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Treatment and outcomes of older versus younger women with HER2-positive metastatic breast cancer in the real-world national ESME database

Mylène Annonay, MD [a], Lisa Gauquelin, MD [b, c], Romain Geiss, MD [d], Mony Ung, MD [e], Laurence Cristol-Dalstein, MD [f], Marie-Ange Mouret-Reynier, MD PHD [g], Anthony Goncalves, MD PHD [h], Sophie Abadie-Lacourtoisie, MD [i], Eric Francois, MD [j], Christophe Perrin, MD [k], Johan Le Fel, MD [l], Véronique Lorgis, MD [m], Véronique Servent, MD [n], Lionel Uwer, MD [o], Christelle Jouannaud, MD [p], Marianne Leheurteur, MD [l], Florence Joly, MD PHD [q], Loic Campion, MD [r, s], Coralie Courtinard, MPH [c, t], Olivier Villacroux, MD [u], Thierry Petit, MD PHD [v], Pierre Soubeyran, MD [a], Catherine Terret, MD [w], Carine Bellera, PHD [b, c], Etienne Brain, MD PHD [d], Suzette Delaloge, MD MPH [x, *]

[a] Department of Medical Oncology, Institut Bergonié, Bordeaux, France
[b] Clinical and Epidemiological Research Unit, Institut Bergonié, Bordeaux, France
[c] Epicene Team (Cancer & Environnement), Bordeaux Population Health Center, ISPED, Centre INSERM U1219, INSERM, Bordeaux, France
[d] Department of Medical Oncology, Institut Curie, Saint-Cloud, France
[e] Department of Oncology, Institut Claudius Regaud, IUCT-Oncopole, Toulouse, France
[f] Department of Medical Oncology, Institut du Cancer de Montpellier, Montpellier, France
[g] Department of Medical Oncology, Centre Jean Perrin, Clermont Ferrand, France
[h] Department of Medical Oncology, Institut Paoli-Calmettes, Marseille, France
[i] Department of Medical Oncology, Institut de Cancérologie de l'Ouest Nantes & Angers, France
[j] Department of Medical Oncology, Centre Antoine Lacassagne, Nice, France
[k] Department of Medical Oncology, Centre Eugéne Marquis, Rennes, France
[l] Department of Medical Oncology, Centre Henri Becquerel, Rouen, France
[m] Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France
[n] Department of Medical Oncology, Centre Oscar Lambret, Lille, France
[o] Department of Medical Oncology, Institut de Cancérologie de Lorraine, Vandœuvre-lès-Nancy, France
[p] Department of Medical Oncology, Institut de Cancérologie Jean-Godinot, Reims, France
[q] Department of Medical Oncology, Centre François Baclesse, Caen, France
[r] Oncology Data Factory and Analytics, Institut de Cancérologie de l'Ouest, France
[s] CRCINA, University of Nantes, INSERM UMR 1232, CNRS-ERL6001, Nantes, France
[t] Unicancer, Direction des Données, Paris, France
[u] Institut de Cancérologie de l'Ouest Nantes & Angers, France
[v] Department of Medical Oncology, Centre Paul Strauss, Strasbourg, France
[w] Department of Medical Oncology, Centre Leon Berard, Lyon, France
[x] Department of Cancer Medicine, Gustave Roussy, Villejuif, France

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ABSTRACT

Background: Treatment and outcomes of patients with HER2-positive (HER2+) metastatic breast cancer (MBC) have dramatically improved over the past 20 years. This work evaluated treatment patterns and outcomes according to age.

Methods: Women who initiated a treatment for HER2+ MBC between 2008 and 2016 in one of the 18 French comprehensive centers part of the ESME program were included. Objectives were the description of first-line treatment patterns, overall survival (OS), first-line progression-free survival (PFS), and prognostic factors among patients aged 70 years or more (70+), or less than 70 (<70).

* Corresponding author. Department of Medical Cancer medicine, Institut Gustave Roussy, 114 Rue Edouard Vaillant, 94805, Villejuif, France.
E-mail address: suzette.delaloge@gustaveroussy.fr (S. Delaloge).

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Results: Of 4045 women diagnosed with an HER2+ MBC, 814 (20%) were 70+. Standard first-line treatment (chemotherapy combined with an anti-HER2 therapy) was prescribed in 65% of 70+ versus 89% of <70 patients ($p < 0.01$). Median OS was 49.2 (95% CI, 47.1–52.4), 35.3 (95% CI, 31.5–37.0) and 54.2 months (95% CI, 50.8–55.7) in the whole population, in patients 70+ and <70, respectively. Corresponding median PFS1 were 12.8 (95% CI, 12.3–13.3), 11.1 (95% CI, 10.0–12.3) and 13.2 months (95% CI, 12.7–13.9), respectively. In 70+ women, initiation of non-standard first-line treatment had an independent detrimental time-varying effect on both OS and PFS (HR on OS at 1 year: chemotherapy without anti-HER2 2.79 [95% CI: 2.05–3.79]; endocrine therapy and/or anti-HER2 1.96 [95% CI: 1.43–2.69]).
Conclusions: In this large retrospective real-life database, older women with HER2+ MBC received standard first-line treatment less frequently than younger ones. This was independently associated with a worse outcome, but confounding factors and usual selection biases cannot be ruled out.

1. Introduction

Aging is the most important risk factor for developing cancer. Breast cancer (BC) is not an exception to the rule, with a median age of 62 years at diagnosis, 40–50% being diagnosed at age 70 or older in western countries [1]. Human epidermal growth factor receptor 2-positive (HER2+) BC, defined by an overexpression of *HER2* or a HER2 gene amplification accounts for 20% of metastatic BC (MBC) and 10% of older patients with cancer [2,3]. Since the early 2000s, many anti-HER2 therapies have revolutionized the prognosis of HER2+ MBC patients, from trastuzumab added to first-line chemotherapy [4] to the more recent dual anti-HER2 blockade adding a second antibody, pertuzumab, increasing further overall survival (OS) by 16 months [5]. Both lapatinib and T-DM1 contributed also to the global improvement of HER2+ MBC prognosis [6–8], and the list of anti-HER2 treatments has been updated very recently with tucatinib and new antibody-drug conjugates as DS-8201 [9,10]. Most of these strategies show a good safety profile, although data available are sparse in older patients [11–13]. Indeed, older patients remain underrepresented in clinical trials. Moreover, when enrolled, they do not reflect those seen in routine oncology practice because of restrictive eligibility criteria [14,15]. Older patients also show poorer outcome compared with younger ones, even when adjusted for classical prognostic tumours characteristics [16].

The American Society of Clinical Oncology supports high-quality observational studies as complementary to randomized controlled trials (RCTs) to improve evidence-based practice [17]. Unveiling information absent in highly selected settings as most RCTs, observational data can help generating hypotheses, especially for populations underrepresented in RCTs, such as older patients. Observational data however require cautious interpretation to address the usual confounding factors and lack of control [18]. Large observational real-life datasets, such as the longitudinal Epidemiology Strategy and Medical Economics (ESME) MBC database, represent an opportunity to investigate treatment real-life patterns and outcomes for distinct subgroups of MBC patients. RCT data on anti-HER2 treatments and outcome in older patients with MBC being limited, objectives were to describe treatment patterns, overall survival (OS) and first-line progression-free survival (PFS) in women with HER2+ MBC aged 70 and older (70+), as compared to younger ones (<70) over the last decade, based on the ESME real-life database [19].

2. Patients and methods

2.1. Overall study design

The French ESME MBC database (NCT03275311) is a national multicenter observational program. It collects real world data from all consecutive MBC patients aged ≥18 years who initiated their care at the time of MBC diagnosis, in the network of 18 French comprehensive cancer centers, starting from 2008 [2,20]. Patients referred "secondary" after they have initiated their first-line treatment elsewhere are not eligible for the cohort. Data are updated annually and include latest patients' and tumours' characteristics, outcomes and treatment patterns. ESME does not collect data on toxicity or patient reported outcomes.

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 re-use of their electronically recorded data. In compliance with French regulations, the ESME MBC database was authorized by the French data protection authority (Registration ID 1704113 and authorization N°DE-2013.-117). Moreover, in compliance with the applicable European regulations, a complementary authorization was obtained on 14-Oct-2019 regarding the ESME research Data Warehouse.

2.2. Patients selection

For the present study, all women in the ESME database who had a metastatic breast cancer classified as "HER2-positive" (HER2+) were selected. As described before, HER2 and HR status are derived from existing results about metastatic tissue sampling where available, or, if not available, from last sampling on early disease [8]. HER2+ means that the latest available sample of the tumor has a HER2 immunohistochemical score (IHC) 3+, or 2+ with a positive chromogenic/fluorescence in situ hybridization (CISH/FISH), whether hormone receptor positive or negative.

2.3. Definitions and endpoints

Tumours were defined as hormone receptors (HR) positive if ER and/or PgR expression was >10% by IHC. Metastases-free interval (MFI) was defined as the time between initial diagnosis and metastatic relapse, and categorized in three groups (≤6, 7–24, >24 months). First-line treatment was categorized as anti-HER2 therapy-based [combined with either chemotherapy (defined as "standard" 1st line treatment), or endocrine therapy, or their combination] or not anti-HER2 therapy-based (i.e. chemotherapy alone or endocrine therapy alone or their combination). The size of the treating centre was categorized according to the number of patients included in the ESME cohort (<700, 700–1399, ≥1400 patients). OS and PFS were defined as the delay between the date of diagnosis of MBC and the date of death (any cause), or the date of disease progression or death (any cause), respectively.

2.4. Statistical analyses

Qualitative variables were described using frequency, percentage and 95% confidence interval (95%CI) (binomial law). They were compared using a Chi^2 test or a Fisher's exact test whenever appropriate. Quantitative variables were described using mean and standard deviations if the normality assumption was satisfied; otherwise non-parametric statistics (median, range, quartiles) were reported and compared using non-parametric Wilcoxon tests. Median follow up was estimated using the reverse Kaplan–Meier estimator [21]. Survival times were described using the Kaplan-Meier method and the median survival times and rates with 95% CI were reported.

Regarding prognostic factors for time-to-event endpoints, independent analyses were carried out in the whole population, in the older one (70+) and in the younger one (<70). Univariate analyses were first performed using Cox's proportional hazards (PH) models. Variables significant at the 15%-level were fitted in multivariable models with final significance level set at 5%. The strength of the association was estimated using the hazard ratio (HR) reported with 95%CI. Prognostic factors investigated included: age at diagnosis of metastasis (<70 vs 70+ for the analysis in the whole population, continuously for the analysis per age group); tumour hormonal receptor status (ER+ and/or PgR + vs ER- and PgR-); number of metastatic sites (1, 2, 3 or more) at diagnosis of metastasis; visceral metastases at diagnosis of metastasis; de novo metastatic disease; MFI; choice of first-line treatment; size of the treating centre. Baseline performance status (PS) and body mass index (BMI) were not considered because of missing data exceeding 30%. The hypothesis of proportional hazards was assessed. When this assumption was not verified, variables were included in the Cox model using an interaction with time in order to provide unbiased estimations.

All analyses were conducted with SAS software, version 9.4 (SAS institute Inc., Cary NC, USA).

3. Results

3.1. Patients, tumours and first-line treatments characteristics

Of the 22463 patients available in the ESME MBC database and diagnosed between January 2008 and December 2016, 4045 (18.0%) had an HER2+ MBC, 814 of them (20.1%) being 70+ (Fig. 1). Median age in the whole population, in the 70+ and <70 groups was 57 (range: [20–93]), 77 (range: [70–93]) and 53 (range: [20–69]) years, respectively. Among older patients, 524 (64.4%) were 70–79, 274 (33.7%) 80–89, and 16 (2%) 90 years old and over. Additional patients and tumours' characteristics are reported in Table 1. Compared with women <70, older women had more often ER+ and/or PgR + disease (68.8% versus 63.0%, p = 0.01).

First line treatments received are described in Table 2. The distribution of standard first-line treatment (chemotherapy combined with an anti-HER2 treatment) was different according to the age group (p < 0.01). Younger women received standard first-line treatment more often than older women (89.1% vs 65.0%). They also overall received anti-HER2 therapy (alone or in combination) more often than women aged 70+ (92.3% vs 76.5%).

3.2. Overall survival and first-line progression free survival by age category

With a median follow up of 53.4 months (95% CI, 50.9–55.4), 2049 patients (50.7%) were alive at data cut off. Median overall survival was 49.2 months (95% CI, 47.1–52.4) in the whole cohort; 35.3 months (95% CI, 31.5–37.0) and 54.2 months (95% CI, 50.8–55.7) among women aged 70+ and <70, respectively (Fig. 2). Corresponding results for PFS were 12.8 (95% CI, 12.3–13.3), 11.1 (95% CI, 10.0–12.3) and 13.2 months (95% CI, 12.7–13.9), respectively (see Fig. 3).

3.3. Multivariate analyses

Table 3 describes the multivariate analysis of factors associated with OS in the different groups of patients. Within the whole cohort, this analysis retrieved classical prognostic factors associated with shorter OS, including increasing age (HR = 1.55; 95% CI, 1.38–1.73), higher number of metastatic sites (for modality 3 or more sites, HR = 2.10; 95% CI, 1.85–2.39), 6–24 months MFI (HR = 2.58; 95% CI, 2.25–2.95), presence of visceral metastases (HR = 2.67 at one year; 95% CI, 2.10–3.38). Longer OS was associated with positive hormone receptors (HR = 0.63 at one year; 95% CI, 0.56–0.71) and centers with a higher patient load (for 1400 or

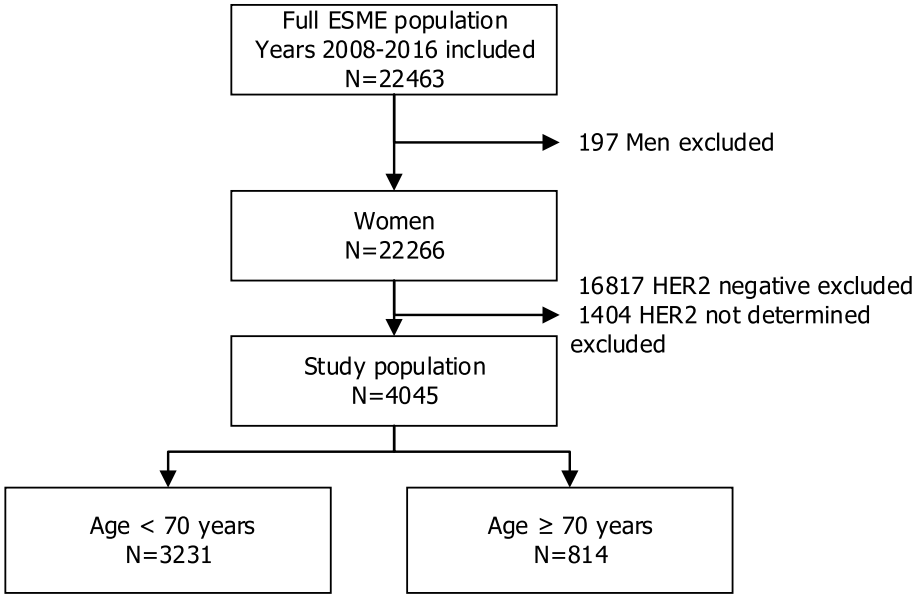

Fig. 1. Study flowchart.

