Breast Cancer Research and Treatment (2019) 176:227–234
https://doi.org/10.1007/s10549-018-05081-z

EPIDEMIOLOGY

Lapatinib activity in metastatic human epidermal growth factor receptor 2-positive breast cancers that received prior therapy with trastuzumab, pertuzumab, and/or ado-trastuzumab emtansine (T-DM1)

Luis Baez-Vallecillo[1] · Akshara S. Raghavendra[3] · Kenneth R. Hess[2] · Carlos H. Barcenas[3] · Stacy L. Moulder[3] · Debu Tripathy[3] · Vicente Valero[3] · Rashmi K. Murthy[3]

Received: 25 May 2018 / Accepted: 3 December 2018 / Published online: 11 April 2019

Abstract

Purpose Lapatinib (L) is approved in combination with capecitabine or letrozole for patients with trastuzumab-resistant HER2-positive metastatic breast cancer (MBC). However, there is no efficacy data of L in patients who received prior pertuzumab (P) and ado-trastuzumab emtansine (T-DM1), now included as standard first- and second-line therapies, respectively. The goal of this study was to assess the efficacy of L in a contemporary patient population that received prior P and/or T-DM1.

Methods We identified patients with HER2-positive MBC who received L ($n=520$) between 2003 and 2017 at MD Anderson Cancer Center and selected a *target cohort* who received L after prior P or T-DM1 ($n=43$) with the remaining included in the *comparison cohort* ($n=477$). We evaluated outcome measures including clinical benefit rate (CBR), best tumor response (BTR), duration on L, and time to progression (TTP). Survival analyses used Kaplan–Meier statistics.

Results CBR was 28% (95% CI 10–32) for the *target cohort* and 40% (95% CI 36–45) for the *comparison cohort*. The median duration on L was 5 months (95% CI 3.0–9.0) in the *target cohort* and 6.7 months (5.9–8.0) in the *comparison cohort*. In both cohorts, the median time to progression (TTP) and overall survival (OS) were longer in patients with de novo metastatic disease compared to patients with disease recurrence.

Conclusion L-based therapy is an active therapeutic option and remains a viable option for HER2 + MBC after prior trastuzumab, P and/or T-DM1.

Keywords Lapatinib · Trastuzumab · Pertuzumab · T-DM1 · HER2 · Breast cancer · Metastatic

Introduction

The discovery of the HER-2 (erbB2/neu) gene and recognition of its overexpression in approximately 20% of invasive breast carcinomas have led to the subsequent development of HER2-targeted therapies and have dramatically improved outcomes for women with early-stage and advanced HER2-positive breast cancer. The gene encodes a growth factor tyrosine kinase receptor [1] and its overexpression is associated with increased metastatic potential, resistance to hormonal and chemotherapy, higher relapse rates, and decreased OS rate [2]. Despite the remarkable success of trastuzumab (Herceptin; Genentech, South San Francisco, CA),nearly all patients with HER-2 positive metastatic breast cancer will eventually progress on trastuzumab and a number experience relapse after trastuzumab—containing adjuvant and

Part of these data were presented at the 39th Annual San Antonio Breast Cancer Symposium (SABCS) December 6–10, 2016 (Abstract P4-21-20).

✉ Rashmi K. Murthy
rmurthy1@mdanderson.org

[1] Division of Cancer Medicine – Hematology/Oncology Fellowship Program, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[2] Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

[3] Division of Cancer Medicine, Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

neoadjuvant therapy [3–6]. A number of newer anti-HER2 targeted therapies have been approved including lapatinib (metastatic, 2007) [7–9]; pertuzumab (metastatic, 2012) (neoadjuvant, 2013) [10–13]; ado-trastuzumab emtansine (T-DM1) (metastatic 2013) [14].

The FDA initially approved lapatinib (Tykerb; Novartis Pharmaceuticals Co., East Hanover, New Jersey) in combination with capecitabine in March 2007 based on a randomized control trial of patients who progressed on an anthracycline, taxane, and trastuzumab, which showed statistically significant increase in response rates and TTP, but not OS when compared to capecitabine alone [7]. At the time of lapatinib's approval, the standard first-line metastatic treatment was trastuzumab in combination with a taxane resulting in a 2nd line indication for lapatinib [3, 15, 16]. The use of lapatinib was also studied in combination with trastuzumab in a randomized, phase 3 trial, EGF104900, of patients having progressed on prior trastuzumab-based therapy. This trial showed that despite progression on prior trastuzumab, patients receiving combination lapatinib and trastuzumab had increased progression-free survival (PFS) and OS compared to patients receiving lapatinib alone [8]. Furthermore, lapatinib alone and in combination with capecitabine has also shown activity in clinical trials for the treatment of breast cancer brain metastases [17–19]. The LANDSCAPE trial, a single-group phase 2 study, showed a nearly 2/3 objective CNS volumetric response rate in forty-four patients receiving combination lapatinib and capecitabine as first-line treatment of breast cancer brain metastases [17].

