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Clinical outcomes of patients with breast cancer relapsing after (neo) adjuvant trastuzumab and receiving trastuzumab rechallenge or lapatinib-based therapy: a multicentre retrospective cohort study

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ABSTRACT

Background In the prepertuzumab era, we evaluated the clinical outcomes of patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer who underwent first-line trastuzumab-based or lapatinib-based therapy according to prior exposure to (neo)adjuvant trastuzumab.

Materials and methods In this multicentre retrospective cohort study conducted in 14 Italian centres of the Gruppo Italiano Mammella, consecutive patients undergoing first-line trastuzumab or lapatinib-based therapy were included. Analyses were performed according to the type of first-line therapy for metastatic disease (trastuzumab or lapatinib). Dichotomous clinical outcomes were analysed using logistic regression and time-to-event outcomes using Cox proportional hazard models controlling for relevant demographic, clinicopathological and therapy characteristics.

Results Out of 450 patients included in the study, 416 (92%) received trastuzumab and 34 (7.5%) lapatinib. As compared with the trastuzumab cohort, more patients in the lapatinib cohort had a trastuzumab-free interval <1 month (37% vs 13.9%; p=0.017) and brain metastasis as first site of relapse (38.2% vs 9.4%; p<0.001). Among the 128 patients who relapsed after prior (neo)adjuvant trastuzumab, 101 (78.9%) received first-line trastuzumab and 27 (21.1%) first-line lapatinib. The following outcomes were observed with first-line lapatinib or trastuzumab, respectively: overall response rate 45.5% vs 61.3% (p=0.184), clinical benefit rate 68.2% vs 72.5% (p=0.691), median progression-free survival (PFS) 11.4 vs 12.0 months (p=0.814) and median overall survival (OS) 34.7 vs 48.2 months (p=0.722). In patients with brain metastasis as first site of relapse, median PFS was 12.2 vs 9.9 months (p=0.093) and median OS 33.7 vs 28.5 months (p=0.280), respectively.

Conclusions In patients with HER2-positive breast cancer relapsing after prior (neo)adjuvant trastuzumab, first-line treatment with trastuzumab or lapatinib was not associated with a significant difference in the clinical outcomes. A non-significant trend favouring the use of lapatinib was observed in patients with brain metastasis as the first site of relapse.

Key questions

What is already known about this subject?

► There is a paucity of evidence on clinical outcomes of patients with metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer previously exposed to trastuzumab in the (neo)adjuvant setting and in those with brain metastasis as the first site of disease relapse.

What does this study add?

► This study provides real-world data on the use of first-line trastuzumab-based or lapatinib-based therapy in patients pretreated with trastuzumab in the early setting and in those with brain metastasis.

How might this impact on clinical practice?

► Our results might support the use of lapatinib in low-income countries where new anti-HER2 agents (ie, pertuzumab or trastuzumab emtansine) are not available, especially in patients pretreated with trastuzumab or in those with brain metastasis.

INTRODUCTION

Approximately 15%–25% of all breast cancers are characterised by amplification of the human epidermal growth factor receptor 2 gene or overexpression of its protein product (ie, HER2-positive disease).[1] Trastuzumab has been the first anti-HER2 agent approved for the treatment of patients with HER2-positive

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disease.[2 3] The introduction of trastuzumab in the early setting radically changed the prognosis of women with HER2-positive breast cancer.[4–6] However, despite its use, 25%–30% of patients relapse up to 10 years after diagnosis.[7–9] Large randomised trials with the monoclonal antibody pertuzumab added to trastuzumab and chemotherapy in patients with trastuzumab sensitive tumours and with the antibody-drug conjugate trastuzumab emtansine (T-DM1) in patients whose disease progressed during or shortly after trastuzumab exposure have established current first-line and second-line treatment paradigms.[3 10–13] Yet, open issues remain as the optimal treatment of patients failing adjuvant treatment with monoclonal antibodies and, in particular of those with brain metastasis as the first site of relapse.

Lapatinib is a tyrosine kinase inhibitor with inhibitory activity against both HER2 and epidermal growth factor receptor 1 (EGFR).[14] It was the second anti-HER2 agent approved based on the EGF100151 randomised trial showing the safety and efficacy of the lapatinib-capecitabine combination in patients with advanced disease.[15 16] Lapatinib is currently available for the treatment of patients with HER2-positive metastatic breast cancer in combination with capecitabine, endocrine therapy or trastuzumab.[3 11] Lapatinib showed clinical activity in patients previously exposed to trastuzumab.[17 18] Moreover, the combination of lapatinib and capecitabine was shown to be active as first-line treatment of brain metastasis in patients with HER2-positive advanced breast cancer.[19]

The present study aimed to compare retrospectively the clinical outcomes of patients with metastatic HER2-positive breast cancer treated with first-line trastuzumab-based or lapatinib-based therapy, with a particular focus to women previously exposed to trastuzumab in the (neo) adjuvant setting and to those presenting with brain metastasis as the first site of disease relapse.

METHODS

Study design and patient selection

This is a multicentre retrospective cohort study conducted in 14 Italian centres of the Gruppo Italiano Mammella aiming to compare the clinical outcomes of patients with HER2-positive metastatic breast cancer treated with first-line trastuzumab or lapatinib.

Eligibility criteria for study inclusion were previously reported.[20–22] Briefly, the study included consecutive patients with HER2-positive breast cancer treated from January 2000 to December 2013 with trastuzumab-based therapy as first-line treatment. For the present analysis, consecutive patients treated at the same centres and exposed to lapatinib as first-line treatment were also eligible. The type of anti-HER2 agent used as first-line therapy was the criteria used to divide patients in two cohorts: those exposed to first-line trastuzumab (trastuzumab cohort) and those exposed to first-line lapatinib (lapatinib cohort).

Treatment and study procedures

The following information was retrieved from medical records and anonymous data entered in a database: date of breast cancer diagnosis, pathological and biological features of primary breast cancer, (neo)adjuvant treatment administered, date of disease relapse, number and type of sites involved at the time of disease relapse, treatment received as first-line and subsequent lines, clinical outcomes for each line of treatment and date of last follow-up or death.

In the presence of multiple organs involved at the time of diagnosis of metastatic disease, sites of relapse were defined by importance in the following order: brain, liver, lung, bone and others. Other sites of disease relapse included soft tissues, skin, lymph nodes and pleura. The Institutional Review Boards of participating centres approved the study protocol and the retrospective data collection for the current study. Informed consent was obtained by each patient before study entry.

Objectives and end point assessment

The current analysis aimed to compare the clinical outcomes of patients previously exposed to (neo)adjuvant trastuzumab and treated with first-line trastuzumab or lapatinib. Study endpoints were progression-free survival (PFS), overall survival (OS), objective response rate (ORR) and clinical benefit rate (CBR). A secondary objective was to compare clinical outcomes of patients with brain metastasis as first site of disease relapse and treated with first-line trastuzumab or lapatinib. The factors associated with the choice of first-line lapatinib over trastuzumab-based therapy were described. Moreover, the clinical effect of first-line trastuzumab versus lapatinib in the whole cohort of patients enrolled in the study regardless of prior exposure to (neo) adjuvant trastuzumab was also analysed.

Treatment response was assessed locally by participating centre. Radiological evaluation of tumour response was performed according to routine clinical practice. ORR was defined as complete response (CR) plus partial response (PR) and CBR as CR plus PR plus stable disease for at least 6 months. PFS was computed from date of diagnosis of metastatic disease to date of documented progression or death. OS was computed from date of diagnosis of metastatic disease to date of death or last follow-up.

Patients were excluded from the analysis of treatment response in case of lack of response data, non-measurable disease, radiotherapy before or during first-line medical treatment and brain metastasis as only site of relapse treated with whole-brain surgery or radiotherapy.

