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REVIEW

Long-term survival in HER2-positive metastatic breast cancer treated with first-line trastuzumab: results from the french real-life curie database

E. Kaczmarek[1,2,3,4,5] · C. Saint-Martin[1,2,3,4,5] · J.-Y. Pierga[1,2,3,4,5] · E. Brain[1,2,3,4,5] · R. Rouzier[1,2,3,4,5] · A. Savignoni[1,2,3,4,5] · E. Mouret-Fourme[1,2,3,4,5] · V. Dieras[1,2,3,4,5] · I. Piot[1,2,3,4,5] · C. Dubot[1,2,3,4,5] · M. Carton[1,2,3,4,5] · F. Lerebours[1,2,3,4,5]

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Abstract

Background Outcome of HER2-positive metastatic breast cancer (MBC) patients has improved since the use of trastuzumab. However, most HER2-positive MBC patients will progress within 1 year of trastuzumab-based therapy. Only limited data are available concerning long-term responders.

Methods The primary objective of this study was to compare overall survival (OS) of HER2+ MBC patients with long-term response to first-line trastuzumab with overall survival of those with non-long-term response, based on two institutional databases: the French Epidemiological Strategy and Medical Economics program and the Breast Database. Long-term responders (LTR) were defined as patients with non-progressive disease for ≥ 2 years on first-line trastuzumab. Secondary objectives included progression-free survival (PFS), and predictive factors for LTR status.

Results From 2004 to 2014, 422 HER2-positive MBC patients received first-line trastuzumab. With a median follow-up of 48 months, median OS and PFS were 63 months (CI95%, 50–71), and 18 months (CI95%, 15–21) respectively. In 111 patients (26.3%) classified as LTR, median OS was 110 months (CI95%, 95-not reached) versus 56 months in non-LTR patients (CI95%, 47–68). In multivariate logistic regressions, the following factors were independently associated with LTR status: number of metastatic sites (≤ 2 versus > 2, $p = 0.01$); endocrine therapy for metastatic disease ($p = 0.001$) and taxane-based first-line chemotherapy ($p = 0.003$).

Conclusion Several features are associated with long-term response to trastuzumab: few metastatic sites, taxane-based chemotherapy and maintenance endocrine therapy in HR+ patients. Further studies are needed to identify patients in whom trastuzumab can be stopped after several years of sustained response.

Keywords Trastuzumab · Long-term responders · Metastatic breast cancer

Introduction

About 20% of breast cancer patients will develop distant metastases [1]. HER2-positive (HER2+) disease has been commonly associated with poorer prognosis. However, the outcome of HER2+ breast cancer patients has dramatically improved since the use of trastuzumab: a recent analysis of the Epidemiological Strategy and Medical Economics (ESME) database showed a median overall survival of 51.1 months in 2012, compared to 38.7 months in 2008 [2].

Treatment of HER2-positive MBC is based on first-line anti-HER2 therapy, particularly trastuzumab and more recently pertuzumab, in combination with chemotherapy. Prospective randomized trials have demonstrated survival benefit from these treatments, in the first-line setting, and

✉ E. Kaczmarek
e-kaczmarek@o-lambret.fr

1 Department of Medical Oncology, Oscar Lambret Center, Lille, France

2 Department of Biostatistics, Institut Curie, Paris, France

3 Department of Medical Oncology, Institut Curie, Paris, France

4 Department of Surgical Oncology, Institut Curie, Paris, France

5 R&D, Unicancer, UCBG, Paris, France

also after progression [3–5]. Median OS ranges from 25 to 30 months and PFS ranges from 7 to 11 months in patients treated with first-line trastuzumab and taxanes.

Few data are available on the optimal duration of anti-HER2 therapy in metastatic disease. Although several case reports and studies have reported exceptional survival in patients who stopped trastuzumab, most studies support maintenance of anti-HER2 therapy, and it is now generally accepted that anti-HER2-therapy should be maintained until disease progression, except in the presence of unacceptable toxicity or at the patient's request [6, 7].

Whereas most patients will experience disease progression within 1 year, some patients have been reported to be long-term responders [8–16]. Few data are available on these patients with extended survival. Results from several observational studies have distinguished clinicopathological factors that may be associated with better prognosis [8–15]. However, the results are sometimes discordant and no risk factor has been clearly identified to be associated with better outcome.

The primary objective of the present study was to assess overall survival (OS) of HER2-positive MBC patients who experienced a long-term response under first-line trastuzumab. Secondary objectives were progression-free survival and identification of potential predictive factors of long-term survival.

Materials and methods

Study design

Patient inclusion was based on institution-specific data included in 2 databases: data from Institut Curie patients included in the Curie ESME program established in 2014 by UNICANCER, which included patients from 2008 to 2014 [2]; and the Institut Curie "breast database" containing data from 2004 to 2008. Inclusion criteria were the same for both databases.

HER2 positivity was centrally reviewed and was defined on primary tumor or, when available, on metastasis biopsies according to ASCO/CAP guidelines [17].

Patients with a simultaneous diagnosis of another non-breast malignancy and those who did not receive first-line trastuzumab were excluded.

Patients were considered to be de novo metastatic when metastases were discovered at diagnosis or within 6 months after diagnosis.

Long-term responders (LTR) were defined as patients with non-progressive disease for at least 2 years on first-line trastuzumab.

Long-term responders and non-long-term responders (non-LTR) were compared in terms of the following features: clinical characteristics, including age at diagnosis and age at metastatic relapse, body mass index (BMI), menopausal status; tumor characteristics: histological type, histological grade, Hormone Receptor (HR) positivity; treatments for primary and metastatic disease: chemotherapy, endocrine therapy, anti-HER2 therapy; and metastatic disease characteristics: localization and number of metastatic sites, disease-free interval (< 6 months, 6–24 months, > 24 months).

Study analysis

Baseline characteristics were summarized as number and percentage for qualitative data, mean and standard deviation or median with minimum and maximum for continuous variables. Associations between categorical variables were evaluated using Chi-2 or Fisher's exact test, as appropriate. Continuous variables were compared by Student's *t* test.

Univariate and multivariate logistic regression analyses were used to identify independent predictors of LTR status.

Follow-up was defined as the time from initiation of first-line trastuzumab to the date of last news and calculated by the reverse Kaplan–Meier method.

Overall Survival (OS) was defined as time between initiation of first-line trastuzumab and the date of death for deceased patients. Patients still alive were censored at the date of last news.

Progression-free survival (PFS) was defined as the time between initiation of first-line trastuzumab and first progression and/or death. Patients still alive were censored at the date of last news.

OS and PFS were estimated using the Kaplan–Meier Method and OS were compared using the log-rank test.

To avoid the immortality bias (LTR > 24 months), OS was calculated on the population who survived more than 24 months [18].

A p value less than 0.05 was considered to be statistically significant.

Analyses were performed using R 3.4.2. software (http://cran.r-project.org).

Ethical and regulatory considerations

Databases (Curie ESME and Curie "breast database") were approved by an independent Ethics Committee (Comité De Protection Des Personnes Sud-Est II- 2015-79 and Comité de Revue Interne) and were authorized by the French data protection authority (authorization No. 1704113).

Results

Patients

From 2008 to 2014, 2990 patients with MBC were identified in the Curie-ESME database, including 460 patients with HER2+ disease. Sixteen patients with other non-breast malignancies were excluded. Of the 444 remaining patients, 340 were included in the present analysis (centrally reviewed HER2 positive disease and first-line trastuzumab as single anti-HER2 treatment).

From 2004 to 2008, 82 patients with HER2+ MBC who received first-line trastuzumab were identified from the Curie "breast database".

After merging these two databases, from 2004 to 2014, 422 patients were included and analyzed. The median follow-up was 48 months (1–154 months; CI95%, 46.5–59.0) (Fig. 1).