Table 1
Characteristics of the patients.

Population (N)	All (4045)	70+ (814)	<70 (3231)
Patients characteristics			
Median age at diagnosis (years) (Q1;Q3)	57 (47–67)	77 (73–82)	53 (45–60)
PS at MBC diagnosis			
0	723 (17.9%)	67 (8.2%)	656 (20.3)
1	607 (15.0%)	123 (15.1%)	484 (15.0%)
2	175 (4.3%)	53 (6.5%)	122 (3.8%)
3	66 (1.6%)	18 (2.2%)	48 (1.5%)
4	10 (0.2%)	3 (0.4%)	7 (0.2%)
Missing	2464 (60.9%)	550 (67.6%)	1914 (59.2%)
BMI, median (Q1;Q3)	24.7 (21.6; 28.7)	25.2 (22.2; 29.3)	24.6 (21.5; 28.6)
Missing	1349 (33.3%)	319 (39.2%)	1030 (31.9%)
Tumours characteristics			
Histological type (primary tumor)			
IDC	3319 (82.1%)	633 (77.8%)	2686 (83.1%)
ILC	226 (5.6%)	69 (8.5%)	157 (4.9%)
IDC + ILC	36 (0.9%)	9 (1.1%)	27 (0.8%)
Breast cancer origin	17 (0.4%)	2 (0.2%)	15 (0.5%)
Other	399 (9.9%)	89 (10.9%)	310 (9.6%)
Missing	48 (1.2%)	12 (1.5%)	36 (1.1%)
Histological grade (primary tumor)			
Grade I	179 (4.4%)	49 (6.0%)	130 (4.0%)
Grade II	1629 (40.3%)	328 (40.3%)	1301 (40.3%)
Grade III	1589 (39.3%)	288 (35.4%)	1301 (40.3%)
Missing (Not determined, not available or not done)	648 (16.0%)	149 (18.3%)	499 (15.5%)
ER/PgR status			
ER + and/or PgR + (>10%)	2594 (64.1%)	560 (68.8%)	2034 (63.0%)
ER- and PgR-	1414 (35.0%)	247(30.3%)	1167 (36.1%)
Undetermined	37 (0.9%)	7 (0.9%)	30 (0.9%)
MFI (months)			
≤ 6 (de novo MBC)	1626 (40.2%)	311 (38.2%)	1315 (40.7%)
]6–24	562 (13.9%)	104 (12.8%)	458 (14.2%)
>24	1850 (45.7%)	398 (48.9%)	1452 (44.9%)
Missing	7 (0.2%)	1 (0.1%)	6 (0.2%)
Number of metastatic sites at diagnosis			
1	2099 (51.9%)	429 (52.7%)	1670 (51.7%)
2	1045 (25.8%)	211 (25.9%)	834 (25.8%)
≥ 3	866 (21.4%)	170 (20.9%)	696 (21.5%)
Missing	35 (0.9%)	4 (0.5%)	31 (1.0%)
Presence of visceral disease at diagnosis			
Yes	2606 (64.4%)	510 (62.7%)	2096 (64.9%)
No	1404 (34.7%)	300 (36.9%)	1104 (34.2%)
Missing	35 (0.9%)	4 (0.5%)	31 (1.0%)
Brain metastases at diagnosis			
Yes	591 (14.6%)	92 (11.3%)	499 (15.4%)
No	3454 (85.4%)	722 (88.7%)	2732 (84.6%)

ILC: Invasive lobular carcinoma; FISH: Fluorescence in situ hybridization; CISH: Chromogenic in situ hybridization; ER: Estrogen receptor; PgR: Progesterone receptor; MBC: Metastatic breast cancer; MFI: Metastasis free interval; NA: Not applicable.

more patients load, HR = 0.63; 95% CI, 0.50–0.78). Hormone receptors' effect decreased over time, disappearing at 5 years. On the opposite, the detrimental effect of visceral involvement increased over time. Finally, as compared to standard first-line treatment (chemotherapy combined with anti-HER2 therapy), non-standard treatments were associated with an increased risk of death during the first years.

In the 70+ group, same trends were reported for most variables, although with no time-varying effect for hormone receptor status (HR = 0.77; 95% CI, 0.62–0.95) and no impact of the size of the treating centre. Increased age was associated with shorter OS (HR = 1.05; 95% CI, 1.03–1.07).

Table 2
First-line treatment characteristics.