Statistical analysis

Descriptive statistics were performed and differences were then compared using Pearson's χ^2, Fisher's exact test or Wilcoxon rank-sum test where appropriate. Dichotomous outcomes were analysed using multivariate logistic regression. Cumulative survival probabilities were estimated using the Kaplan–Meier method and univariate analysis of differences between survival rates were tested

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for significance using the log-rank test. Multivariable analysis for survival was performed using the Cox proportional hazards model. Multivariable models included the following covariables: age at diagnosis, menopausal status, de novo metastatic vs recurrent, visceral vs non-visceral involvement, hormone receptor status, disease-free interval and centre size. Departures from the proportional hazards assumption were assessed based on the Schoenfeld residuals. All tests were two-sided with a 95% CI and p<0.05 was considered significant. All data were analysed using Stata 12.3 (Stata, College Station, Texas, USA).

RESULTS

The study included a total of 450 patients with metastatic HER2-positive breast cancer: 416 (92.4%) received trastuzumab (trastuzumab cohort) and 34 (7.6%) lapatinib (lapatinib cohort) as first-line therapy (table 1).

As compared with women in the trastuzumab cohort, more patients in the lapatinib cohort had stage III breast cancer at diagnosis (70.6% vs 32.5% p<0.001), grade 3 tumours (61.8% vs 44.0% p=0.019), received prior (neo) adjuvant chemotherapy (94.1% vs 52.2% p=0.005) and were previously exposed to (neo)adjuvant trastuzumab (79.4% vs 24.3% p<0.001; table 1). Specifically, 128 women relapsed after prior (neo)adjuvant trastuzumab and were the main focus of the present analysis: 27 (21.1%) received first-line lapatinib and 101 (78.9%) first-line trastuzumab. Baseline characteristics of this subgroup of patients are reported as supplementary material (online supplementary table 1).

At the time of disease relapse, patients in the lapatinib cohort had a higher incidence of brain metastasis as compared with those in the trastuzumab cohort (38.2% vs 9.4%, respectively; p<0.001; table 2). Patients in the lapatinib cohort showed a shorter trastuzumab-free interval (TFI, defined as the time from the last administration of (neo)adjuvant trastuzumab and diagnosis of metastatic disease) than those in the trastuzumab cohort (table 2). A total of 37.0% of patients in the lapatinib cohort had a TFI <1 month vs 13.9% in the trastuzumab cohort; conversely, 25.9% of patients in the lapatinib cohort vs 55.4% of patients in trastuzumab cohort had a TFI higher than 12 months (p=0.017; table 2). The majority of patients, 91.2% in the lapatinib cohort and 89.9% in the trastuzumab cohort, received first-line anti-HER2 therapy in association with chemotherapy (table 2). As expected, capecitabine was the preferred chemotherapy combination with lapatinib (received by more than 80% of patients in the lapatinib cohort), while taxane-based chemotherapy regimens were administered to 67.4% of patients in the trastuzumab cohort (table 2).

Clinical outcomes to first-line therapy after prior exposure to (neo)adjuvant trastuzumab

Median follow-up for PFS was 2.61 years (IQR 1.57–4.59). Among the 128 patients who relapsed after prior exposure to (neo)adjuvant trastuzumab, median PFS was 11.4 months in the lapatinib cohort and 12.0 months in the trastuzumab cohort (HR=1.20; 95% CI, 0.77 to 1.88; p=0.42). The multivariate analysis confirmed no difference in PFS (adjusted HR=1.06; 95% CI, 0.65 to 1.72; p=0.81) (figure 1A).

At a median follow-up of 2.85 years (IQR 1.79–4.91), median OS was 34.7 months and 48.2 months in the lapatinib and in the trastuzumab cohorts, respectively (HR=1.45; 95% CI, 0.77 to 2.70; p=0.25). The multivariate analysis showed no significant difference in OS (adjusted HR=1.13; 95% CI, 0.57 to 2.23; p=0.72) (figure 1B).

ORR was 45.5% and 61.3% in patients treated with first-line lapatinib and trastuzumab, respectively (OR=0.66; 95% CI 0.196 to 2.240; p=0.508). CBR was 68.2% in the lapatinib cohort and 72.5% in the trastuzumab cohort (OR=0.64; 95% CI 0.165 to 2.491; p=0.52) (online supplementary table 2).