With the introduction of pertuzumab (Perjeta; Genentech, South San Francisco, CA) and T-DM1 (Kadcyla; Genentech, South San Francisco, CA), lapatinib is commonly used after patients have received 2 or more lines of HER 2-directed therapy in the metastatic setting. Currently, the standard first-line therapy for metastatic HER2-positive breast cancer is pertuzumab in combination with trastuzumab and a taxane based on the landmark randomized phase 3 CLEOPATRA trial that showed a PFS and OS benefit, resulting in FDA approval for pertuzumab in the metastatic setting in June 2012 [10, 11]. Since 2013, T-DM1 has been established as the preferred second-line agent based on the results of the landmark, randomized phase 3 EMILIA trial, which demonstrated increased PFS and OS for T-DM1 compared to lapatinib plus capecitabine in patients previously treated with trastuzumab and a taxane [14, 20, 21]. In a subsequent randomized phase 3 study (TH3RESA trial), T-DM1 showed an increased PFS and OS when compared to physician's choice therapy in patients having received and progressed on prior treatment with both trastuzumab and lapatinib [22, 23]. Based on these data, T-DM1 is the current 2nd-line therapy for metastatic HER2-positive MBC after progression on one previous line of taxane and trastuzumab-based therapy. T-DM1 is also used in the first-line metastatic setting in patients who have received neoadjuvant pertuzumab and/or have progressed within 1 year of completing adjuvant trastuzumab. Prior to the FDA approval of T-DM1, lapatinib was used in earlier lines and now, lapatinib is commonly used after progression on trastuzumab, pertuzumab, and T-DM1. There are no published data to predict tolerability and efficacy of lapatinib in this setting. The goal of this project is to assess the efficacy and tolerability of lapatinib in routine clinical practice in a contemporary patient population that includes patients who have received prior therapy with trastuzumab, pertuzumab, and/or T-DM1.

Methods

Patient population

Electronic pharmacy records and a prospectively maintained departmental database were used to identify patients with HER2- positive MBC who received L-based therapy between August 1, 2003 and January 1, 2017 at MD Anderson Cancer Center. Most patients received HER2 targeted therapy as per standard guidelines and routine clinical care. Only18 patients were treated in the *comparison cohort* with L-based therapy prior to the approval in 2007 (lapatinib was approved by the US Food and Drug Administration in the United States on March 13th, 2007); however, these patients were all treated with standard lapatinib-based combinations (in combination with capecitabine, trastuzumab, or endocrine therapy). This study was approved by the institutional review board at MD Anderson Cancer Center, and waivers for obtaining informed consent were granted.

Data collection

For each record, a data acquisition form was completed and the following data items were collected: patient demographics including date of birth and race; tumor characteristics, including date of diagnosis of primary breast cancer and metastatic recurrence; estrogen receptor (ER) and progesterone receptor (PR) status of the primary tumor and metastatic lesions if the receptor status was reassessed; HER2 status including immunohistochemistry (IHC) and fluorescent in-situ hybridization (FISH) results if both were available; and sites of metastases at the time of starting lapatinib including bone, visceral, brain, or soft tissue (i.e., skin, lymph node, or breast). ER/PR status and HER2 status were assigned according to the 2010 and 2013 ASCO/College of American Pathologists guidelines, respectively, on the basis of local pathology results [24, 25]. Treatment history was also collected including prior neoadjuvant and/or adjuvant chemotherapy regimens, adjuvant endocrine regimens, and the number and types of chemotherapy given

in the metastatic setting. The first treatment administered for metastatic disease was counted as the first-line therapy. The next new treatment administered at the time of progression during or after first-line therapy was recognized as second-line therapy, and the numbering of the lines of treatment continued in this manner. The dates of first and last courses of trastuzumab, pertuzumab, T-DM1, and lapatinib as well as the combinations of chemotherapy used in conjunction with lapatinib were also included. Tumor response was based on the treating physician assessment and judgment in the context of routine clinical care. Radiology reports and results of clinical assessments during lapatinib-based therapy were reviewed as documented in the medical record to assign tumor response. Reasons for discontinuation of lapatinib were also extracted from medical records as well as date of death, if applicable.