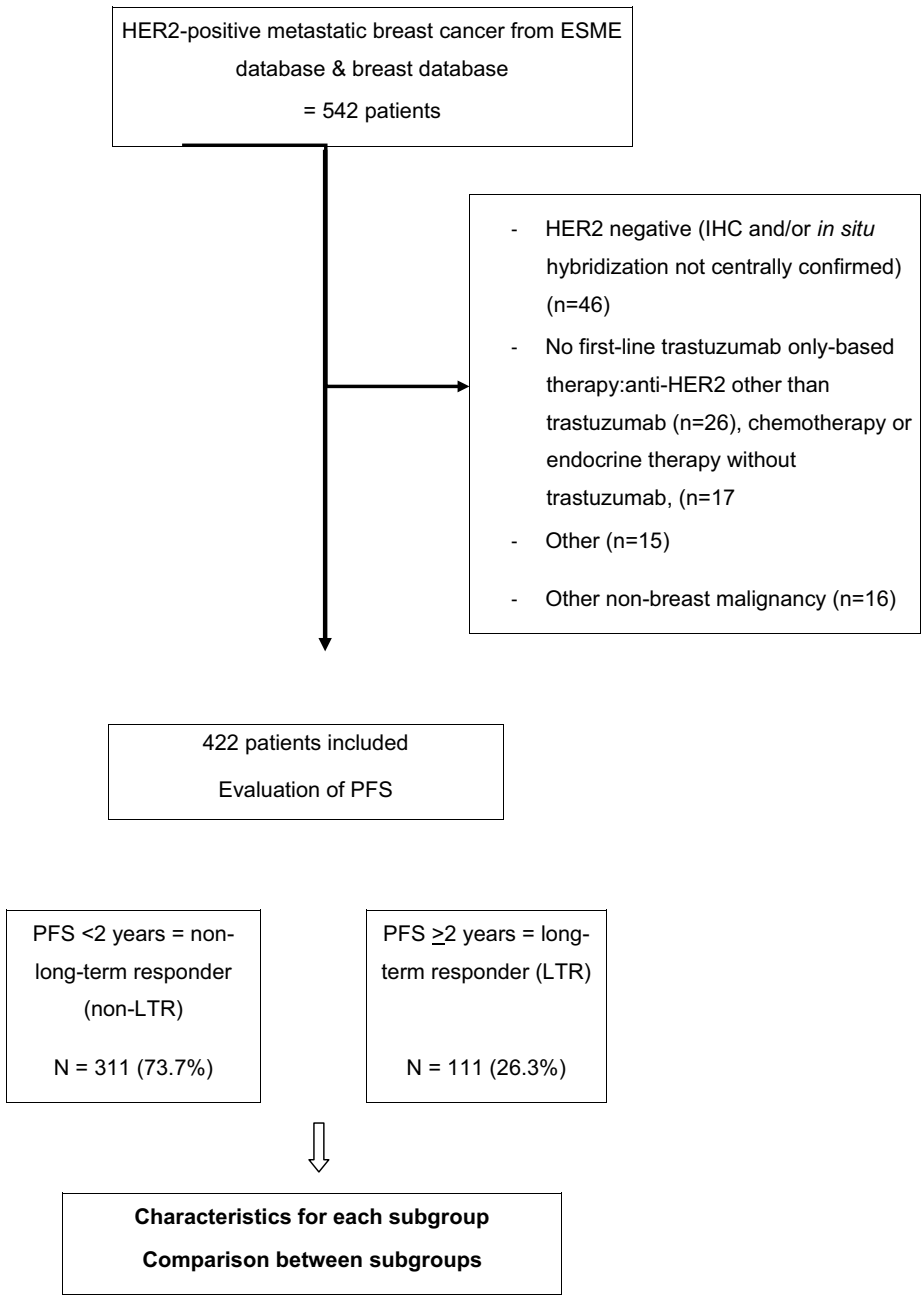

Fig. 1 Consort plot

Patient and tumor characteristics

Primary breast cancer

The mean age at primary breast cancer diagnosis was 52.3 years (sd = 13.7).