	All (N = 4045)	Women 70+ (N = 814)	Women <70 (N = 3231)
First-line treatment			
Anti-HER2 therapy + chemotherapy	3409 (84.3%)	529 (65.0%)	2880 (89.1%)
Chemotherapy without anti Her2	222 (5.5%)	68 (8.4%)	154 (4.8%)
Anti-HER2 + endocrine therapy	113 (2.8%)	63 (7.7%)	50 (1.5%)
Anti-HER2 therapy alone	85 (2.1%)	31 (3.8%)	54 (1.7%)
Endocrine therapy alone	117 (2.9%)	79 (9.7%)	38 (1.2%)
Missing	99 (2.4%)	44 (5.4%)	55 (1.7%)
Center size (number of patients/site)			
< 700	202 (5.0%)	31 (3.8%)	171 (5.3%)
700–1399	2865 (70.8%)	599 (73.6%)	2266 (70.1%)
≥1400	978 (24.2%)	184 (22.6%)	794 (24.6%)

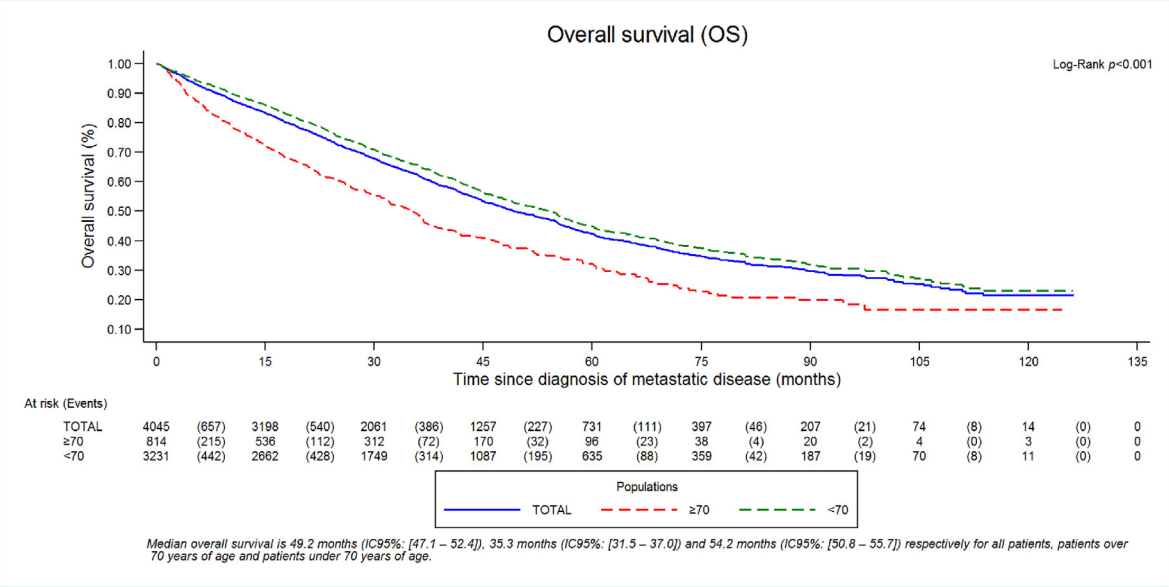

Fig. 2. OS in the whole study population and in the 70+ and <70 groups.

Results on the <70 group were similar to those found in the whole population.

Table 4 describes the multivariate analysis for PFS. In the whole population, independent prognostic factors for shorter PFS were similar to those for OS. As compared to chemotherapy with anti-HER2, both chemotherapy without anti-HER2 and treatment without chemotherapy/anti-HER2 were associated with an increased risk of progression over the first 3 years: HR = 1.93 [95% CI: 1.67–2.23] and HR = 1.75 [95%CI: 1.51–2.03] at 1 year, respectively.

In the 70+ group, same trends were observed for most variables. No association was found with the size of the treating centre. Older age was associated with shorter PFS (HR = 1.03; 95% CI, 1.01–1.04). Compared with chemotherapy + anti-HER2 therapy, chemotherapy alone had a deleterious non time-dependent effect on PFS (HR = 1.54 [95% CI: 1.18–2.02]), while treatment without chemotherapy had no real impact (HR = 0.86 [95% CI: 0.70–1.05]).

4. Discussion

To our knowledge, this report describes the largest real-life cohort of women aged 70 or older with HER2+ MBC treated with recent anti-HER2 therapies. Older patients being largely under-represented in clinical trials, including those investigating anti-HER2 therapies, very few data are available for this subpopulation [19,22]. For example, CLEOPATRA included only 126 patients aged 65 years or older, with a median age of 69 years [13]. Moreover, of 808 patients enrolled, only 19 were aged 75 or older. With striking numbers, we report on 814 women 70 years or older, with a median age of 77 years, more representative of daily clinical practice.

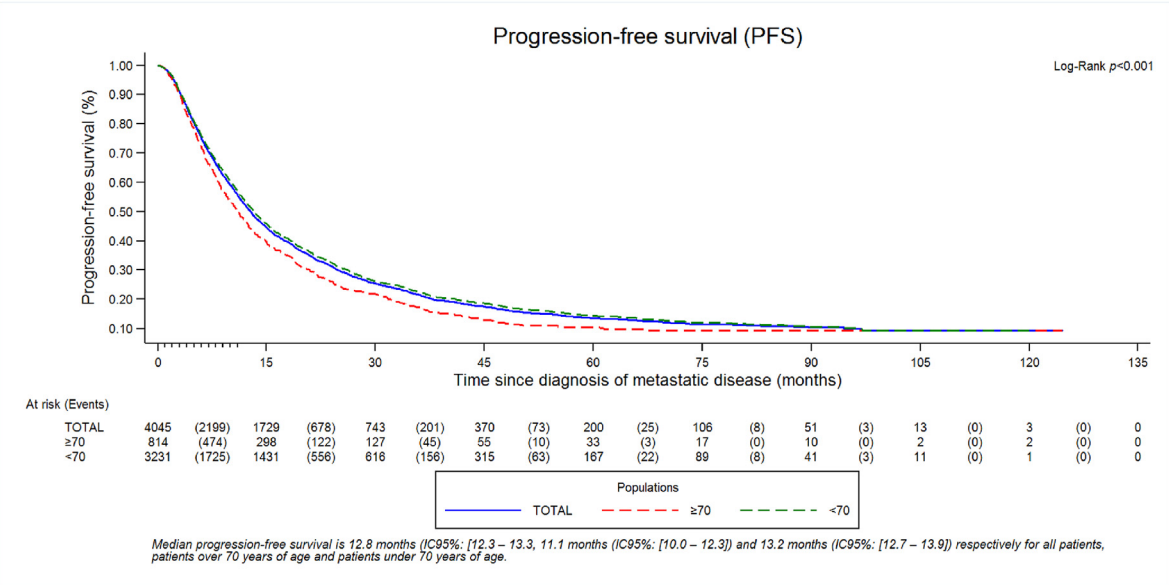

Fig. 3. First-line PFS in the whole study population and in the 70+ and <70 groups.

Table 3
Prognostic factors of overall survival in metastatic breast cancer patients in the ESME real-life database according to age.

	All women			70+			<70		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (reference: < 70) ≥70	1.55	[1.38; 1.73]	<0.01	NA			NA		
Age (continuous variable)	NA			1.05	[1.03; 1.07]	<0.01	1.01	[1.00; 1.01]	0.05
Number of metastatic sites at metastatic diagnosis (reference: 1 site)						<0.01			<0.01
2 sites	1.32	[1.18; 1.49]		1.29	[1.01; 1.65]		1.34	[1.17; 1.53]	
3 sites or more	2.10	[1.85; 2.39]	<0.01	1.87	[1.43; 2.45]		2.17	[1.88; 2.51]	
Visceral metastatic disease (reference: none) (*)			<0.01			<0.01			<0.01
Time-varying effect:									
Estimated HR at 1 year	2.67	[2.10; 3.38]		1.91	[1.21; 3.03]		3.11	[2.33; 4.14]	
Estimated HR at 3 years	3.89	[3.07; 4.94]		2.48	[1.56; 3.92]		4.75	[3.56; 6.32]	
Estimated HR at 5 years	5.68	[4.47; 7.20]		3.20	[2.02; 5.07]		7.24	[5.44; 9.65]	
ER/PgR status (reference: both ER- and PgR-)			<0.01			0.02			<0.01
If no time-varying effect, estimated average HR									
Positive ER or positive PgR	NA	NA		0.77	[0.62; 0.95]		NA		
Undetermined ER/PgR status	NA	NA		1.67	[0.68; 0.95]		NA		
If time-varying effect, estimated HR at 1 year									
Positive ER and/or PgR	0.63	[0.56; 0.71]		NA			0.60	[0.52; 0.68]	
Undetermined ER/PgR status	0.54	[0.32; 0.91]		NA			0.45	[0.24; 0.83]	
If time-varying effect, estimated HR at 3 years									
Positive ER and/or PgR	0.79	[0.71; 0.89]		NA			0.76	[0.67; 0.87]	
Undetermined ER/PgR status	0.68	[0.40; 1.14]		NA			0.57	[0.31; 1.06]	
If time-varying effect, estimated HR at 5 years									
Positive ER and/or PgR	1.00	[0.89; 1.12]		NA			0.97	[0.85; 1.12]	
Undetermined ER/PgR status	0.85	[0.50; 1.43]		NA			0.73	[0.39; 1.36]	
First-line treatment (reference: chemotherapy + anti-HER2 therapy)			0.01			<0.01			
If time-varying effect, estimated HR at 1 year									
Chemotherapy without anti-HER2 therapy (±endocrine therapy)	3.40	[2.86; 4.05]		2.79	[2.05; 3.79]		3.77	[3.04; 4.66]	
Anti-HER2 therapy alone or endocrine therapy alone or both	2.26	[1.80; 2.84]		1.96	[1.43; 2.69]		1.24	[0.78; 1.96]	
If time-varying effect, estimated HR at 3 years									
Chemotherapy without anti-HER2 therapy (±endocrine therapy)	2.00	[1.68; 2.38]		2.04	[1.50; 2.78]		2.11	[1.40; 2.61]	
Anti-HER2 therapy alone or endocrine therapy alone or both	1.33	[1.05; 1.67]		1.44	[1.04; 1.97]		0.69	[0.43; 1.10]	
If time-varying effect, estimated HR at 5 years									<0.01
Chemotherapy without anti-HER2 therapy (±endocrine therapy)	1.17	[0.99; 1.40]		1.49	[1.10; 2.03]		1.18	[0.95; 1.46]	
Anti-HER2 therapy alone or endocrine therapy alone or both	0.78	[0.62; 0.98]		1.05	[0.77; 1.45]		0.39	[0.24; 0.61]	
MFI (months) (reference: < 6 months)						0.05			<0.01
6–24 months	2.58	[2.25; 2.95]		1.42	[1.05; 1.92]		3.06	[2.62; 3.58]	
24 months and more	1.37	[1.24; 1.52]	<0.01	1.01	[0.82; 1.26]		1.52	[1.35; 1.71]	
Center size (number of patients/site) (reference: less than 700 patients)			<0.01						<0.01
700 to 1399 patients	0.87	[0.71; 1.06]		NS			0.91	[0.73; 1.13]	
1400 patients and more	0.63	[0.50; 0.78]		NS			0.63	[0.50; 0.80]	

HR: Hazard ratio.
ER: Estrogen receptor.
PgR: Progesterone receptor.
MFI: Metastasis free interval.
NS: Not significant.
NA: Not applicable.