Statistical analysis

The primary outcome measure was clinical benefit rate (CBR), defined as complete response, partial response, or stable disease for more than 6 months on L-based therapy. Other outcomes measured include best tumor response (BTR), median duration on L, time to progression (TTP), and overall survival (OS). Best tumor response (BTR) was based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, defined as physician-reported response on the basis of imaging and clinical assessment: PD, progressive disease; SD, stable disease; PR, partial response; CR complete response. Duration on L-based therapy was measured from the date of a patient's first lapatinib treatment to the date of the last lapatinib treatment. TTP was measured from the date of a patient's first L treatment to the date of progression. OS was measured from the date of a patient's first L treatment to date of death or last follow-up. Descriptive statistics were calculated for all patients and reported with point estimates and 95% exact binomial confidence intervals. These metrics were calculated for the *target cohort* and the *comparison cohort* separately as well as by subsets: ER-positive and/or PR-positive (HR-positive) tumors, ER-negative and PR-negative (HR-negative) tumors, de novo metastatic disease, metastatic recurrence < 1 year after initial diagnosis, and metastatic recurrence > 1 year after initial diagnosis. The Kaplan–Meier method was used to estimate survival curves from the time of first L-based treatment and to calculate time on L and time to progression distributions for each cohort.

Results

Of 520 patients identified, a *target cohort* of 43 patients was identified who received lapatinib-based therapy after receiving trastuzumab, pertuzumab, and/or T-DM1. The remaining 477 patients who received lapatinib without prior exposure to pertuzumab or T-DM1 were labeled as the *comparison cohort*. In both cohorts, all patients were available for response analysis; One patient in the *comparison cohort*, had missing follow-up data for overall survival and freedom from progression analyses. Table 1 shows the patient characteristics. Median age at primary diagnosis was higher for the *comparison* cohort compared to the *target* cohort; 30% of the *comparison cohort* had de novo disease versus 19% in the *target cohort*; 33% of the *comparison* cohort had brain metastases versus 19% in the *target* cohort. The median number of lines of therapy prior to lapatinib was higher in the *target cohort* versus the *comparison cohort*, 2.5 and 1.0, respectively. Of note, 35% of patients received lapatinib-based therapy in the first-line setting in the *comparison* cohort. In the *target cohort*, nearly 48% ($n=21$) had received 3 or more lines of therapy prior to lapatinib compared to 21% ($n=101$) in the *comparison cohort*. Similar distribution of metastatic sites was found in both cohorts; there were fewer brain metastases in the *target cohort* 19% compared to 33% in the *comparison cohort*. Discontinuation of lapatinib due to toxicity was low in both groups with only 2 patients (5%) stopping lapatinib in the *target cohort* due to thrombocytopenia and 43 patients (9%) discontinuing lapatinib in the *comparison cohort*. Reasons for discontinuation in the *comparison cohort* include diarrhea ($n=21$), skin toxicity ($n=4$), hepatotoxicity ($n=3$), intractable emesis ($n=2$), cardiotoxicity ($n=2$), hand-foot syndrome ($n=3$), pancreatitis ($n=1$), and not otherwise specified ($n=7$).

Table 2 shows the types of prior therapies for metastatic disease before lapatinib in the *target cohort*. The majority 93% had received trastuzumab, 77% had received pertuzumab, and 77% had received TDM-1. Most patients received L in combination with capecitabine (L + C), followed by L in combination with trastuzumab (L + T) and only a small proportion of patients received L with endocrine therapy (L + E) or other chemotherapies (as shown in Fig. 1).