Subgroup analysis according to hormone-receptor status did not show differences according to the type of first-line therapy used (online supplementary figure 1).

Incidence of central nervous system progression after first-line lapatinib or trastuzumab therapy was 1 out of 17 (5.9%) in the lapatinib cohort and 12 out of 85 (14.1%) in the trastuzumab cohort.

Clinical outcomes to first-line therapy in the whole cohort irrespective of prior exposure to (neo)adjuvant trastuzumab

In the whole cohort of 450 patients, median PFS was 11.4 months in the lapatinib cohort as compared with 14.4 months in the trastuzumab cohort (HR=1.43; 95% CI, 1.00 to 2.06; p=0.053). The multivariate analysis showed no significant difference in PFS (adjusted HR=1.32; 95% CI 0.90 to 1.93; p=0.150; figure 2A).

Median OS was 34.7 vs 52.5 months in the lapatinib and trastuzumab cohorts, respectively (HR=1.55; 95% CI 0.96 to 2.51; p=0.075). The multivariate analysis showed no significant difference in OS (adjusted HR=1.33; 95% CI 0.79 to 2.23; p=0.28; figure 2B).

ORR in the lapatinib and trastuzumab was 50.0% and 68.5%, respectively (OR=0.49; 95% CI 0.18 to 1.34; p=0.16). CBR was 67.9% in the lapatinib cohort and 76.7% in the trastuzumab cohort (OR=0.55; 95% CI 0.19 to 1.61; p=0.28; online supplementary table 3).

Clinical outcomes of patients with brain metastasis as first site of disease relapse

A total of 52 patients had brain metastasis as first site of disease relapse: 39 (75%) women received trastuzumab and 13 (25%) lapatinib.

Median PFS was 12.2 months with lapatinib and 9.9 months with trastuzumab (adjusted HR=0.48; 95% CI 0.21 to 1.13; p=0.093; figure 3A).

Median OS was 33.7 months in patients treated with lapatinib and 28.5 months in those treated with trastuzumab (adjusted HR=0.61; 95% CI 0.25 to 1.50; p=0.28; figure 3B).

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Table 1 Patients' characteristics at the time of breast cancer diagnosis

Characteristic	Trastuzumab cohort n=416 (%)	Lapatinib cohort n=34 (%)	P value
Median age (IQR), years	53.76 (43.40–62.63)	49.78 (45.48–61.78)	0.843
Menopausal status			0.876
Premenopausal	177 (42.5)	14 (41.2)	
Postmenopausal	239 (57.5)	20 (58.8)	
Tumour stage at diagnosis			<0.001
I	54 (13.0)	1 (2.9)	
II	110 (26.4)	7 (20.6)	
III	135 (32.5)	24 (70.6)	
IV	112 (26.9)	1 (2.9)	
Unknown	5 (1.2)	1 (2.9)	
Histological type			0.207
Ductal carcinoma	372 (89.4)	29 (85.3)	
Lobular carcinoma	13 (3.1)	2 (5.9)	
Mixed ductal-lobular carcinoma	4 (1.0)	0 (0.0)	
Others	14 (3.4)	3 (8.8)	
Unknown	13 (3.1)	0 (0.0)	
Hormone receptor status			0.457
Positive (ER and/or PR positive)	250 (60.1)	18 (52.9)	
Negative (ER and PR negative)	159 (38.2)	15 (44.1)	
Unknown	7 (1.7)	1 (2.9)	
Grade (G)			
G1	5 (1.2)	0 (0.0)	0.019
G2	123 (29.6)	3 (8.8)	
G3	183 (44.0)	21 (61.8)	
Unknown	105 (25.2)	10 (29.4)	
Prior chemotherapy			0.005
Neoadjuvant chemotherapy	59 (14.2)	15 (44.1)	
Adjuvant chemotherapy	158 (38.0)	17 (50.0)	
None	199 (47.8)	2 (5.9)	
Type of chemotherapy			0.006
Anthracycline only	91 (41.9)	4 (12.5)	
Anthracycline plus taxane	95 (43.8)	22 (68.8)	
Taxane only	8 (3.7)	2 (6.3)	
Others	23 (10.6)	1 (3.1)	
Prior endocrine therapy	157 (37.7)	13 (38.2)	0.954
Prior radiotherapy	191 (45.9)	19 (55.9)	0.263
Prior (neo)adjuvant trastuzumab	101 (24.3)	27 (79.4)	<0.001

ER, estrogen receptor; IQR, interquartile range; PR, progesterone receptor.