In this large retrospective cohort, we observed that only 65% of patients 70+ received anti-HER2 treatment with chemotherapy, defined as standard first-line treatment, compared with 89.1% of those <70 (global statistical test of first-line treatment distribution, $p < 0.01$). Older patients may have impaired cardiac function, limiting the prescription of anti-HER2 treatments and chemotherapy combinations. Increased toxicity is also feared, even in the absence of such condition [23,24]. Our results suggest that these differences in treatment choice may have an impact on the outcome of older patients. Indeed, both PFS and OS in the 70+ group were significantly lower than those in patients <70 with median survival of 11.1 months (95% CI, 10.0–12.3) and 35.3 months (95% CI, 31.5–37.0) versus 13.2 months (95% CI, 12.7–13.9) and 49.2 months (95% CI, 47.1–52.4), respectively. After adjustment for tumour characteristics, this effect of different treatment choices on OS seemed to be present early, at 12 and 36 months, declining later at 60 months. Of note, 11.5% of women 70+ received anti-HER2 alone or with endocrine therapy vs 3.2% in patients <70, stressing the high interest for chemo-free combinations or combinations with milder chemotherapy in the older population, as supported by the recommendations by the Société Internationale d'Oncogériatrie (SIOG) [19]. Moreover, although anti-HER2 alone or with endocrine therapy had a detrimental effect on OS compared with standard treatment, outcome was still better than chemotherapy alone.

As previously described, misestimating women's capacity and remaining life expectancy may have contributed to undertreatment, resulting in worse outcomes in older patients. However, some older patients with cancer have many competing risks of death due to multimorbidities. These should be carefully assessed before treatment decision, especially because older persons may develop more often important side effects, related to changes in pharmacodynamic parameters, polypharmacy and underlying frailty [25]. As advocated by SIOG, treatment of BC in older patients should not be based on chronological age alone [26]. Screening for

Table 4
Prognostic factors of progression-free survival in metastatic breast cancer patients in the ESME real-life database according to age.

	All women			70+			<70		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Age (reference: < 70)			<0.01						
≥70	NS			NA			NA		
Age (continuous variable)						<0.01			
	NA			1.03	[1.01; 1.04]		NS		
Number of metastatic sites at metastatic diagnosis (reference: 1 site)			<0.01			<0.01			<0.01
2 sites	1.20	[1.10; 1.31]		1.21	[1.00; 1.48]		1.29	[1.16; 1.42]	
3 sites or more	1.45	[1.31; 1.61]		1.55	[1.24; 1.94]		1.72	[1.54; 1.93]	
Visceral metastatic disease (reference: none) (*)			<0.01			<0.01			<0.01
If no time; varying effect: Global HR	NA			1.35	[1.12; 1.63]		NA		
Time; varying effect:									
Estimated HR at 1 year	1.47	[1.22; 1.76]		NA			1.59	[1.30; 1.95]	
Estimated HR at 3 years	1.71	[1.43; 2.05]		NA			2.02	[1.65; 2.47]	
Estimated HR at 5 years	2.00	[1.67; 2.40]		NA			2.56	[2.09; 3.13]	
ER/PgR status (reference: both ER; and PgR;)			<0.01	NS					
If no time; varying effect, estimated average HR				NS					<0.01
Positive ER and/or PgR	NA						NA	NA	NA
Undetermined ER/PgR status	NA						NA	NA	NA
If time; varying effect, estimated HR at 1 year									
Positive ER and/or PgR	0.92	[0.85; 0.99]					0.87	[0.80; 0.95]	
Undetermined ER/PgR status	0.86	[0.58; 1.26]					0.78	[0.50; 1.22]	
If time; varying effect, estimated HR at 3 years									
Positive ER and/or PgR	1.13	[1.05; 1.22]					1.08	[1.00; 1.18]	
Undetermined ER/PgR status	1.05	[0.71; 1.55]					0.97	[0.62; 1.51]	
If time; varying effect, estimated HR at 5 years									
Positive ER and/or PgR	1.39	[1.28; 1.50]					1.35	[1.24; 1.46]	
Undetermined ER/PgR status	1.29	[0.88; 1.90]					1.20	[0.77; 1.87]	
First-line treatment (vs chemotherapy + anti; HER2 therapy ± endocrine therapy)			<0.01	1.54 0.86	[1.18; 2.02] [0.70; 1.05]	<0.01			<0.01
If no time-varying effect: Estimated average HR									
chemotherapy without anti-HER2 therapy (±endocrine therapy)	NA						NA	NA	
anti-HER2 therapy alone or endocrine therapy alone or both	NA						NA	NA	
At 1 year									
chemotherapy without anti-HER2 therapy (±endocrine therapy)	1.93	[1.67; 2.23]					1.68	[1.41; 2.00]	
anti-HER2 therapy alone or endocrine therapy alone or both	1.75	[1.51; 2.03]					0.64	[0.49; 0.84]	
At 3 years									
chemotherapy without anti-HER2 therapy (±endocrine therapy)	1.17	[1.01; 1.36]					1.29	[1.08; 1.54]	
anti-HER2 therapy alone or endocrine therapy alone or both	1.06	[0.92; 1.23]					0.49	[0.38; 0.64]	
At 5 years									
chemotherapy without anti; HER2 therapy (±endocrine therapy)	0.71	[0.62; 0.83]					0.99	[0.83; 1.18]	
anti-HER2 therapy alone or endocrine therapy alone or both	0.65	[0.56; 0.75]					0.38	[0.29; 0.49]	
MFI (months) (reference: < 6 months)			<0.01			<0.01			
6–24 months	2.10	[1.87; 2.35]		1.71	[1.33; 2.23]		2.42	[2.14; 2.74]	<0.01
24 months and more	1.46	[1.35; 1.58]		1.09	[0.91; 1.29]		1.43	[1.31; 1.56]	
Center size (number of patients/site) (reference: < 700 patients)			<0.01						<0.01
700 to 1399 patients	0.83	[0.71; 0.98]		NS			0.80	[0.68; 0.95]	
1400 patients and more	0.74	[0.62; 0.88]		NS			0.68	[0.57; 0.82]	