Table 3 shows the overall efficacy results. Median duration on lapatinib was 5 months (95% CI 3.0–9.0) for the *target cohort* versus 6.7 months (95% CI 5.9–8.0) for the *comparison cohort*. The duration on L-based therapy by regimen for the *target cohort* is shown in Fig. 1. CBR was 28% (95% CI 10–32) in the *target cohort* versus 41% (95% CI 36–45) in *comparison cohort*. Median TTP was 6.0 months (95% CI 4.7–9.0) in the *target cohort* and 8.7 months (95% CI 7.7–10.0) in the *comparison cohort* (Fig. 2). Longer median TTP was seen with de novo metastatic disease compared to recurrent disease in both the *target and comparison cohorts*. The median TTP was shortest for patients with recurrence within 1 year of diagnosis: 2.8 months (95% CI 2.3, NR) in the *target cohort* compared to 8.3 months (6.5,11.0) in the *comparison cohort*. Median OS was 23.9 months (95%

Table 1 Patient characteristics

	Target cohort ($N=43$)	Comparison cohort ($N=477$)
Median age, years (range)	44 (26,70)	51 (24,85)
Hormone receptor status, *n* (%)		
ER and/or PR positive	27 (63)	253 (53)
ER and/or PR negative	16 (37)	224 (47)
Disease-free interval, *n* (%)		
De Novo	8 (19)	140 (30)
Recurrent	35 (81)	337 (70)
Metastatic recurrence ≤ 1 year after diagnosis	7 (16)	48 (10)
Metastatic recurrence > 1 year after diagnosis	28 (65)	289 (60)
Sites of metastasis at start of L, *n* (%)		
Soft tissue[a]	31 (72)	255 (53)
Lung	18 (42)	152 (32)
Liver	20 (47)	166 (35)
Bone	22 (51)	225 (47)
Brain	8 (19)	156 (33)
Prior lines of metastatic therapy prior to lapatinib, *n* (range)		
0	1 (2)	168 (35)
1	7 (16)	133 (28)
2	13 (30)	75 (16)
3	11 (25)	49 (10)
4	3 (7)	25 (5)
≥ 5	7 (16)	27 (6)
Number of distinct sites of metastases, *n*		
1	10 (23)	190 (40)
2	16 (37)	152 (32)
3	11 (26)	89 (19)
4	6 (14)	37 (7)
5	0 (0)	9 (2)
Discontinuation of lapatinib due to toxicity, *n* (%)	2 (5)	43 (9)

[a]Soft tissue includes lymph nodes, skin, pleura, and peritoneum

ER estrogen receptor, *PR* progesterone receptor

CI 18.4-NR) in the *target cohort* and 25.8 months (95% CI 22.8–30.7) in the *comparison cohort* (Fig. 3). Longer OS was seen in patients with de novo compared to recurrent disease and in patients with HR+ compared to HR- in both groups.

Discussion

This is the first report demonstrating the efficacy of L in a contemporary patient population that has received prior trastuzumab, pertuzumab, and/or T-DM1 (*target cohort*) compared to the efficacy of L in a *comparison cohort* who received L in a different setting. Our findings show that the CBR of L in the *target cohort* is lower at 28% and the CBR of L in the *comparison cohort* is higher at 41% compared to historical trials. In the pivotal phase 3 trial, which led to the establishment of capecitabine plus lapatinib as the 2nd line treatment, the CBR was 29% [7]. Later, a chemotherapy-free treatment option with lapatinib plus trastuzumab was evaluated in a more heavily treated patient population with a slightly lower CBR of 25% [8, 9]. The *target cohort* in our study was heavily treated with over 48% of patients receiving 3 or more lines of therapy and 16% of patients receiving at least 5 lines of therapy. Further, patients in the *target cohort* had a lower incidence of brain metastases, which may be explained by the higher exposure to effective HER2-directed therapies early in the disease course. In both cohorts, TTP and OS were higher for patients with de novo stage IV metastatic breast cancer compared to recurrence disease. Additionally, L was well tolerated with 5% discontinuing L-based therapy in the *target cohort* due to

Table 2 Type of prior therapies for metastatic disease before lapatinib in target cohort ($n=43$)

Prior therapy	Number of patients (%)
Trastuzumab	40 (93)
Pertuzumab	33 (77)
TDM-1	33 (77)
Taxane	35 (81)
Hormonal therapy	11 (26)
Capecitabine	4 (9)
Vinorelbine	6 (14)
Doxorubicin	6 (14)
Cyclophosphamide	5 (12)
Carboplatin	5 (12)
Gemcitabine	2 (5)
Ixabepilone	1 (2)
Eribulin	1 (2)
Tucatinib (ONT-380)	4 (9)

thrombocytopenia and 9% in the *comparison cohort* mainly due to diarrhea.