Mean BMI was 24.9 kg/m^2 (sd = 5.3). Histology revealed ductal carcinoma in 84.8% of cases, histological grade was mostly 2 (40.5%) and 3 (52.5%), and 57.5% had HR-positive disease.

Primary breast cancer systemic treatments were mostly based on anthracyclines (77%) and taxanes (59.9%). Ninety-nine (50.5%) patients received adjuvant trastuzumab.

Metastatic disease

In this population of 422 patients, 41.9% had de novo metastatic disease at diagnosis. The mean age at MBC diagnosis was 55.3 years (sd = 13.6). Seventy-eight percent of patients had ≤ 2 metastatic sites, mainly bone, liver, soft tissues and lung. In combination with first-line trastuzumab, patients mostly received taxane-based therapy (78.2%) and endocrine therapy (30.1%) as maintenance after first-line chemotherapy.

One-hundred and eleven patients (26.3%) were defined as LTR, whereas 311 patients (73.7%) were defined as non-LTR.

Survival analysis

In this population of 422 patients, median overall survival was 63 months (CI95%, 50–71) and median progression-free survival was 18 months (CI95%, 15–21): 296 events were identified.

To avoid immortality bias on long-term responders, survival analysis was limited to patients still alive at 24 months [18]. Results are shown in Fig. 2. Eighteen events were observed in the LTR-group ($n = 111$), with a median overall survival of 110 months (CI95%, 95-not reached), whereas 86 events were observed in the non-LTR-group ($n = 174$), with a median overall survival of 56 months (CI95%, 47–68).

Comparison between LTR and non-LTR

Primary breast cancer characteristics according to LTR status are shown in Table 1. Median age, menopausal status, and pathological characteristics (HR status, histological grade, histological type) were similar in the LTR and non-LTR groups.

Primary breast cancer treatments are reported in 245 patients who were metastasis-free at diagnosis. Primary breast cancer treatments were also similar in the two groups. Neither chemotherapy nor trastuzumab-based therapy influenced LTR or non-LTR status (Table 2).