DISCUSSION

In our multicentre retrospective cohort study, we evaluated the clinical outcomes of patients with HER2-positive metastatic breast cancer treated with first-line trastuzumab-based or lapatinib-based therapy. In this real-world setting, we confirmed that first-line trastuzumab-based therapy is associated with better outcomes as compared with lapatinib treatment. In the subgroup of patients previously exposed to (neo)adjuvant trastuzumab, no difference was observed between the two treatment options. In the small cohort of patients with brain metastasis as first site of disease relapse, a trend towards better outcomes was observed with the use of lapatinib.

Thanks to the current availability of several anti-HER2 targeted agents, women with HER2-positive metastatic breast cancer tend to receive the highest number of lines

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Table 2 Patients' characteristics at diagnosis of stage IV disease and patterns of care to first-line treatment

Characteristic	Trastuzumab cohort n=416 (%)	Lapatinib cohort n=34 (%)	P value
Median disease-free interval (IQR range), years	2.326 (0.036–4.485)	1.854 (1.139–2.916)	0.361
Trastuzumab-free interval			0.017
<1 month	14 (13.9)	10 (37.0)	
≥1–6 months	15 (14.9)	5 (18.5)	
≥6–12 months	16 (15.8)	5 (18.5)	
≥12 months	56 (55.4)	7 (25.9)	
First-site of distant relapse			<0.001
Brain	39 (9.4)	13 (38.2)	
Liver	140 (33.7)	6 (17.6)	
Lung	83 (20.0)	5 (14.7)	
Bone	95 (22.8)	3 (8.8)	
Others	59 (14.2)	7 (20.6)	
Median number of metastatic sites (IQR)	2 (1–2)	1 (1–3)	0.335
Strategy as first-line therapy			0.747
CT (±ET)+trastuzumab	374 (89.9)	31 (91.2)	
ET+anti-HER2	35 (8.4)	3 (8.8)	
Anti-HER2 alone	7 (1.7)	0 (0)	
Type of first-line chemotherapy drugs			
Taxane-based	252 (67.4)	5 (16.1)	<0.001
Vinorelbine	93 (24.9)	1 (3.2)	
Capecitabine	10 (2.7)	25 (80.6)	
Others	19 (5.1)	0 (0.0)	
None	42 (10.1)	3 (8.8)	
Type of first-line chemotherapy regimen			0.026
Monochemotherapy	302 (80.7)	30 (96.8)	
Polychemotherapy	72 (19.3)	1 (3.2)	
Type of first-line endocrine therapy			0.256
Tamoxifen±LHRHa	12 (11.2)	0 (0.0)	
AI±LHRHa	87 (81.3)	2 (66.7)	
Fulvestrant	8 (7.5)	1 (33.3)	
None	309 (74.3)	31 (91.2)	
Lines of therapy for metastatic disease, median (min – max)			
Chemotherapy	2 (0–8)	2 (0–6)	0.723
Anti-HER2 therapy	2 (1–9)	2 (1–5)	0.299
Endocrine therapy	0 (0–5)	0 (0–3)	0.015

AI, aromatase inhibitor; CT, chemotherapy; ET, endocrine therapy; IQR, interquartile range; LHRHa, luteinising hormone-releasing hormone analogues; NA, not applicable; OS, overall survival; PFS, progression-free survival.

of therapy, to have the longest duration of treatment and the longest survival compared with those with other breast cancer subtypes.[23] This highlights the importance of optimising treatment strategy and sequencing in this population.

Following the results of the CLEOPATRA trial, international guidelines recommend the use of the anti-HER2 dual blockade with trastuzumab and pertuzumab as first-line therapy in women with HER2-positive metastatic breast cancer.[3 11] However, in CLEOPATRA trial, patients with brain metastasis were excluded and only 88 out of 808 (10.9%) patients received prior (neo)adjuvant trastuzumab (with a TFI>12 months as per study inclusion criteria).[24] Moreover, there are low-income countries where the new anti-HER2 monoclonal antibodies are not available yet; on the contrary, in these countries, lapatinib

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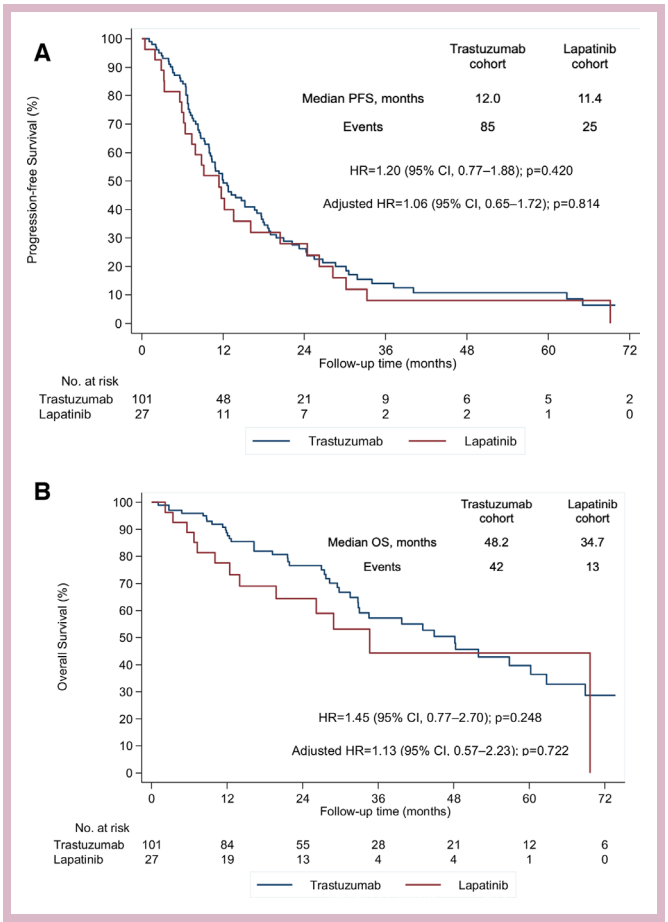

Figure 1 (A) PFS to first-line therapy with trastuzumab or lapatinib in patients who received a prior exposure to trastuzumab in the (neo)adjuvant setting. (B) OS in patients who received a prior exposure to trastuzumab in the (neo)adjuvant setting and who were treated with first-line trastuzumab or lapatinib. OS, overall survival; PFS, progression-free survival.