Regarding limitations, this is a retrospective study performed at a single institution, which is a high volume referral center. Given the heterogeneous patient population, only limited comparisons can be made with prior trial results. Our *comparison cohort* includes patients with similar criteria to historical trials; however, we note higher response rates which may be due to selection bias. We use duration on therapy as an approximation of PFS or time to treatment failure. This is a reasonable surrogate for PFS given that the majority of patients discontinued L-based therapy due to disease progression and not toxicity. Other limitations of this study are inherent to the retrospective comparison of non-randomized and unbalanced groups which may introduce bias of unmeasured variables. Further, the *target cohort* is a small number of patients as illustrated by the wide confidence intervals reported in some of the clinical outcomes, thereby limiting statistical comparisons that can be made between the two cohorts. Additionally, there is inherent selection bias in the target cohort as all of these patients had

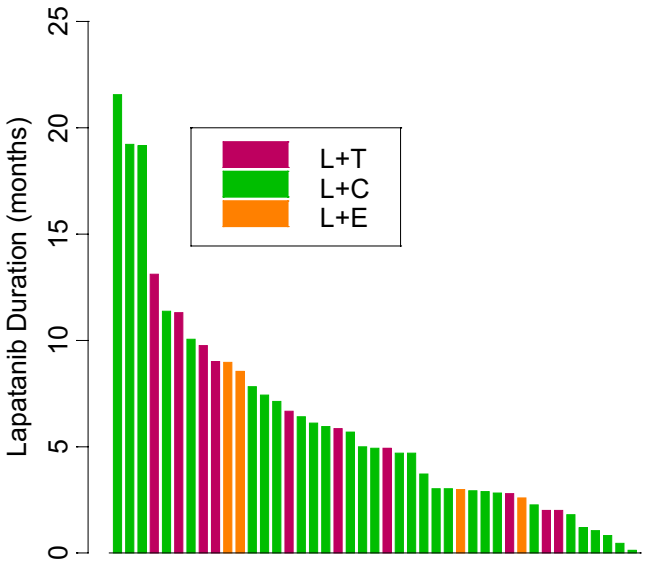


Fig. 1 Duration on lapatinib-based therapy by regimen in the target cohort ($n=43$)

L+T: lapatinib plus trastuzumab (n=10); L+C: lapatinib plus capecitabine (n=29); L+E: lapatinib + endocrine therapy (n=4).

Characteristic	**Target Cohort (N=43)**	**Comparison Cohort (N=477)**
Type of L-based therapy (Figure 1)		
C + L	29 (67%)	346 (73%)
T+ L	10 (23%)	119 (25%)
ET + L	4 (9%)	12 (2%)

Abbreviations: C – capecitabine; T – trastuzumab; L-lapatinib; ET – endocrine therapy;

Table 3 Results

Characteristic	Target cohort ($N=43$)	Comparison cohort ($N=477$)
Median duration on lapatinib, months (95% CI)	5.0 (3.0, 9.0)	6.7 (5.9, 8.0)
De novo	7.8 (7.4, NR)	5.9 (5.0, 9.0)
Recurrence < 1 year	2.8 (2.3, NR)	6.9 (5.8, 10.0)
Recurrence > 1 year	4.9 (3.0, 9.0)	6.8 (5.8, 8.3)
HR positive	5.0 (3.0, 10.1)	6.5 (5.8, 8.2)
HR negative	4.9 (2.3, NR)	6.7 (5.7, 8.8)
BTR, *n* (%)		
PD	25 (58%)	155 (32%)
SD	15 (35%)	267 (56%)
PR	3 (7%)	26 (5%)
CR	0 (0%)	6 (1%)
Too early?		23 (5%)
CBR, *n* (%)	12 (28%)	186/454 (41%)
De novo[a]	2 (25%)	39/97 (40%)
Recurrence ≤ 1 year[b]	0 (0%)	37/79 (47%)
Recurrence > 1 year[c]	10 (36%)	110/278 (40%)
HR positive	8 (30%)	85/213 (40%)
HR negative	4 (25%)	101/240 (42%)
Median TTP, mo. (95% CI)	6.0 (4.7, 9.0)	8.7 (7.7, 10.0)
De novo[a]	7.8 (7.4, NR)	9.0 (5.9, 16.3)
Recurrence ≤ 1 year[b]	2.8 (2.3, NR)	8.3 (6.5, 11.0)
Recurrence > 1 year[c]	5.0 (3.0, 10.1)	8.7 (7.7, 10.8)
HR positive	5.0 (4.7, 10.1)	9.0 (7.3, 11.0)
HR negative	6.1 (2.3, NR)	8.5 (6.9, 10.0)
Median OS, mo. (95% CI)	23.9 (18.4, NR)	25.8 (22.8, 30.7)
De novo	23.9 (NA, NR)	23.4 (18.7, 37.2)
Recurrence ≤ 1 year	18.4 (14.0, NR)	22.5 (18.7, 35.8)
Recurrence > 1 year	19.3 (15.3, NR)	26.5 (23.2, 35.8)
HR positive	NR (15.3, NR)	31.9 (26.0, 39.4)
HR negative	19.3 (18.4, NR)	20.7 (16.3, 25.5)

HR hormone receptor, *BTR* best tumor response, *PD* progressive disease, *SD* stable disease, *PR* partial response, *CR* complete response, *CBR* clinical benefit rate, *TTP* time to progression, *OS* overall survival, *NR* not reached, *CI* confidence interval

[a]Presented with de novo stage IV disease; de novo defined as identified to have metastatic disease within 3 months of diagnosis

[b]Presented with recurrent disease within 1 year of initial diagnosis

[c]Presented with recurrent disease after 1 year from initial diagnosis

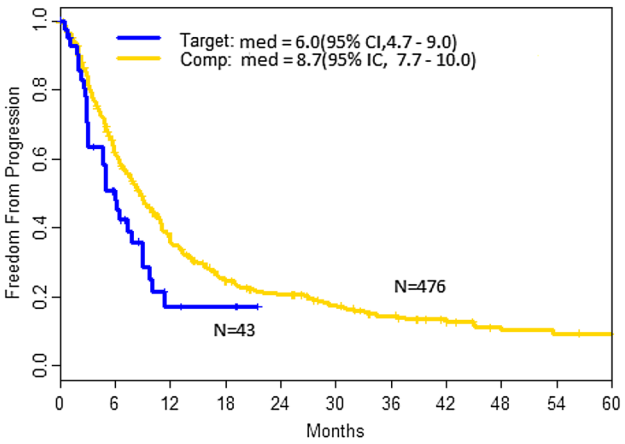
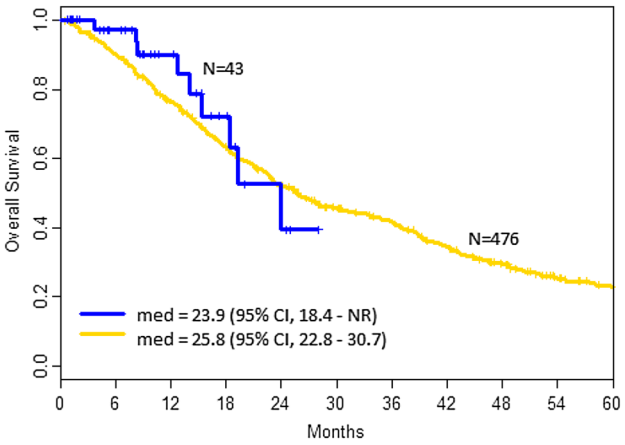


Fig. 2 Kaplan–Meier estimate of freedom from progression



Note: of the 477 patients, 1 patient was missing follow-up data.

Fig. 3 Kaplan–Meier estimate of overall survival

prior exposure to trastuzumab, pertuzumab, and TDM-1 and were well enough to receive lapatinib-based therapy.

Our data provide context for ongoing clinical trials and future trials being designed which may enroll a similar population of patients as our *target cohort*, who have exposure to trastuzumab, pertuzumab, and/or T-DM1. Of note, 9% of patients in the *target cohort* had received treatment on a clinical trial with an investigational HER2-specific inhibitor, tucatinib (ONT-380) that is currently being evaluated in a randomized phase 2 clinical trial is actively enrolling patients who have received prior taxane, trastuzumab, pertuzumab, and T-DM1(HER2CLIMB; NCT02614794) [26, 27]. Despite prior exposure to a kinase inhibitor, this small number of patients received varying levels of benefit from L-based treatment as noted in Fig. 1.

In conclusion, L remains a therapeutic option for patients with HER2-positive metastatic breast cancer despite being previously treated with multiple anti-HER2 therapies. The *target cohort* experience reported here provides additional information for the activity of L-based therapy and management of a contemporary patient population after treatment with multiple novel HER2-directed therapies. Although only 28% of patients experienced clinical benefit after prior trastuzumab, P, and T-DM1, toxicity was limited and patients

with de novo stage IV metastatic disease gained more benefit than patients with recurrent disease. Our findings are in alignment with what is known in the treatment of metastatic breast cancer—that the chance of responding to and benefiting from therapy diminishes with each successive line of therapy. Yet, L continues to be active in later lines in a clinically relevant manner.

Author contributions Design/conception: LB, VV, RM. Data collection: LB, AR. Statistical analysis: KH. Data interpretation: All authors. Manuscript writing: All authors.

Funding The database used for this work is supported by the Breast Medical Oncology departmental funds at MD Anderson Cancer Center. KR Hess was supported by the NIH/NCI under award number P30CA016672 and used the Biostatistics Resource Group shared resource.

Compliance with ethical standards

Conflict of interest Luiz Baez-Vallecillo, Akshara S. Raghavendra, Kenneth R. Hess, Carlos H. Barcenas, and Vicente Valero report no conflict of interest relevant to this work. Stacy L. Moulder serves or has served as a consultant for Novartis, Oncothyreon, Pfizer, and Immunogenics. Debu Tripathy serves as a consultant for Novartis and Pfizer, and also receives funding from Novartis. Rashmi K. Murthy receives research funding from Cascadian therapeutics, Daiichi Sankyo, Gnentech, and Pfizer (all in research support paid to the institution).

Ethical approval This article does not contain any studies with human participants or animals.

Informed consent This study was approved by the institutional review board at MD Anderson Cancer Center, and waivers for obtaining informed consent were granted.

References

1. Yarden Y et al (1987) Human proto-oncogene c-kit: a new cell surface receptor tyrosine kinase for an unidentified ligand. EMBO J 6(11):3341–3351
2. Slamon DJ et al (1987) Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235(4785):177–182
3. Slamon DJ et al (2001) Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344(11):783–792
4. Slamon D et al (2011) Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med 365(14):1273–1283
5. Romond EH et al (2005) Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med 353(16):1673–1684
6. Piccart-Gebhart MJ et al (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353(16):1659–1672
7. Geyer CE et al (2006) Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 355(26):2733–2743
8. Blackwell KL et al (2010) Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. J Clin Oncol 28(7):1124–1130
9. Blackwell KL et al (2012) Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. J Clin Oncol 30(21):2585–2592
10. Baselga J et al (2012) Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 366(2):109–119
11. Swain SM et al (2013) Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Oncol 14(6):461–471
12. Schneeweiss A et al (2013) Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol 24(9):2278–2284
13. Gianni L et al (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 13(1):25–32
14. Verma S et al (2012) Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 367(19):1783–1791
15. Esteva FJ et al (2002) Phase II study of weekly docetaxel and trastuzumab for patients with HER-2-overexpressing metastatic breast cancer. J Clin Oncol 20(7):1800–1808
16. Burstein HJ et al (2007) Trastuzumab plus vinorelbine or taxane chemotherapy for HER2-overexpressing metastatic breast cancer: the trastuzumab and vinorelbine or taxane study. Cancer 110(5):965–972
17. Bachelot T et al (2013) Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol 14(1):64–71
18. Lin NU et al (2009) Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res 15(4):1452–1459
19. Lin NU et al (2008) Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 26(12):1993–1999
20. Amiri-Kordestani L et al (2014) FDA approval: ado-trastuzumab emtansine for the treatment of patients with HER2-positive metastatic breast cancer. Clin Cancer Res 20(17):4436–4441
21. Dieras V et al (2017) 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 18(6):732–742
22. Krop IE et al (2014) Trastuzumab emtansine versus treatment of physician's choice for pretreated HER2-positive advanced breast cancer (TH3RESA): a randomised, open-label, phase 3 trial. Lancet Oncol 15(7):689–699
23. Krop IE et al (2017) 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 18(6):743–754
24. Wolff AC et al (2013) Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. J Clin Oncol 31(31):3997–4013
25. Hammond ME et al (2010) American Society of Clinical Oncology/College Of American Pathologists guideline

recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol 28(16):2784–2795

26. Moulder SL et al (2017) Phase I study of ONT-380, a HER2 inhibitor, in patients with HER2+-advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer (MBC). Clin Cancer Res
27. Murthy R, Borges VF, Conlin A, Chaves J, Chamberlain M, Gray T, Vo A, Hamilton E (2018) Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. Lancet Oncol 19:880–888