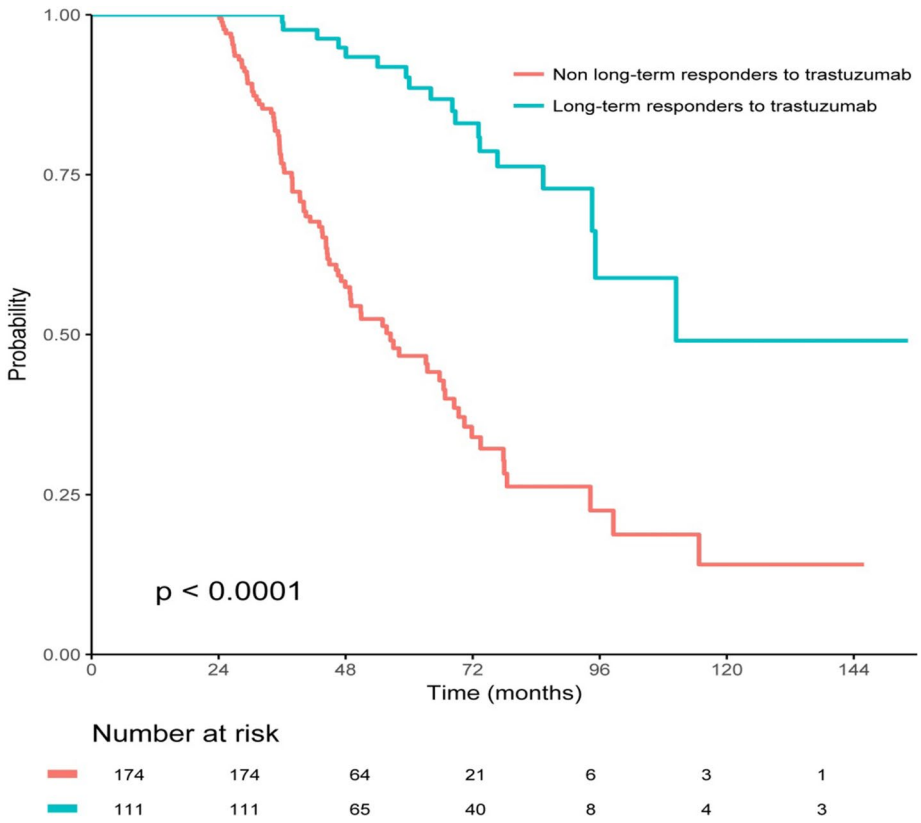

Fig. 2 Overall survival in patients still alive at 24 months

Table 1 Primary breast cancer characteristics in LTR and non-LTR patients

Characteristics	LTR $n=111$ (%)	Non-LTR $n=311$ (%)	p
Age at diagnosis (mean, years)	51.5	52.6	0.41
Menopausal status			
Pre-menopausal	31 (39.7)	85 (40.5)	0.91
Post-menopausal	47 (60.3)	125 (59.5)	
ND	33	101	
Hormone receptors			
Positive	66 (59.5)	176 (56.8)	0.62
Negative	45 (40.5)	134 (43.2)	
ND		1	
Histological type			
IDC	91 (86.7)	261 (88.2)	0.92
ILC	6 (5.7)	15 (5.1)	
Other	8 (7.6)	20 (6.8)	
ND	6	15	
Histological grade			
1	6 (5.8)	10 (3.5)	0.58
2	44 (42.7)	125 (43.4)	
3	53 (51.5)	153 (53.1)	
ND	8	23	

Table 2 Primary breast cancer treatments in LTR and non-LTR patients without *de novo* metastatic MBC ($n=245$)

Treatment	LTR $n=63$ (%)	Non-LTR $n=182$ (%)	p
Anthracyclines			
No	10 (21.3)	34 (23.6)	0.74
Yes	37 (78.7)	110 (76.4)	
ND	16	38	
Taxanes			
No	19 (40.4)	58 (40)	0.96
Yes	28 (59.6)	87 (60)	
ND	16	37	
Trastuzumab			
No	25 (53.2)	72 (48.3)	0.56
Yes	22 (46.8)	77 (51.7)	
ND	16	33	
Other chemotherapy			
No	13 (28.9)	35 (24.6)	0.57
Yes	32 (71.1)	107 (75.4)	
ND	18	40	
Endocrine therapy			
No	26 (41.3)	97 (53.3)	0.1
Yes	37 (58.7)	85 (46.7)	
Radiotherapy			
No	8 (12.7)	25 (13.7)	0.84
Yes	55 (87.3)	157 (86.3)	

Metastatic breast cancer characteristics and treatments are shown in Table 3.

On univariate analysis, the following factors were significantly associated with LTR status: small number of metastatic sites (≤ 2 versus >2, $p=0.002$), absence of central nervous system metastases ($p=0.024$), endocrine therapy for metastatic disease ($p<0.001$) and taxane-based first-line CT ($p=0.007$) (Table 4). In contrast, older age, long disease-free interval, and absence of visceral disease were not associated with LTR status.

On multivariate analysis, the number of metastatic sites, taxane-based first-line CT and endocrine therapy in combination with trastuzumab, remained significantly associated with LTR status (Table 4).

Discussion

In this study, a subgroup representing about one-quarter of long-term responders was defined and analyzed. Overall survival was 110 months in this group, compared to 56 months in the non-long-term responders group, with a median follow-up of 4 years.

"Long-term responders" were defined as patients with non-progressive disease for at least 2 years on first-line trastuzumab. This 2-year cut-off was considered to be sufficiently long to distinguish an adequate proportion of patients with prolonged response to trastuzumab with respect to the PFS and OS observed in the overall population treated with trastuzumab, as phase III randomized trials evaluating survival of patients treated with first-line trastuzumab have reported PFS of about 7–11 months and OS of about 25–30 months [3–5].