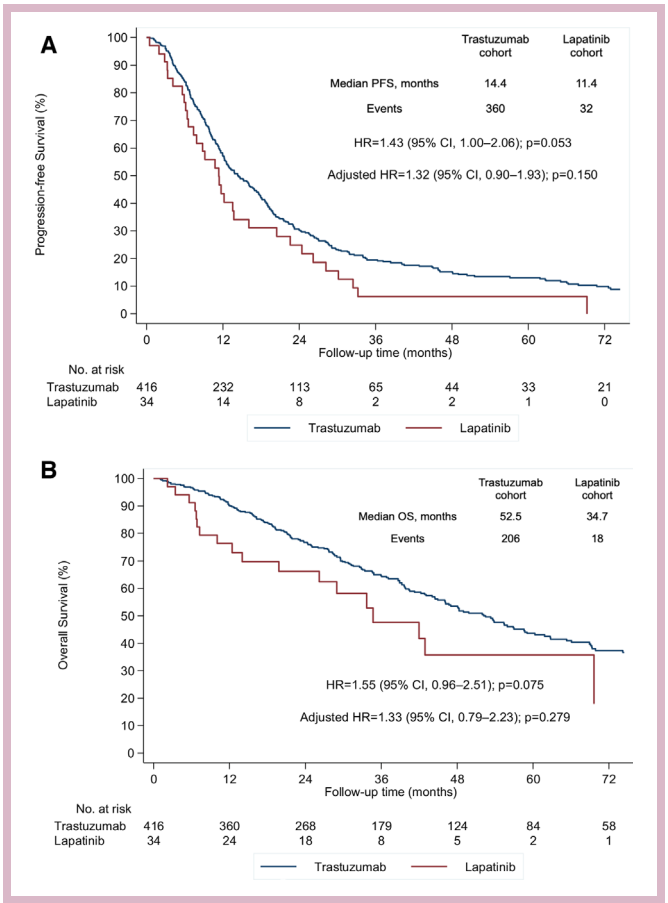

Figure 2 (A) PFS to first-line therapy with trastuzumab-based or lapatinib-based therapy in the overall study population. (B) OS in patients treated with first-line trastuzumab-based or lapatinib-based therapy in the overall study population. OS, overall survival; PFS, progression-free survival.

might be more easily available because of the lower cost and the oral administration.[25]

In our study, patients in the lapatinib cohort had received more frequently prior (neo)adjuvant trastuzumab (p<0.001), had lower TFI (p=0.017) and higher incidence of brain metastasis (p<0.001). These factors have likely influenced the preference towards a drug with a different mechanism of action (tyrosine-kinase inhibitor) and with documented activity in brain metastasis like lapatinib.

So far, there is paucity of data regarding the clinical outcome of patients relapsing after (neo)adjuvant trastuzumab.[24 26–29] International guidelines[3 11] recommend the use of pertuzumab in patients relapsing more than 12 months following the completion of adjuvant anti-HER2 therapy and T-DM1 for those developing disease relapse within 12 months based on the results of the EMILIA trial.[12] However, patients relapsing between 6 and 12 months from adjuvant trastuzumab were excluded from EMILIA trial; therefore, we lack clear data on anti-HER2 treatment performance in this subgroup of patients. In our study, lapatinib and trastuzumab showed similar outcomes and can be considered treatment options if TDM1 is not available.

Patients with HER2-positive disease have a higher risk of developing brain metastasis than those with other tumour subtypes: up to 20%–50% of women with metastatic HER2-positive breast cancer develop brain metastasis during the course of the disease.[30 31] In our study, brain metastasis were reported in 52/450 (11.6%) of patients as first-site of disease-relapse. Moreover, incidence of central nervous system progression after first line therapy was higher in the trastuzumab cohort (14.1%) compared with the lapatinib cohort (5.9%), although formal statistical comparison could not be done due to the small number of patients in both cohorts. A retrospective exploratory analysis of EMILIA trial in patients with baseline brain metastasis showed an improvement in OS for patients treated with T-DM1 compared with capecitabine and lapatinib.[32] Recently, the new tyrosine kinase inhibitor tucatinib showed to be an active compound with capecitabine and trastuzumab in heavily pretreated HER2-positive breast cancer patients, even for patients

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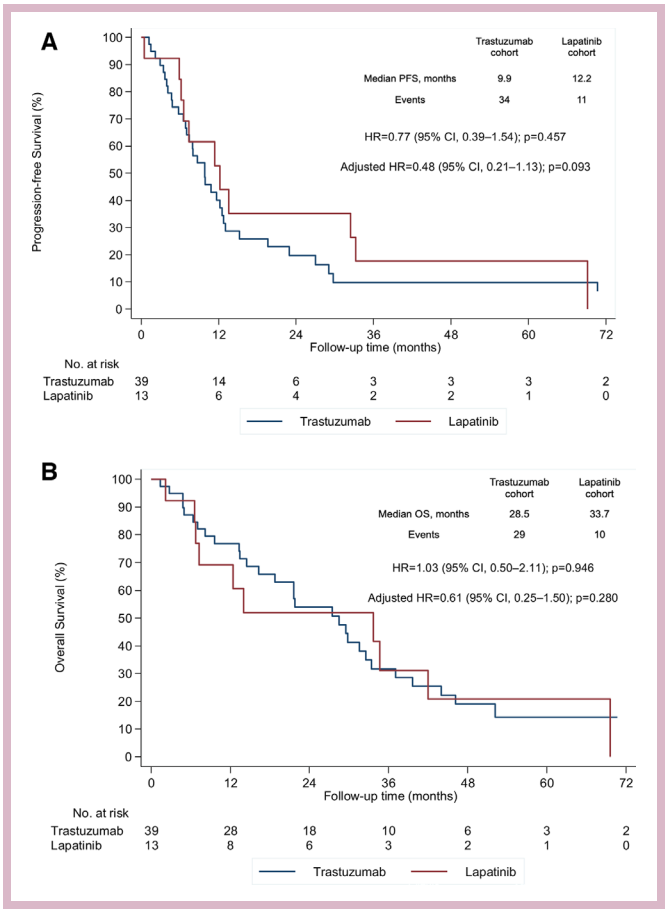

