Central Nervous System Metastasis in Patients with HER2-Positive Metastatic Breast Cancer: Patient Characteristics, Treatment, and Survival from SystHERs

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Abstract

Purpose: Patients with HER2-positive metastatic breast cancer (MBC) with central nervous system (CNS) metastasis have a poor prognosis. We report treatments and outcomes in patients with HER2-positive MBC and CNS metastasis from the Systemic Therapies for HER2-positive Metastatic Breast Cancer Study (SystHERs).

Experimental Design: SystHERS (NCT01615068) was a prospective, U.S.-based, observational registry of patients with newly diagnosed HER2-positive MBC. Study endpoints included treatment patterns, clinical outcomes, and patient-reported outcomes (PRO).

Results: Among 977 eligible patients enrolled (2012–2016), CNS metastasis was observed in 87 (8.9%) at initial MBC diagnosis and 212 (21.7%) after diagnosis, and was not observed in 678 (69.4%) patients. White and younger patients, and those with recurrent MBC and hormone receptor-negative disease, had higher risk of CNS metastasis. Patients with CNS metastasis at diagnosis received first-line lapatinib more commonly (23.0% vs. 2.5%), and trastuzumab less commonly (70.1% vs. 92.8%), than patients without CNS metastasis at diagnosis. Risk of death was higher with CNS metastasis observed at or after diagnosis [median overall survival (OS) 30.2 and 38.3 months from MBC diagnosis, respectively] versus no CNS metastasis [median OS not estimable; HR 2.86; 95% confidence interval (CI), 2.05–4.00 and HR 1.94; 95% CI, 1.52–2.49]. Patients with versus without CNS metastasis at diagnosis had lower quality of life at enrollment.

Conclusions: Despite advances in HER2-targeted treatments, patients with CNS metastasis continue to have a poor prognosis and impaired quality of life. Observation of CNS metastasis appears to influence HER2-targeted treatment choice.

Introduction

HER2-positive metastatic breast cancer (MBC) is associated with a high incidence of central nervous system (CNS) metastasis (1–6), a development typically associated with poor survival and a negative impact on quality of life (7). Diagnoses of CNS metastasis have increased over time in patients with HER2-positive MBC, likely due to improved detection and longer survival associated with the advent of HER2-targeted therapies over the past two decades (8). The first HER2-targeted treatment, trastuzumab, was approved in the United States in 1998. An analysis of data from registHER, a prospective, observational study that enrolled patients with HER2-positive MBC, found that trastuzumab-based regimens were significantly associated with increased overall survival (OS) in patients with CNS metastasis (3).

In the time since registHER completed enrollment, several additional HER2-targeted therapies have been approved for HER2-positive MBC in the United States, including lapatinib, a small-molecule tyrosine kinase inhibitor, in 2007; pertuzumab, a HER2-targeted antibody, in 2012; and trastuzumab emtansine (T-DM1), an antibody–drug conjugate, in 2013. On the basis of results from the pivotal phase III CLEOPATRA trial (9–11), the
Translational Relevance

Patients with HER2-positive metastatic breast cancer (MBC) and central nervous system (CNS) metastasis generally have a poor prognosis, but there are limited data to describe treatment and clinical outcomes in this population since the introduction of modern HER2-targeted therapies. SystHERs, a prospective, observational, U.S.-based registry of 977 patients enrolled from 2012 to 2016, provided a unique opportunity to assess contemporary treatment patterns and outcomes. We found disparities in first-line MBC treatment between patients with versus without CNS metastasis at MBC diagnosis, and shorter median survival associated with CNS metastasis at or after MBC diagnosis (30.2 and 38.3 months, respectively) versus no CNS metastasis (median not reached). However, we observed that survival in all subgroups improved over the past decade. Development of new HER2-targeted treatments, and optimization of treatment regimens and management, may continue to improve outcomes in patients with HER2-positive MBC and CNS metastasis.

Materials and Methods

Study design and participants
SystHERs (NCT01615068) was a U.S.-based, multicenter, prospective, observational registry study designed to explore real-world treatment patterns and outcomes in patients with recently diagnosed HER2-positive MBC. Here, we report baseline characteristics and clinical outcomes in three key cohorts: patients diagnosed HER2-positive MBC soon after the approval of pertuzumab. In addition to significantly prolonging progression-free survival (PFS) and OS (9–11), the addition of pertuzumab (vs. placebo) to trastuzumab and docetaxel has been suggested to delay the onset of CNS metastasis (12).

Patients with CNS metastasis are commonly excluded from enrollment in clinical trials, providing an incomplete understanding of its natural history and management in the real world. Hence, limited data are available regarding the incidence, treatment, risk factors, and outcomes associated with CNS metastasis in the era of modern HER2-targeted therapies. Furthermore, while guidelines for treatment have been developed based on the limited available data (13), the level of guideline implementation is unknown.

The Systemic Therapies for HER2-positive Metastatic Breast Cancer Study (SystHERs) was a fully enrolled, U.S.-based, prospective, observational registry study designed to explore real-world treatment patterns and outcomes in patients with recently diagnosed HER2-positive MBC. Here, we report baseline characteristics and clinical outcomes in three key cohorts: patients with CNS metastasis observed at initial MBC diagnosis, patients with CNS metastasis observed after MBC diagnosis, and patients with no reported CNS metastasis by the data cutoff for this analysis. Additionally, systemic treatment patterns and patient-reported outcomes (PRO) are presented in patient cohorts with versus without CNS metastasis at MBC diagnosis.

Combination of pertuzumab with trastuzumab and a taxane became a standard of care for the first-line treatment of HER2-positive MBC soon after the approval of pertuzumab. In addition to significantly prolonging progression-free survival (PFS) and OS (9–11), the addition of pertuzumab (vs. placebo) to trastuzumab and docetaxel has been suggested to delay the onset of CNS metastasis (12).

Patients with CNS metastasis are commonly excluded from enrollment in clinical trials, providing an incomplete understanding of its natural history and management in the real world. Hence, limited data are available regarding the incidence, treatment, risk factors, and outcomes associated with CNS metastasis at MBC diagnosis and on study by treating physicians; screening for CNS metastasis was not required and was based on each physician’s standard clinical practices. