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ORIGINAL RESEARCH

Evolution of overall survival and receipt of new therapies by subtype among 20 446 metastatic breast cancer patients in the 2008-2017 ESME cohort

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Background: Treatment strategies for metastatic breast cancer (MBC) have made great strides over the past 10 years. Real-world data allow us to evaluate the actual benefit of new treatments. ESME (Epidemio-Strategy-Medico-Economical)-MBC, a nationwide observational cohort (NCT03275311), gathers data of all consecutive MBC patients who initiated their treatment in 18 French Cancer Centres since 2008.

Patients and methods: We evaluated overall survival (OS) in the whole cohort ($N = 20\,446$) and among subtypes: hormone receptor positive, human epidermal growth factor 2 negative (HR+/HER2−; $N = 13\,590$), HER2+ ($N = 3919$), and triple-negative breast cancer (TNBC; $N = 2937$). We performed multivariable analyses including year of MBC diagnosis as one of the covariates, to assess the potential OS improvement over time, and we described exposure to newly released drugs at any time during MBC history by year of diagnosis (YOD).

Results: The median follow-up of the whole cohort was 65.5 months (95% CI 64.6-66.7). Year of metastatic diagnosis appears as a strong independent prognostic factor for OS [Year 2016 HR 0.89 (95% CI 0.82-0.97); $P = 0.009$, using 2008 as reference]. This effect is driven by the HER2+ subcohort, where it is dramatic [Year 2016 HR 0.52 (95% CI 0.42-0.66); $P < 0.001$, using 2008 as reference]. YOD had, however, no sustained impact on OS among patients with TNBC [Year 2016 HR 0.93 (95% CI 0.77-1.11); $P = 0.41$, using 2008 as reference] nor among those with HR+/HER2− MBC [Year 2016 HR 1.02 (95% CI 0.91-1.13); $P = 0.41$, using 2008 as reference]. While exposure to newly released anti-HER2 therapies appeared very high (e.g. >70% of patients received pertuzumab from 2016 onwards), use of everolimus or eribulin was recorded in less than one-third of HR+/HER2− and TNBC cohorts, respectively, whatever YOD.

Conclusion: OS has dramatically improved among HER2+ MBC patients, probably in association with the release of several major HER2-directed therapies, whose penetrance was high. This trend was not observed in the other subtypes, but the impact of CDK4/6 inhibitors cannot yet be assessed.

Key words: metastatic breast cancer, real-life, overall survival, HER2, new drugs

INTRODUCTION

Metastatic breast cancer (MBC) remains an incurable disease, and is the second leading cause of death from cancer among women worldwide.[1,2] Molecular and prognostic classifications have divided breast cancer into three subtypes: human epidermal growth factor receptor 2 amplified

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(HER2+), hormone receptor positive and HER2 negative (HR+/HER2−, also called 'luminal'), and HR negative, HER2− known as 'triple-negative breast cancer' (TNBC).[3] Over the past two decades, this division has enabled the development of therapies adapted to each subtype. Considering new drugs approved for HER2+ MBC until 2017 inclusive, pertuzumab administered in combination with trastuzumab and chemotherapy as first-line treatment was demonstrated in the CLEOPATRA trial to increase overall survival (OS) by >16 months.[4] Trastuzumab emtansine, administered in second or later lines, also demonstrated clinically meaningful OS improvements (4 and 6.9 months, respectively).[5,6] In luminal MBC, several classes of targeted therapies have emerged, which globally allowed doubling of progression-free survival when combined with endocrine therapies. These drugs include everolimus, a mechanistic target of rapamycin (mTOR) inhibitor used in aromatase inhibitor (AI)-resistant settings[7]; and three CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) in both AI-sensitive and AI-resistant settings.[8-13] Beyond progression-free survival benefits, two of these CDK4/6 inhibitors have demonstrated improvements in OS.[10,13] Finally, eribulin allowed a 2-months OS improvement in HER2− MBC patients and was released in this indication in the early 2010s[14] (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100114).

Beyond clinical trials, it is of utmost interest to evaluate whether the expected benefits of these new drugs are finally confirmed in the real-life setting.[15,16] ESME (Epidemio-Strategy-Medico-Economical)-MBC is a very large, nationwide, multicenter real-life database of patients with MBC treated in the 18 French comprehensive cancer centres (FCCC).[17-19] In France, the public health insurance system covers the entire population and all fees for serious or chronic illnesses.[20] Once a drug has been approved by the European Medicine Agency, the formal pricing and reimbursement decision are carried out by the 'Haute Autorité de Santé' (HAS).[21] Bridging mechanisms are widely available for coverage of drugs before reimbursement. Once granted, full reimbursement of cancer drugs is provided for all patients for whom the drugs are indicated. France can therefore be considered adequate for real-life assessment of treatment progresses made over time.

In this study, we analyse the effect of year of diagnosis (YOD) on OS by breast cancer subtype, among 20 446 women who initiated treatment for MBC in the multicentre French ESME cohort between 1 January 2008 and 31 December 2016. We also provide a description of patients' receipt of drugs that were approved and reimbursed in France during the inclusion and follow-up period.

PATIENTS AND METHODS

Study population

ESME-MBC (Data registration: clinicaltrials.gov identifier NCT03275311) is a retrospective national cohort gathering routinely collected real-world data from all consecutive MBC women over 18 who initiated their MBC treatment in one of the 18 FCCCs. Data are updated annually and include patient demographics, histopathology, outcomes, and treatment patterns. The collected information integrates patient data from medical records, multidisciplinary team meeting reports, hospitalization reports, and hospitals' pharmacy records. More details can be found in previously published descriptions of the cohort.[17-19] For this study, we used data from MBC patients who entered the cohort between 1 January 2008 and 31 December 2016. Data were collected until the cut-off date for data extraction (i.e. 14 April 2020). Male patients and patients whose breast cancer subtype could not be assessed were excluded from the analyses. Of note, the global ESME database identification algorithm in local centres does not allow to capture all eligible patients at the first round of selection. Patients who entered the cohort after 2016 were therefore excluded.

Ethics approval and data protection

This 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 have been informed about the use of their electronically recorded data and can access, rectify, limit, or require withdrawal of their data on a dedicated web platform at any time.[22] French data protection authority authorized the ESME MBC database in 2013 (registration ID 1704113 and authorization NbrDE-2013.-117). In compliance with the applicable European regulations, a complementary authorization was obtained on 14 October 2019 regarding the ESME research Data Warehouse.

Definitions

Breast cancer subtypes were defined according to immunohistochemical (IHC) analyses carried out using metastatic samples or, if not available, the last sample obtained from early disease. Tumours are considered HR+ if the oestrogen receptor (ER) and/or the progesterone receptor (PR) expression was observed in ≥10% of tumour cells. HER2+ breast cancer includes HER2 IHC 3+ scores and HER2 2+ associated with an amplification of the *HER2* gene using *in situ* hybridization. A negative fluorescence or chromogenic *in situ* hybridization (FISH/CISH) test, with HER2 IHC 0-2+ score or without HER2 IHC information, leads to an HER2− status.[23-25] An HER2 IHC 2+ score without available FISH/CISH test was considered as indeterminate HER2 status and patients were excluded from the present analyses. The HR+/HER2− subtype was defined by an HR+ status (either ER or PR positive) and an HER2− status; the HER2+ subtype by HER2 positivity; and TNBC subtype by the absence of ER, PR, and HER2 expression. *De novo* metastatic disease is defined as the presence of metastases diagnosed within 6 months from the diagnosis of the primary tumour. 'Relapsed' MBC is defined as non-*de novo*. Metastatic disease identified on symptoms means the patient-reported symptoms or complaints that lead to the discovery of metastatic involvement. Systematic examination means that metastatic disease has been identified through systematic

examinations including clinical examination, imaging, or blood tests, either as initial metastatic work-up (for *de novo* MBC) or during follow-up. Metastasis free-interval is the time between diagnosis of the primary breast cancer and that of metastatic disease.

Treatments

The receipt of newly released MBC treatments in the ESME cohort was described in this report as a key objective according to YOD of metastatic disease and subtype. Treatments studied include all drugs which gained new or extended approval from the European Medicine Agency for metastatic/advanced breast cancer, and which were granted reimbursement in France during the study period, including the selection and follow-up periods. Treatments administered in the course of a clinical trial, an expanded access program, or for compassionate use were also included, provided the drug complied with the prespecified criteria. They were, however, not taken into account if the administration of the drug within the trial was blinded. Out of all women diagnosed with MBC in a given year, treatment receipt is the percentage of patients who received a specific newly released drug (or drug class) at any time during their care, until death, or last follow-up, whatever the setting (clinical trial, expanded access, or post approval). For HER2+ MBC, drugs of interest, which were approved by the European Medicines Agency (EMA) during the period described and were granted reimbursement, are lapatinib (16 July 2008), pertuzumab (04 March 2013), and trastuzumab emtansine (19 March 2014). For HR+/HER2− MBC, drugs of interest are fulvestrant (modified 500 mg dosage; EMA approval 15 March 2010), everolimus (23 July 2012), CDK4/6 inhibitors (palbociclib, 17 November 2016; ribociclib, 22 June 2017; abemaciclib, 26 July 2018), and eribulin (17 March 2011). For TNBC, the only drug of interest is eribulin (EMA approval 17 March 2011; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100114).

Objectives

The main objective of these analyses was to analyse the long-term impact of YOD on OS by breast cancer subtype, and in the whole cohort. The key secondary objective was to describe the receipt of newly released drugs over the MBC history, by YOD.

Statistical analysis. We first described patients' characteristics according to the year of metastatic diagnosis, in the whole cohort, as well as in the three breast cancer subtypes (HR+/HER2−, HER2+, and TNBC). The metastasis-free interval is defined as the time between the diagnosis of primary breast cancer and the diagnosis of metastatic disease. Quantitative variables are described using the number of observations, median, and first and third quartile values. Qualitative variables are described using the number of observations and percentage distribution. The number of missing data are presented but not considered for the percentage calculation. We carried out Cochran−Armitage trend tests to assess for trend in proportions of *de novo* HER2+ MBC across years of diagnosis, as well as the proportion of systematic examination as identification method across years of diagnosis in HER2+ MBC patients (data not shown). OS is defined as the time from the date of metastatic diagnosis to the date of death (any cause) or to the date of latest news for censored patients and was estimated using the Kaplan−Meier method. The median follow-up was estimated using the reverse Kaplan−Meier method. Multivariable Cox proportional hazard models were carried out using a backward stepwise selection to identify prognostic factors for OS in the whole population and in each cancer subtype. The models were based on the candidate prognostic factors [YOD, age at MBC diagnosis, subtypes, metastasis-free interval ($<$6, 6-24, and $\geq$24 months), number of metastatic sites ($<$3 versus $\geq$3), and presence of visceral metastases (yes/no)] using a conservative P value of 0.10 from univariate analysis, except for variables highly acknowledged as prognostic factors by literature or clinical relevance. The independent prognostic factors included in the final models with a significant P value of 0.05 are presented with their hazard ratios including 95% confidence intervals. Two sensitivity analyses have been carried out in the HER2 population; one among patients with 'relapsed' MBC, and the other in the restricted population of patients for whom performance status was available. These analyses reproduced the same methodology. All analyses were carried out using R Statistical Software (R Foundation for Statistical Computing).

RESULTS

Study population features

Among 23 698 patients enrolled in the ESME database since 2008, 20 446 women were eligible for this present study (Figure 1), of whom 13 590 (66.5%), 3919 (19.2%), and 2937 (14.3%) had HR+/HER2−, HER2+, and TNBC tumours, respectively. Clinical features and patients' characteristics at the date of metastatic diagnosis, for the whole ESME population, are shown in Table 1, whereas those of each subtype are presented in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2021.100114.

Most patients and tumours characteristics, as well as the previous receipt of adjuvant treatments, appeared stable over time in the whole population and in subtypes. However, two changes in the HER2+ MBC cohort were significant. First, the proportion of *de novo* HER2+ MBC significantly increased from 33% in 2008 to over 50% in the most recent years (Cochran−Armitage test; $P < 0.001$), and the rate of MBC diagnosed by systematic examination increased from 50% to over 60% (Cochran−Armitage test; $P < 0.001$). At the meantime, the proportion of *de novo* HR+/HER2− and TNBC MBC increased to a much lesser extent, from 26% and 27%, respectively, to over 30% in the most recent years.

Overall survival and prognostic analyses in the whole study cohort

The median follow-up in the whole study population was 65.5 months (95% CI 64.6-66.7). The median OS over the

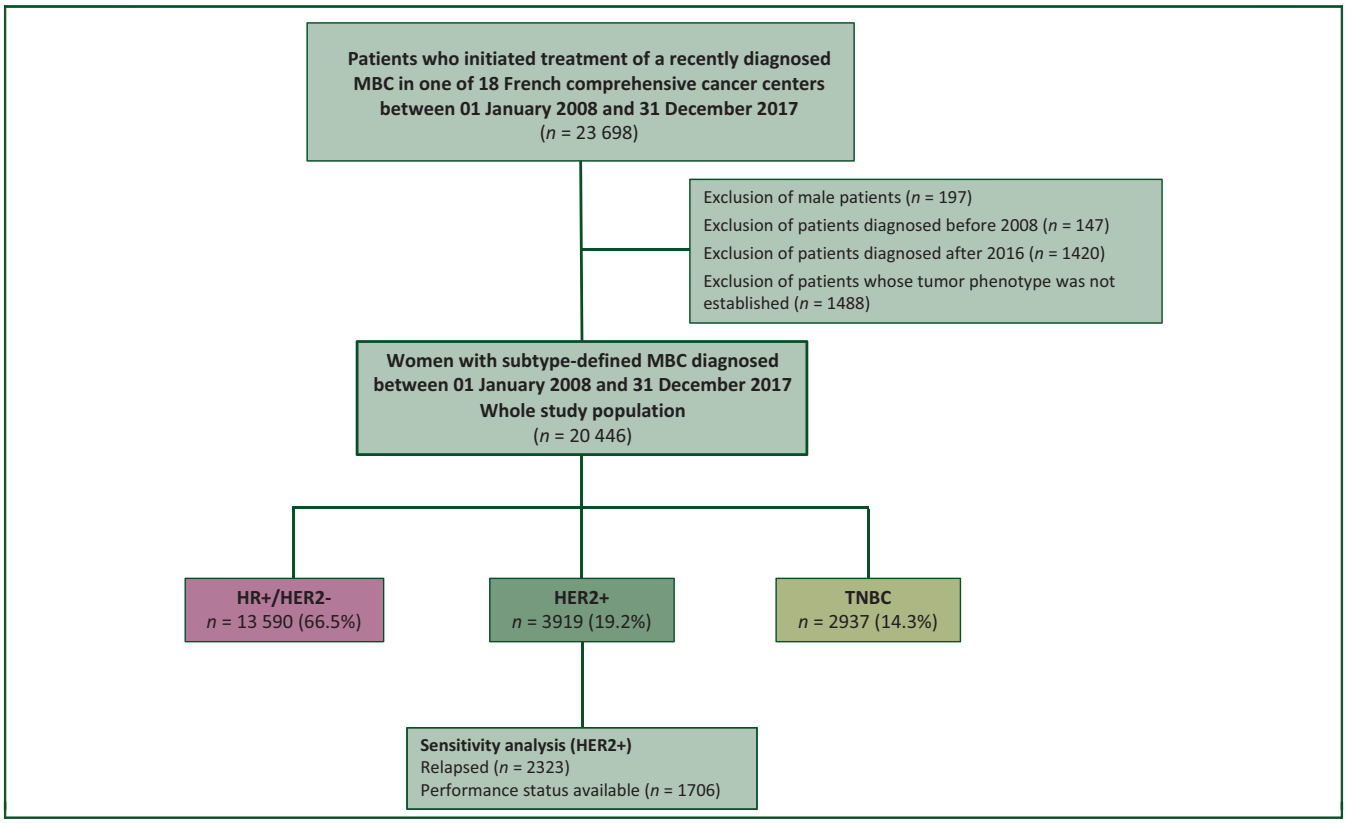

Figure 1. Flowchart.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; TNBC, triple-negative metastatic breast cancer.

full period was 38.8 months (95% CI 38.1-39.7), and the 5-year survival rate was 33.8% (95% CI 33.1%-34.6%). Median OS of the 2008 cohort was 36.4 months (95% CI 34.1-38.7), whereas it was 43.9 months (95% CI 41.7-45.9) in YOD 2016 (Figure 2).

The multivariable analysis in the whole study population identified YOD as a strong independent prognostic factor for OS from 2013 onwards [YOD 2016, HR 0.89 (95% CI 0.82-0.97); $P = 0.009$], using 2008 as reference. Subtypes, age at MBC diagnosis, number of metastatic sites, presence of visceral metastases, and metastasis-free interval also appeared as independent prognostic factors of OS (Table 2).

Overall survival and prognostic analyses among breast cancer subtypes

The median OS of the HR+/HER2− subgroup was 42.9 months (95% CI 42.1-43.8), with a 5-year survival rate of 35.7% (95% CI 34.8%-36.6%). In the HER2+ subgroup, median OS was 50.1 months (95% CI 47.6-53.1), with a 5-year survival rate of 43.8% (95% CI 42.1%-45.6%). Lastly, median OS of TNBC patients was 14.5 months (95% CI 13.8-15.1) with a 5-year survival rate of 11.3% (95% CI 10.0%-12.7%; Figure 2). Median OS appeared very stable over time in both HR+/HER2− patients [2008: 43.4 months (95% CI 40.9-46.5); 2016: 44.8 months (95% CI 42.5-NR)] and TNBC patients [2008: 14.0 months (95% CI 12.3-15.9); 2016: 14.2 months (95% CI 12.1-16.5)]. However, we identified a major improvement of median OS among patients of the HER2+ cohort [2008: 39.1 months (95% CI 36.2-46.5); 2013: 58 months (95% CI 52.0-68.4); not reached from 2014 onwards].

In the multivariable analyses, YOD appeared as a strong, sustained, independent prognostic factor for OS only in the HER2+ subtype, and this effect increased over time from 2011 to 2016 [HR 0.83 (95% CI 0.71-0.98); $P = 0.032$ and HR 0.52 (95% CI 0.42-0.66); $P < 0.001$, respectively, using year 2008 as reference]. In the three cohorts, the other independent prognostic factors of OS were age at MBC diagnosis, number of metastatic sites, presence of visceral metastases, and metastases-free interval (Table 2).

As a sensitivity analysis in the HER2+ subcohort, we repeated the multivariable analysis in the subgroup of 'relapsed' HER2+ patients ($N = 2323$). Their median OS was 41.5 months (95% CI 38.4-44.0) with a median duration of follow-up of 69.2 months (95% CI 65.4-73.0; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100114). The same results were observed regarding the impact of YOD on OS [e.g. Year 2016 versus 2008, HR 0.53 (95% CI 0.39-0.70); $P < 0.001$]. Age at MBC diagnosis, number of metastatic sites, presence of visceral metastases, and metastases-free interval were also independent prognostic factors of OS in this cohort (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2021.100114).

As a second sensitivity analysis, we repeated the multivariable analysis in the HER2+ patients for which performance status was available ($N = 1706$). Their median OS was 61.9 months (95% CI 58.0-66.7) with a median duration

Table 1. Clinical features and patients' characteristics in the whole population

Year of diagnosis	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total
N	2082	2169	2237	2344	2399	2453	2389	2232	2141	20 446
Age at MBC diagnosis (years)										
Median	60	59	60	60	61	61	60	61	60	60
q1q3	(50, 70)	(50, 70)	(50, 70)	(50, 70)	(51, 72)	(50, 70)	(50, 70)	(51, 71)	(50, 71)	(50, 70)
Performance status, *n* (%)										
0	260 (45%)	309 (46%)	296 (43%)	341 (45%)	390 (44%)	498 (48%)	464 (41%)	450 (41%)	489 (42%)	3497 (44%)
1	210 (36%)	233 (35%)	272 (40%)	275 (36%)	325 (37%)	339 (32%)	410 (37%)	398 (37%)	424 (36%)	2886 (36%)
2-4	111 (19%)	126 (19%)	114 (17%)	142 (19%)	170 (19%)	206 (20%)	248 (22%)	242 (22%)	262 (22%)	1621 (20%)
Missing	1501	1501	1555	1586	1514	1410	1267	1142	966	12 442
MBC diagnosis circumstances, *n* (%)										
Symptom(s)	974 (49%)	962 (46%)	961 (45%)	1003 (45%)	1003 (45%)	1097 (45%)	1124 (47%)	1016 (46%)	785 (37%)	8925 (45%)
Systematic examination	1033 (51%)	1117 (54%)	1187 (55%)	1207 (55%)	1241 (55%)	1343 (55%)	1252 (53%)	1195 (54%)	1328 (63%)	10 903 (55%)
Missing	75	90	89	134	155	13	13	21	28	618
Metastasis-free interval, *n* (%)										
<6 months (*de novo*)	570 (27%)	567 (26%)	650 (29%)	715 (30%)	733 (30%)	795 (32%)	768 (32%)	796 (36%)	805 (38%)	6399 (31%)
6-24 months	302 (15%)	302 (14%)	326 (15%)	325 (14%)	327 (14%)	330 (14%)	369 (16%)	302 (13%)	254 (12%)	2837 (14%)
>24 months	1210 (58%)	1300 (60%)	1261 (56%)	1304 (56%)	1339 (56%)	1328 (54%)	1252 (52%)	1134 (51%)	1082 (50%)	11 210 (55%)
Breast cancer subtype, *n* (%)										
HR+/HER2−	1378 (66%)	1405 (65%)	1473 (66%)	1591 (68%)	1609 (67%)	1636 (67%)	1602 (67%)	1487 (67%)	1409 (66%)	13 590 (67%)
HER2+	378 (18%)	408 (19%)	407 (18%)	451 (19%)	461 (19%)	490 (20%)	451 (19%)	429 (19%)	444 (21%)	3919 (19%)
TNBC	326 (16%)	356 (16%)	357 (16%)	302 (13%)	329 (14%)	327 (13%)	336 (14%)	316 (14%)	288 (13%)	2937 (14%)
Visceral metastases, *n* (%)										
Yes	1171 (56%)	1245 (57%)	1305 (58%)	1381 (59%)	1370 (57%)	1412 (58%)	1362 (57%)	1303 (58%)	1182 (55%)	11 731 (57%)
No	911 (44%)	924 (43%)	932 (42%)	963 (41%)	1029 (43%)	1041 (42%)	1027 (43%)	929 (42%)	959 (45%)	8715 (43%)
Number of metastatic sites at MBC diagnosis, *n* (%)										
<3	1711 (82%)	1766 (81%)	1787 (80%)	1875 (80%)	1885 (79%)	1927 (79%)	1878 (79%)	1715 (77%)	1639 (77%)	16 183 (79%)
≥3	371 (18%)	403 (19%)	450 (20%)	469 (20%)	514 (21%)	526 (21%)	511 (21%)	517 (23%)	502 (23%)	4263 (21%)
Chemotherapy in neoadjuvant setting (in relapsed patients), *n* (%)										
Yes	1050 (69%)	1147 (72%)	1114 (70%)	1187 (73%)	1184 (71%)	1201 (72%)	1190 (73%)	1062 (74%)	980 (73%)	10 115 (72%)
No	462 (31%)	455 (28%)	473 (30%)	442 (27%)	482 (29%)	457 (28%)	431 (27%)	374 (26%)	356 (27%)	3932 (28%)

Metastasis-free interval is the period between the date of primary breast cancer diagnosis and the date of the metastatic diagnosis.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; TNBC, triple-negative metastatic breast cancer.

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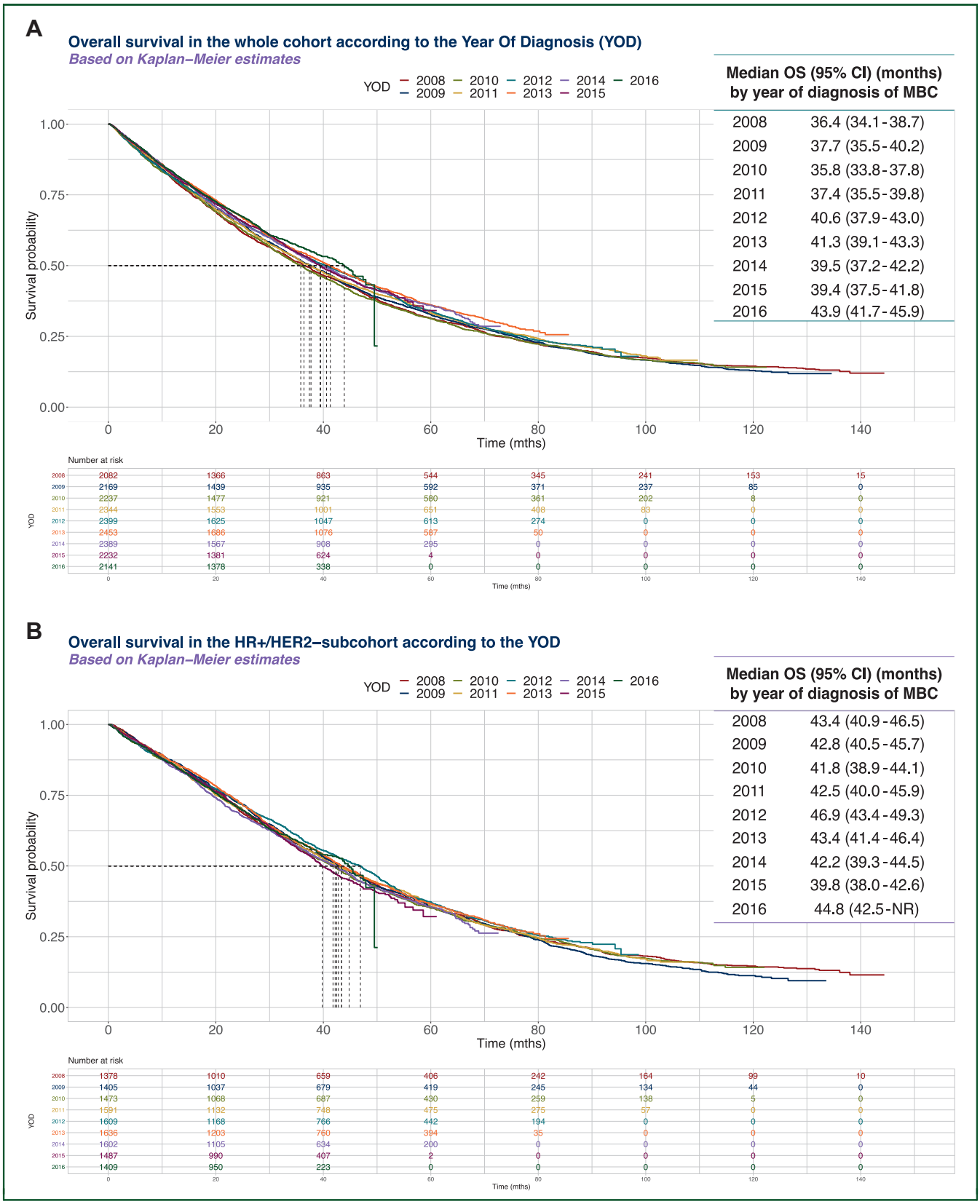

Figure 2. Overall survival in the whole ESME population and in breast cancer subtypes according to the YOD.
(A) Overall survival in the whole ESME population by year of metastatic diagnosis. (B) Overall survival in the HR+/HER2− MBC subcohort by year of metastatic diagnosis. (C) Overall survival in the HER2+ MBC subcohort by year of metastatic diagnosis. (D) Overall survival in the TNBC MBC subcohort by year of metastatic diagnosis. CI, confidence interval; ESME, Epidemio-Strategy-Medico-Economical; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; mths, months; NR, not reached; OS, overall survival (median); TNBC, triple-negative metastatic breast cancer; YOD, year of metastatic diagnosis.

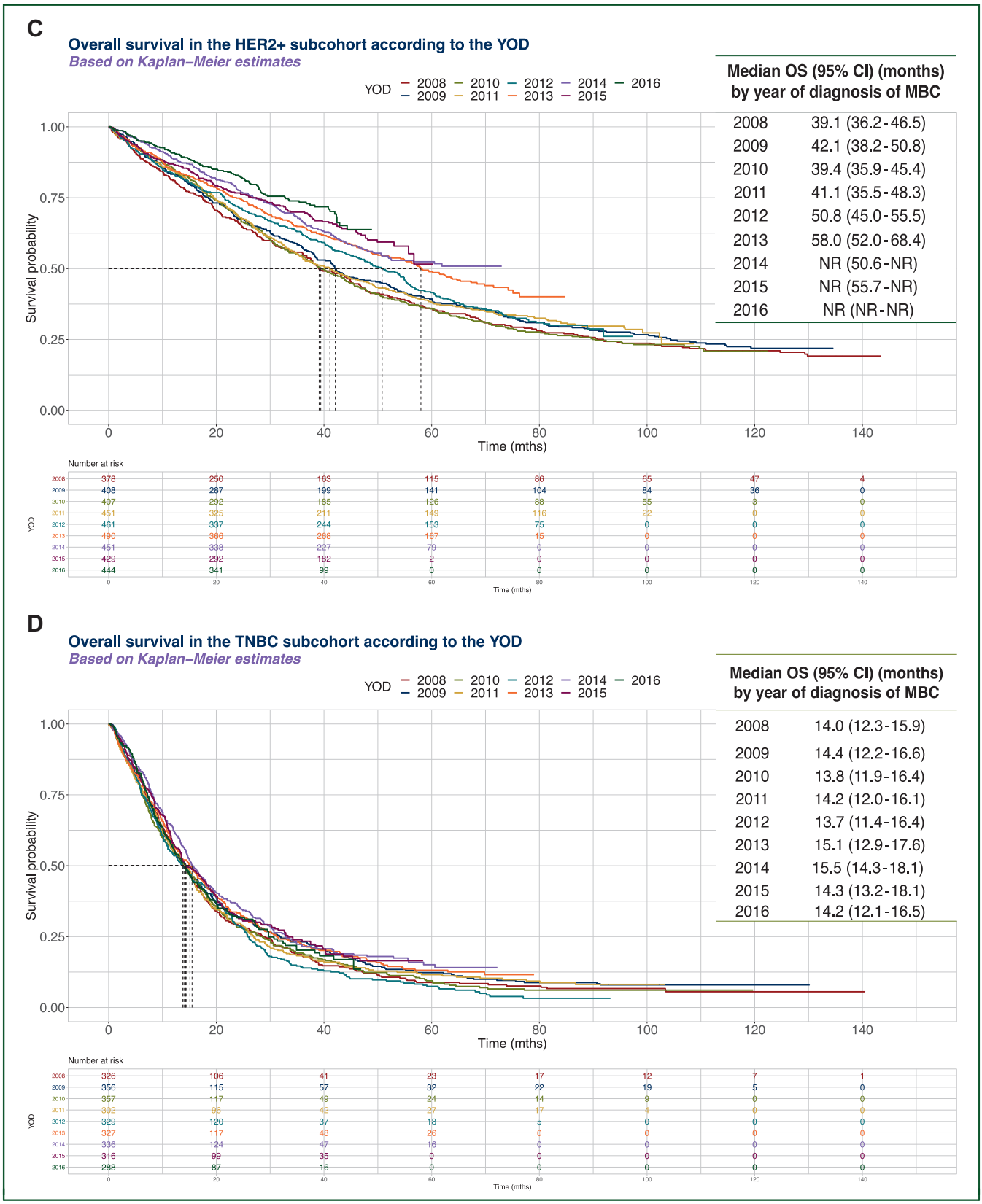

Figure 2. **(Continued)**

Table 2. Multivariable analysis of OS within the whole ESME population and among subtypes

Characteristic	Whole cohort			HR+/HER2−			HER2+			TNBC		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Year of MBC diagnosis												
2008	1			1			1			1		
2009	0.99	0.92-1.06	0.67	1.04	0.95-1.13	0.41	0.91	0.77-1.07	0.24	0.94	0.80-1.10	0.42
2010	1.00	0.93-1.07	0.91	1.02	0.94-1.11	0.61	0.92	0.78-1.08	0.31	0.97	0.82-1.13	0.67
2011	0.97	0.90-1.03	0.31	1.01	0.93-1.10	0.80	0.83	0.71-0.98	**0.032**	0.90	0.76-1.06	0.21
2012	0.95	0.89-1.02	0.14	0.94	0.86-1.03	0.17	0.84	0.71-0.99	**0.039**	1.08	0.92-1.27	0.36
2013	0.90	0.84-0.96	**0.003**	0.97	0.88-1.05	0.44	0.72	0.60-0.85	**<0.001**	0.87	0.74-1.03	0.10
2014	0.91	0.84-0.98	**0.009**	1.04	0.95-1.14	0.42	0.63	0.52-0.76	**<0.001**	0.78	0.66-0.93	**0.005**
2015	0.90	0.84-0.98	**0.011**	1.03	0.94-1.14	0.52	0.62	0.50-0.76	**<0.001**	0.83	0.70-0.99	**0.038**
2016	0.89	0.82-0.97	**0.009**	1.02	0.91-1.13	0.77	0.52	0.42-0.66	**<0.001**	0.93	0.77-1.11	0.41
Age at MBC diagnosis (10-year increase)												
	1.12	1.11-1.14	**<0.001**	1.14	1.12-1.16	**<0.001**	1.18	1.14-1.22	**<0.001**	1.04	1.01-1.07	**0.008**
No. of metastatic sites at MBC diagnosis												
<3	1			1			1			1		
≥3	1.54	1.47-1.60	**<0.001**	1.40	1.32-1.48	**<0.001**	1.75	1.57-1.94	**<0.001**	1.84	1.67-2.04	**<0.001**
Presence of visceral metastases												
No	1			1			1			1		
Yes	1.46	1.40-1.52	**<0.001**	1.48	1.41-1.55	**<0.001**	1.56	1.41-1.73	**<0.001**	1.43	1.30-1.57	**<0.001**
Metastasis-free interval												
<6 months (*de novo*)	1			1			1			1		
6-24 months	2.29	2.17-2.42	**<0.001**	2.37	2.19-2.57	**<0.001**	2.70	2.38-3.06	**<0.001**	1.67	1.51-1.85	**<0.001**
>24 months	1.15	1.10-1.20	**<0.001**	1.15	1.09-1.21	**<0.001**	1.37	1.24-1.51	**<0.001**	0.87	0.78-0.97	**0.009**
Cancer subtype												
HR+/HER2−	1											
HER2+	0.79	0.75-0.83	**<0.001**									
TNBC	2.28	2.17-2.39	**<0.001**									

Bold value indicates the significant *P* value < 0.05.
CI, confidence interval; ESME, Epidemio-Strategy-Medico-Economical; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; OS, overall survival; TNBC, triple-negative metastatic breast cancer.

follow-up of 61.3 months (95% CI 58.2-64.3). The same trends were observed regarding the impact of YOD on OS, although they lost significance in most YOD cohorts (e.g. Year 2016 versus 2008, HR 0.75; 95% CI 0.54-1.05; $P = 0.093$). Age at MBC diagnosis, number of metastatic sites, presence of visceral metastases, and metastases-free interval again were independent prognostic factors of OS in this cohort (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2021.100114).

Metastatic treatments over the MBC history, by year of diagnosis and subtypes

Figure 3 and Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2021.100114, describe the rate of patients in a given YOD who received at least once during the management of their MBC a drug that was released and reimbursed in France during the study period. Among patients in the HER2+ cohort, receipt of pertuzumab increased very rapidly, up to >70% of patients from 2016 onwards. Receipt of trastuzumab emtansine was confirmed in up to 42% of the patients (cohort 2014). By contrast, among patients with HR+/HER2− MBC, exposure to everolimus and eribulin has never exceeded 26% (higher score observed in YOD 2012 and 2013). Fulvestrant has been used in up to 43% of the patients (YOD 2012). By contrast, exposure to CDK4/6 inhibitors seems to increase rapidly, with already 31% of patients (YOD 2016) being exposed. Finally, among patients with TNBC, eribulin use never exceeded 32% (YOD 2014).

DISCUSSION

MBC represents a major social, medical, and economic burden worldwide, with over 620 000 deaths in 2018.[26] Several MBC innovative treatments have been released on the market over the past 12 years, with ranking according to the ESMO Magnitude of Clinical Benefit Scale (MCBS) ranging from 2 to 5.[27] Regarding the high medical need, and also the costs of these medications, it is of utmost importance to carefully scrutinize whether the expected impacts of these drugs are observed in real-life. The ESME-MBC cohort is one of the largest real-world databases of MBC, in a country with universal drug access. It therefore provides an appropriate material for such evaluation.

Our study provides two major results: one is the description of the evolution of OS over time, together with evaluation of the independent effect of YOD on outcome in the whole population and among each MBC subtype; the other is the description of the uptake of newly released drugs in the same cohorts of patients classified by YOD.

Among nearly 20 500 women with MBC diagnosed between 2008 and 2016 and followed until April 2020, we observed a modest OS improvement, which appeared to be almost fully driven by the HER2+ subgroup. In this subgroup, median OS was 39.1 months (95% CI 36.2-46.5) in

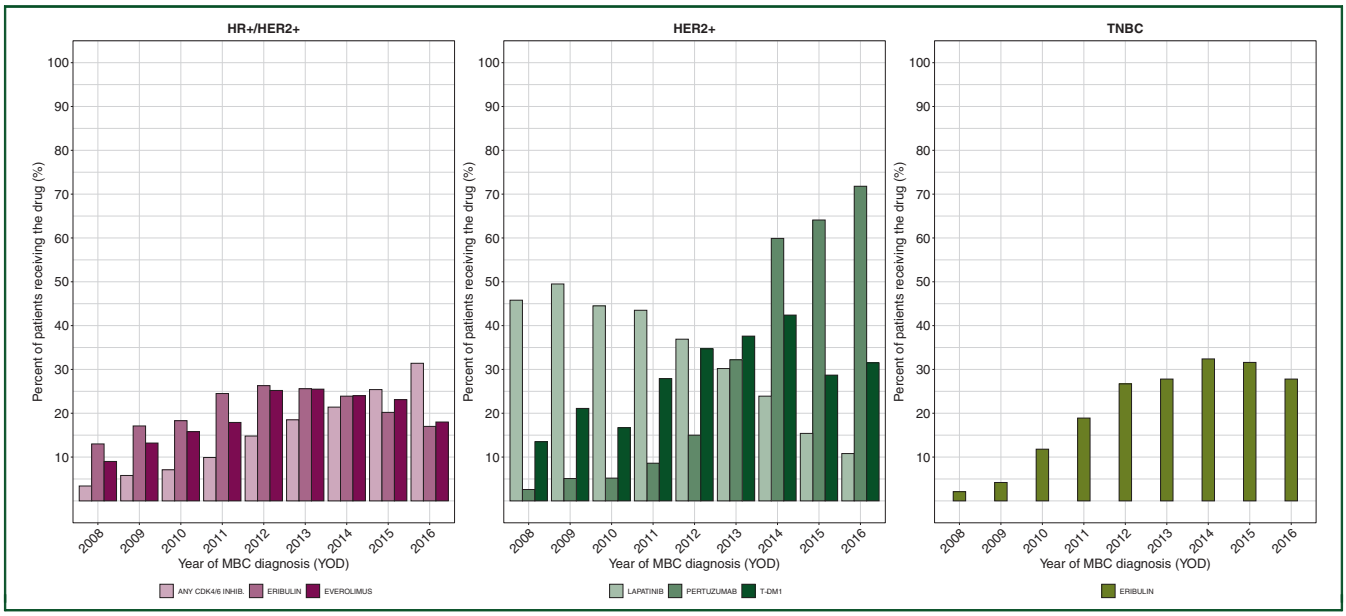

Figure 3. Receipt of newly released treatments per subtype and year of diagnosis.
*Proportion of all patients diagnosed with an MBC subtype in a given year who received a specific newly released drug at any time during their care, until death, or end of follow-up, whatever the setting (drugs could be used within clinical trials, expanded access programs, or post approval). Any CDK4/6 inhib, palbociclib, ribociclib, abemaciclib; MBC, metastatic breast cancer; T-DM1, trastuzumab-emtansine.

2008; 58 months (95% CI 52.0-68.4) in 2013; and was not reached from 2014 onwards. Multivariable analyses, including year of metastatic diagnosis as a covariate, confirm the independent impact of YOD on OS in the HER2+ cohort with a smaller effect in the whole population, a marginal one among TNBC patients, and none among women with HR+/HER2− cancers.

Of note, the structure of the HER2+ MBC population has notably changed over time. The proportion of *de novo* HER2+ MBC significantly increased from 33% in 2008 to over 50% more recently, and the proportion of MBC diagnosed by systematic examination significantly increased from 50 to over 60%. Of note, the proportion of *de novo* MBC patients also increased in the other cohorts, but with less magnitude. This observation among HER2+ MBC patients is consistent with recent studies and registries.[6,7,21] It reflects, on the one hand, improved care at the localized stage and thus the number of patients cured at this stage;[28-31] and on the other hand, the improved sensitivity of the diagnostic tests allowing better staging.[32] This contributes to increased OS by a Will Rogers phenomenon,[33] as *de novo* MBC patients have a better prognosis than the relapsed ones, who may suffer an adjuvant therapy-related shortening of survival effect (ATRESS).[34,35] However, the present data clearly showed that OS-relative improvement across YOD was maintained among patients with relapsed HER2+ MBC and equivalent to that of the whole HER2+ cohort.

It may be quite surprising that, despite improved early treatments, the number of new HER2+ MBC cases in ESME remains stable over time. As mentioned, changes in indications and use of metastatic work-up at diagnosis (and possibly during follow-up) could explain these figures. This could lead to an artificial survival advantage through earlier diagnosis of the metastatic stage.[36,37] However, the observed effect of YOD on OS is independent of these two covariates and cannot be questioned.

In parallel to OS results by YOD, our study shows that the uptake of newly released drugs has been very heterogenous according to tumour subtypes. On one side, the receipt of pertuzumab appears very high: >70% of HER2+ patients received it from 2016 onwards, which is close to what would be expected given the presence of patients with early relapses under trastuzumab, changes in HER2 status, or contraindication to HER2-targeted therapies. Besides, the receipt of trastuzumab emtansine is quite high and overall in line with expectations in a real-life setting. Indeed, in this setting, long remissions, as in the case of double anti-HER2 blockade, artificially reduce the rate of treatment uptake because patients have not yet been treated during the inclusion period. This is in line with recent real-world data generated from pharmaceutical electronic records in a large cohort of HER2+ BC patients.[38] By contrast, the receipt of eribulin, released in 2011 for HER2− MBC, has never exceeded 32% and 26% of TNBC and HR+/HER2− patients, respectively. Besides, among patients with HR+/HER2− MBC, exposure to everolimus peaked at only 25.5% in patients with YOD 2013. The low fulvestrant use (up to 43% of the patients with YOD 2012) was also unexpected. This major underuse of fulvestrant and everolimus may be explained by the very high rate of chemotherapy use as first-line (and subsequent lines) treatment for HR+/HER2− MBC among French clinicians, until recently.[19] In addition, there may be an underestimation bias in ESME for second lines or over, as treatments potentially administered outside the inclusion centre could be under-reported, but this represents a minority of patients lost to follow-up after the

first line. Moreover, uptake rates as estimated in this study are crude rates, among a given cohort of patients taken at MBC diagnosis; they do not exclude those who would not be candidate for a given drug, as they died meanwhile, for instance. However, exposure to CDK4/6 inhibitors seems, in contrast, to increase rapidly, with 31% of patients (YOD 2016) already receiving these drugs. Of note, our analysis is purely descriptive in ongoing cohorts, and does not intend to assess the exact rates of treatment prescriptions in specific, approved situations, which is almost not feasible in such an observational cohort. Furthermore, treatments' receipt includes postreimbursement access, as well as prescription as part of clinical trials, expanded access programs, or others.

The median OS of HER2+ ESME MBC patients in YOD 2013 (date of authorization of pertuzumab in France)[39] was 58.0 months (95% CI 52.0-68.4), which strikingly recapitulates in a real-world setting the impressive 56.5 months' median OS reported in the final analysis of the CLEOPATRA trial.[40] Although we cannot provide a direct causality demonstration, our results confirm that the release of high-impact drugs such as pertuzumab and trastuzumab emtansine (ESMO MCBS impact 5 and 4, respectively), together with a high drug receipt/penetrance, allows for major real-life benefits.

Finally, we have to acknowledge that the low rate of use of drugs with an expected lower clinical impact, such as everolimus and eribulin (ESMO MCBS impact 2 and 2, respectively), does not seem to be associated with an improvement in OS in a public health-level population.[41] The observed underuse of eribulin may be partially linked to restricted reimbursement in late treatment lines, which was not, however, the case for everolimus. This raises major questions on how new drugs should be managed at a public health level, and whether releasing costly drugs that are not used properly is relevant. Of note, our data are too early to allow the evaluation of the impact of CDK4/6 inhibitors in real life. This evaluation shall be possible in 2-3 years from now.

The strengths of our study include a very large number of patients, long follow-up, high-quality data with clinical trial-like methodology to gather data from patients' files and other resources, homogenous multicentric setting in comprehensive cancer centres, large and homogenous access to care, and innovations in the population. All of these factors contribute to establishing confidence in our results in terms of real-world evidence, defined as clinical evidence derived from the analysis of real-world data.

The main limitations of our study are inherent to its retrospective and observational design. It is very difficult to retrospectively define treatment indications, and treatment choices are made by physicians. Drug exposure could therefore only be assessed 'macroscopically'. Data on quality of life and safety are not available. Patients are recruited by FCCCs, which may not fully represent the French or European general population. In particular, the median age of our cohort is a bit lower than expected due to a slight under-representation of older women (26% of women in ESME are aged $\geq$70 years) who are less frequently referred to comprehensive cancer centres. This could lead potentially to a slight overestimation of OS.[42] Performance status, an important predictor of OS, was available in only 40% of the files, and could not be included in the main analyses. Sensitivity analyses conducted among patients with PS data available, however, gave the same results as the main analyses. This real-life public-health-level approach cannot provide a formal demonstration of the causal impact (or absence of impact) of treatments on OS, but only provides time relations and observations, which we nevertheless consider relevant.

In conclusion, in this large-scale, real-life setting and among almost 20 500 patients with MBC, we observed a dramatic improvement of OS among HER2+ MBC patients since 2013, most likely in relation to the release of two several major HER2-directed therapies, whose penetrance was high. This was not observed in HR+/HER2− and TNBC subtypes, where OS has not improved over time, and penetrance of new drugs released during the period (eribulin and everolimus) was low. Our data do not yet allow to evaluate the impact of CDK4/6 inhibitors. These results overall question the necessary public health strategy associated with the release of new drugs if a real-life impact is expected, and the role of real-life data on the final assessment of treatment innovations.

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REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries and 25 major cancers in 2018. *Eur J Cancer.* 2018;103:356-387.
2. Cardoso F, Spence D, Mertz S, et al. Global analysis of advanced/metastatic breast cancer: decade report (2005-2015). *Breast.* 2018;39:131-138.
3. Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. *Nature.* 2000;406(6797):747-752.
4. Swain SM, Miles D, Kim S-B, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519-530.
5. Di V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(6):732-742.
6. Krop IE, Kim S-B, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. *Lancet Oncol.* 2017;18(6):743-754.
7. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2. *Ann Oncol.* 2014;25(12):2357-2362.
8. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med.* 2016;375(20):1925-1936.
9. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med.* 2018;379(20):1926-1936.
10. Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316.
11. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524.
12. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5(1):1-8.
13. Sledge GW Jr, Toi M, Neven P, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy-MONARCH 2: a randomized clinical trial. *JAMA Oncol.* 2019;6(1):116-124.
14. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet.* 2011;377(9769):914-923.
15. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med.* 2016;375(23):2293-2297.
16. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *JNCI J Natl Cancer Inst.* 2017;109(11):djx187.
17. Pérol D, Robain M, Arveux P, et al. The ongoing French metastatic breast cancer (MBC) cohort: the example-based methodology of the Epidemiological Strategy and Medical Economics (ESME). *BMJ Open.* 2019;9(2):e023568.
18. Gobbini E, Ezzalfani M, Dieras V, et al. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur J Cancer.* 2018;96:17-24.
19. Deluche E, Antoine A, Bachelot T, et al. Contemporary outcomes of metastatic breast cancer among 22 000 women from the multicentre ESME cohort 2008-2016. *Eur J Cancer.* 2020;129:60-70.
20. Steffen M. Universalism, responsiveness, sustainability—regulating the French Health Care System. *N Engl J Med.* 2016;374(5):401-405.
21. Martinalbo J, Bowen D, Camarero J, et al. Early market access of cancer drugs in the EU. *Ann Oncol.* 2016;27(1):96-105.
22. Unicancer - Mes données de santé. Available at: https://mesdonnees.unicancer.fr/propos-de-ce-site.
23. MacGrogan G, Mathieu M-C, Poulet B, et al. Pre-analytical stage for biomarker assessment in breast cancer: 2014 update of the GEFPICS' guidelines in France. *Ann Pathol.* 2014;34(5):366-372.
24. Maran-Gonzalez A, Franchet C, Duprez-Paumier R, et al. GEFPICS' guidelines for management of breast cancer tissue samples in the neoadjuvant setting. *Ann Pathol.* 2019;39(6):383-398.
25. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. *Arch Pathol Lab Med.* 2018;142(11):1364-1382.
26. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394-424.
27. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol.* 2015;26(8):1547-1573.
28. Lux MP, Nabieva N, Hartkopf AD, et al. Therapy landscape in patients with metastatic HER2-positive breast cancer: data from the PRAEGNANT real-world breast cancer registry. *Cancers (Basel).* 2019;11(1):10.
29. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med.* 2005;353(16):1659-1672.
30. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. *J Clin Oncol.* 2006;24(34):5381-5387.
31. Gray R, Bradley R, Braybrooke J, et al. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet.* 2019;393(10179):1440-1452.
32. Eubank WB, Mankoff DA, Takasugi J, et al. ^{18}Fluorodeoxyglucose positron emission tomography to detect mediastinal or internal mammary metastases in breast cancer. *J Clin Oncol.* 2001;19(15):3516-3523.
33. Feinstein AR, Sosin DM, Wells CK. The Will Rogers phenomenon. Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer. *N Engl J Med.* 1985;312(25):1604-1608.

34. Fink MK, Kleeberg UR, Bartels S. Adjuvant therapy-related shortening of survival (ATRESS): an underrated phenomenon. *Oncologist.* 2015;20(1):88.
35. Fink MK. Does adjuvant therapy reduce postmetastatic survival? *Ann Oncol.* 2019;30(8):1184-1188.
36. Allgood PC, Duffy SW, Kearins O, et al. Explaining the difference in prognosis between screen-detected and symptomatic breast cancers. *Br J Cancer.* 2011;104(11):1680-1685.
37. Duffy SW, Nagtegaal ID, Wallis M, et al. Correcting for lead time and length bias in estimating the effect of screen detection on cancer survival. *Am J Epidemiol.* 2008;168(1):98-104.
38. Cottu P, Coudert B, Perol D, et al. Evolution in the real-world therapeutic strategies in more than 20 000 women with breast cancer having received human epidermal growth factor receptor 2—targeted treatments: results from the French personalized reimbursement model database (2011-2018). *Eur J Cancer.* 2020;141:209-217.
39. Sabatier R, Gonçalves A. Autorisation de mise sur le marché du pertuzumab (Perjeta®) dans les cancers du sein métastatiques HER2 positifs. *Bull Cancer (Paris).* 2014;101(7-8):765-771.
40. Swain S, Kim S, Cortes J, et al. Final overall survival (OS) analysis from the Cleopatra study of first-line (1L) pertuzumab (Ptz), trastuzumab (T), and docetaxel (D) in patients (Pts) with Her2-positive metastatic breast cancer (Mbc). *Ann Oncol.* 2014;25:v1-v41.
41. Jacot W, Heudel P-E, Fraisse J, et al. Real-life activity of eribulin mesylate among metastatic breast cancer patients in the multicenter national observational ESME program. *Int J Cancer.* 2019;145(12):3359-3369.
42. Defossez G, Le Guyader-Peyrou S, Uhry Z, et al. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Etude À Partir Regist. Cancers Réseau Francim Résultats Préliminaires Synthèse St.-Maurice Fra Santé Publique Fr. 2019:19. Available at: https://import/estimations-nationales-de-l-incidence-et-de-la-mortalite-par-cancer-en-france-metropolitaine-entre-1990-et-2018-tumeurs-solides-etude-a-partirlast. Accessed April 15, 2021.