 [37.8-44.1]	0.79 [0.65-0.97]	**0.024**
gBRCA untested	42.8 [42.0-44.0]	0.90 [0.75-1.08]	0.250

Patients treated with 1st line endocrine therapy

	Median (months) [95%CI]	Time-varying analysis Adjusted HR [95%CI]	p-value
Progression free survival			
gBRCA m	6.9 [3.4-12.7]	1	
gBRCA wt	10.3 [7.8-13.4]	0.63 [0.47-0.85]	**0.003**
gBRCA untested	11.4 [10.8-11.9]	0.69 [0.53-0.91]	**0.009**
Overall survival			
gBRCA m	38.7 [35.1-46.2]	1	
gBRCA wt	51.3 [42.8-65.7]	0.65 [0.43-0.97]	**0.037**
gBRCA untested	48.1 [46.7-49.5]	0.81 [0.56-1.18]	0.273

Patients treated with 1st line chemotherapy

	Median (months) [95%CI]	Time-varying analysis Adjusted HR [95%CI]	p-value
Progression free survival			
gBRCA m	9.5 [7.6-10.7]	1	
gBRCA wt	9.1 [8.1-9.9]	0.92 [0.77-1.11]	0.379
gBRCA untested	10.5 [10.1-10.8]	0.90 [0.77-1.07]	0.238
Overall survival			
gBRCA m	34.9 [26.7-44.1]	1	
gBRCA wt	36.0 [32.2-38.5]	0.89 [0.71-1.13]	0.350
gBRCA untested	37.9 [36.6-39.3]	0.98 [0.79-1.21]	0.844

The survival medians were estimated by the Kaplan-Meier method according to gBRCA status defined at first line initiation and adjusted Hazard Ratios by multivariable Cox model including gBRCA status as a time-varying variable and following covariates: age, type and number of metastases, metastasis-free interval.

Sensitivity analyses

	Analysis at treatment initiation		Landmark analysis at 3 months		Landmark analysis at 6 months	
	Adjusted HR [95%CI]	p-value	Adjusted HR [95%CI]	p-value	Adjusted HR [95%CI]	p-value
Overall population	n=13743		n=11210		n=9090	
Progression free survival						
gBRCA m	1		1		1	
gBRCA wt	0.82 [0.68-0.97]	**0.024**	0.79 [0.66-0.96]	**0.016**	0.77 [0.62-0.95]	**0.014**
gBRCA untested	0.83 [0.70-0.97]	**0.019**	0.81 [0.68-0.96]	**0.013**	0.81 [0.67-0.98]	**0.030**
Overall survival						
gBRCA m	1		1		1	
gBRCA wt	0.82 [0.65-1.02]	*0.081*	0.81 [0.63-1.04]	*0.093*	0.80 [0.60-1.08]	0.143
gBRCA untested	0.82 [0.67-1.00]	*0.056*	0.81 [0.64-1.01]	*0.062*	0.80 [0.62-1.04]	*0.099*
Patients treated with 1st line endocrine therapy	n=6383		n=5100		n=4164	
Progression free survival						
gBRCA m	1		1		1	
gBRCA wt	0.68 [0.49-0.95]	**0.022**	0.60 [0.41-0.88]	**0.009**	0.56 [0.37-0.86]	**0.009**
gBRCA untested	0.73 [0.54-0.99]	**0.046**	0.69 [0.49-0.98]	**0.040**	0.69 [0.46-1.02]	*0.064*
Overall survival						
gBRCA m	1		1		1	
gBRCA wt	0.70 [0.45-1.11]	0.128	0.59 [0.34-1.03]	*0.063*	0.43 [0.23-0.80]	**0.008**
gBRCA untested	0.80 [0.53-1.21]	0.297	0.73 [0.44-1.21]	0.220	0.54 [0.30-0.95]	**0.034**
Patients treated with 1st line chemotherapy	n=7360		n=6110		n=4926	
Progression free survival						
gBRCA m	1		1		1	
gBRCA wt	0.89 [0.72-1.10]	0.283	0.91 [0.73-1.13]	0.393	0.90 [0.71-1.15]	0.409
gBRCA untested	0.86 [0.71-1.04]	0.118	0.86 [0.71-1.05]	0.143	0.88 [0.70-1.10]	0.248
Overall survival						
gBRCA m	1		1		1	
gBRCA wt	0.93 [0.71-1.20]	0.560	0.96 [0.72-1.27]	0.767	1.05 [0.76-1.46]	0.767
gBRCA untested	0.87 [0.69-1.10]	0.253	0.90 [0.70-1.15]	0.400	0.97 [0.72-1.30]	0.838

Sensitivity analyses are carried out by defining gBRCA status at different time points to prevent immortal-time bias: at first line initiation or using a Landmark approach at three or six months after first line initiation

Conclusions

In this large real life cohort of pts treated in the pre-CDK4/6 inhibitors era, *gBRCA* status is an independent adverse prognostic factor for patients treated with 1st line endocrine therapy

By contrast, no prognostic effect of *gBRCA* status was found in patients treated with 1st line chemotherapy.

This finding may reflect differences in the oncogenic processes and driver landscape involved in luminal BRCA-associated metastatic breast tumors compared to sporadic tumors.

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Disclosure

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