HR: Hazard ratio.
ER: Estrogen receptor.
PgR: Progesterone receptor.
MFI: Metastasis free interval.
NS: Not significant.
NA: Not applicable.

frailty, and delving further in the general health status, with a developed and personalized geriatric assessment when frailty is suggested, has become a mandatory and helpful strategy.

Although combination with chemotherapy has been established as the standard use [27,28], older patients are at increased risk of treatment-induced toxicity and require important strategy adjustments [19]. Even in fit ones who may be treated as younger ones, there should be no decreased attention regarding potential toxicity. For those who are frail or unfit, less toxic schedules and combinations are recommended. For example, the EORTC conducted an open label randomized phase II trial in first line HER2+ MBC in older and frail patients [28]. Seventeen percent of patients had a G8 ≤ 14, suggesting potential frailty. Patients were randomized between dual anti-HER2 blockade (pertuzumab + trastuzumab) alone or with metronomic cyclophosphamide, reaching a median PFS of 5.6 months (95% CI 30.2–60.7) and 12.7 months (6.7–24.8), respectively, providing an attractive alternative to the standard combination of dual blockade with taxanes. The TANDEM trial also investigated successfully trastuzumab with endocrine therapy in luminal HER2+ post-menopausal women with MBC [29]. Most recently, the PERTAIN trial, with a median PFS of 27 months in the group of patients who received aromatase inhibitors with

pertuzumab and trastuzumab, highlights that some patients may benefit from this combination, without chemotherapy [30].

The major strength of our work is the size of the cohort, which includes all HER2+ MBC 70+ with no age limitations nor selection based on multimorbidities, making it more representative of daily clinical practice.

However, our study has also major limitations. First, due to missing data, we could not assess relative BC survival to take into account competing risks for death. Furthermore, older patients treated in comprehensive cancer centers may not be representative of all patients, limiting extrapolation to other institutions, because they tend to have less comorbidities and a higher socio economic level than those referred to smaller local clinics and hospitals [31].

Other important limitations are due to the retrospective nature of our cohort. Indicators of frailty like the screening tool G8, PS, comorbidities or geriatric assessment, which provide prognostic information in older populations with or without cancer, were missing. Assessment of treatment safety was not available. We also could not eliminate confounding factors like patient's choice who may have influenced treatment decision. Although it would be of interest, the number of patients aged >70 years did not allow subgroup analyses by age groups.

Finally, the finding that the large size of the treating centre (evaluated though the number of patients accrued in the cohort, which is fully correlated to the total patients' load of the center) had a protective effect in the whole or younger population but not in the older one is counterintuitive. Larger institutions have generally higher resources to contract geriatricians to help tailoring treatments in older patients, unless skewed or selected patients recruitments create uneven access to these. This requires further exploration and may reflect a different patient profile within larger centers. Of note, secondary referrals are much more frequent in bigger centers, but such patients are excluded from ESME and this would not affect our results based on first-line treatments.

5. Conclusion

In this real world cohort, only 65% of women 70+ received standard first-line treatment defined as chemotherapy with anti-HER2 therapy, with or without endocrine therapy. Older women were less likely to receive standard therapy compared with their younger counterparts. These treatment differences were associated with worse PFS and OS, although a causal relationship cannot strictly be demonstrated. Given the lack of information on geriatric assessment (e.g. general health status, functional status, comorbidity, etc.), confounding factors and usual selection biases cannot be ruled out. These results stress the importance to study older populations with specific approaches, not based on the usual transfer of those developed in younger ones, in order to avoid under and overtreatments.

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