Studies in patients with extended survival after first-line trastuzumab define long-term response on the basis of progression-free survival or overall survival. Moreover, these studies have selected different cut-offs to define PFS and OS, either 2, 3 or 5 years [9–15]. While most of these studies described the features of a single LTR group, few of them have compared long-term and short-term responders [10, 13].

We have shown that a small number of metastatic sites, taxane-based first-line chemotherapy and maintenance endocrine therapy were significantly associated with long-term response. These results are consistent with those reported by several other studies. A small number of metastatic sites was associated with good prognosis in two previous studies, one comprising 17 LTR patients who did not progress for at least 3 years on trastuzumab, and another single-institution review of 168 patients, in which 56 (33%) had an overall survival longer than 5 years [9, 14].

The influence of metastatic sites on prognosis is more discordant. The absence of CNS metastases has been correlated

Table 3 Metastatic breast cancer characteristics and treatments in LTR and non-LTR patients

Characteristics	LTR $n=111$ (%)	Non-LTR $n=311$ (%)	p
Age at diagnosis of metastatic disease (median, years)	54.5	55.5	0.46
De novo metastatic (< 6 months)			
No	63 (56.8)	182 (58.5)	
Yes	48 (43.2)	129 (41.5)	0.75
Number of metastatic sites			
≤ 2	99 (89.2)	232 (74.6)	0.001
> 2	12 (10.8)	79 (25.4)	
Disease-free interval (months)			
< 6	48 (43.2)	129 (41.5)	
[6–24]	7 (6.3)	33 (10.6)	0.41
≥ 24	56 (50.5)	149 (47.9)	
Metastatic sites			
Bone			
No	60 (54.1)	168 (54)	0.99
Yes	51 (45.9)	143 (46)	
Liver			
No	79 (71.2)	206 (66.2)	0.34
Yes	32 (28.8)	105 (33.8)	
Lung			
No	86 (77.5)	223 (71.7)	0.24
Yes	25 (22.5)	88 (28.3)	
Soft tissues			
No	70 (63.1)	171 (55)	0.14
Yes	41 (36.9)	140 (45)	
CNS			
No	107 (96.4)	276 (88.7)	0.017
Yes	4 (3.6)	35 (11.3)	
Other			
No	106 (95.5)	292 (93.9)	0.53
Yes	5 (4.5)	19 (6.1)	
Treatments			
Taxanes			
No	14 (12.6)	78 (25.1)	0.006
Yes	97 (87.4)	233 (74.9)	
Capecitabine			
No	95 (85.6)	275 (88.4)	0.43
Yes	16 (14.4)	36 (11.6)	
Vinorelbine			
No	104 (93.7)	291 (93.6)	0.96
Yes	7 (6.3)	20 (6.4)	
Other chemotherapy			
No	106 (95.5)	292 (93.9)	0.53
Yes	5 (4.5)	19 (6.1)	
Endocrine therapy plus trastuzumab			
No	63 (56.8)	232 (74.6)	< 0.001
Yes	48 (43.2)	79 (25.4)	

Table 4 Metastatic breast cancer univariate and multivariate logistic regression analysis for predictive factors of LTR

	Univariate		Multivariate	
	OR [95%CI]	p global	OR [95%CI]	p global
Number of metastatic sites				
≤2	1		1	
>2	0.36 [0.18–0.66]	0.002	0.41 [0.20–0.79]	0.01
Taxanes				
No	1		1	
Yes	2.32 [1.29–4.45]	0.007	2.64 [1.42–5.20]	0.003
Endocrine therapy plus trastuzumab				
No	1		1	
Yes	2.24 [1.42–3.52]	< 0.001	2.16 [1.34–3.48]	0.001
CNS metastases				
No	1		1	
Yes	0.29 [0.09–0.76]	0.024	0.43 [0.12–1.16]	0.13

with better survival in several studies [11–13]. Murthy et al. observed that, among patients with central nervous system disease, present in 39% of patients, only 14% survived more than 5 years [14]. In contrast with the findings of the present study, several other studies have reported better survival for patients with only bone and/or lymph node metastases [9, 12, 13]. Liver metastases were among the main metastatic sites; in our long-term responder group, 28.8% had liver metastasis with no correlation with LTR status compared to 35% of LTR patients in LHORA, and 32.8% of LTR patients in the HER-OS study [10, 12, 14].

First-line taxane-based therapy was more frequent in LTR than in the non-LTR subgroup in our study. These results are consistent with results from the regist-HER cohort (79% of LTR received taxanes, versus 66.3% in the short-term responder cohort). Taxane-based therapy was also the most common first-line treatment associated with trastuzumab in the LTR Australian cohort (54% of cases), and in Fiteni's French cohort of 217 MBC patients (73% of cases), but with no reported correlation with better outcome [10, 15, 21]. No correlation was observed between other common chemotherapies (capecitabine or vinorelbine) and LTR status.

We did not observe any correlation between HR positivity and LTR status. The conclusions of other studies are discordant. Although several studies have reported longer progression-free survival for patients with HR-positive tumors, patients with HR-negative tumors sometimes had better survival in other studies [10, 13, 19, 21]. Montemurro et al. [20] highlighted a poorer response to trastuzumab + chemotherapy in the presence of high HR positivity (more than 30% of cancer cells) compared to the response rate observed in tumors with lower or absent HR expression. HR positivity may account for part of the various anti-HER2 responses, as well as sensitivity to chemotherapy. However, we observed

longer survival in patients treated with endocrine therapy after first-line chemotherapy, although not all HR-positive tumors received maintenance endocrine therapy, as 57.5% of patients were HR-positive, while 30.1% of them received endocrine therapy. A recent study showed that ER positivity together with no evidence of disease after first-line trastuzumab ± pertuzumab were associated with prolonged OS in multivariate analysis [22].

In addition to clinical predictors, gene expression analysis may also help to identify LTR to trastuzumab. In particular, it has been shown that activation of the PI3 K pathway may be associated with early progression [23].

Discontinuation of anti-HER2 drugs in the metastatic setting remains the main unresolved issue, as studies comprising 20–25% of long-term responders have reported discordant data for patients with prolonged survival who experienced time off HER2 therapies [9, 11, 14, 15]. In 108 HER2+ MBC patients who received trastuzumab for more than 2 years as first-line therapy, disease progression occurred in 4 of 27 patients in whom trastuzumab was discontinued [24]. ESMO and ASCO guidelines currently do not recommend breaks in anti-HER2 treatments except after several years of sustained complete remission (6.7).

This study has several limitations. It was based on retrospective analysis of a single-center database (ESME-Curie). One-hundred and four patients were excluded from analyses principally because of non trastuzumab only-based first-line treatment or because of HER2-negative disease after centrally review. The definition of "long-term responders" as non-progressive disease for at least 2 years may be subject to discussion and could limit comparison with other studies that used other cut-offs. However, this analysis includes a large number of 422 patients HER2 positive MBC with sufficient follow-up and exhaustive data. Baseline patient characteristics and treatments are consistent with those of another large cohort of LTR to trastuzumab [15]. Finally, the present study is one of the few to compare the characteristics of long-term versus non-long-term responders [10, 13].

These results need to be confirmed by further studies to propose alternative anti-HER2 treatments, used alone or in combination to improve survival in all patients [25, 26].

Conclusion

We showed that about one-quarter of patients on first-line trastuzumab can achieve a median overall survival of more than 9 years. A small number of metastatic sites, first-line taxane-based chemotherapy, and maintenance endocrine treatment were significantly associated with this long-term response.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human participants performed by any of the authors.

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