Figure 3 (A) PFS to first-line therapy with trastuzumab or lapatinib in patients who had brain metastasis as first site of relapse. (B) OS in patients who had brain metastasis as first site of relapse and who were treated with first-line trastuzumab or lapatinib. OS, overall survival; PFS, progression-free survival.

with brain metastasis.[33] Similarly, neratinib, an irreversible pan-HER tyrosine kinase inhibitor, demonstrated efficacy in patients with HER2-positive breast cancer with brain metastasis.[34] Results of the NALA study comparing neratinib plus capecitabine to lapatinib plus capecitabine were recently presented but full publication of the results is awaited.[35] Another anti-HER2 agent recently available is trastuzumab deruxtecan. In patients with heavily pretreated HER2 metastatic breast cancer (six median previous anticancer regimens), trastuzumab deruxtecan showed an impressive 60.9% ORR with a median PFS of 16.4 months.[36] Among the 24 patients with asymptomatic brain metastases treated with trastuzumab deruxtecan, median PFS was 18.1 months.[36] Yet, further confirmations and new treatment options are awaited to improve the management of HER2-positive patients with brain metastasis. However, lapatinib remains a therapeutic option when other anti-HER2 agents are not available.

In the past few decades, treatment of HER2-positive metastatic breast cancer changed. In our study, patients with consecutive metastatic HER2-positive breast cancer were retrospectively included over a period of time (from 2000 to 2013) in which treatment rapidly changed. In fact, after the publication of the lapatinib-capecitabine results in 2006 and the updated efficacy results in 2008, the use of first-line lapatinib therapy became more frequent especially for patients with brain metastasis.[15 37] In our cohort, only eight patients relapsing after (neo)adjuvant trastuzumab were treated before 2008 and all of them were treated with trastuzumab-based first-line therapy. This could be explained by the fact that, in Italy, adjuvant trastuzumab was routinely used after approval in 2004. Moreover, only 11 out of 52 patients with brain metastasis as first site of relapse were treated before 2008 (data not shown) and all of them received first-line trastuzumab.

Study limitations to be considered in the interpretation of our findings are its retrospective design, the small number (n=34) of patients treated with first-line lapatinib and the fact that patients were treated in the prepertuzumab and T-DM1 era. Despite these limitations, to our knowledge, this is the first study aiming to evaluate the clinical outcomes of patients treated with first-line lapatinib or trastuzumab taking into account prior exposure to (neo)adjuvant trastuzumab. This is a topic of great clinical importance but it remains poorly investigated so far.

In conclusion, our study showed that, despite a trend towards better outcomes in patients receiving first-line trastuzumab- over lapatinib-based therapy, no apparent differences between the two treatment options were observed in the cohort of patients with prior exposure to trastuzumab. In patients with brain metastasis, lapatinib remains an available treatment option. Exploratory analyses from randomised controlled trials are needed to further elucidate the issues faced by patients relapsing after prior exposure to (neo)adjuvant anti-HER2 therapy; several new promising targeted agents are currently under investigation and are expected to continue improving the outcomes of patients with HER2-positive disease including those with brain metastasis.

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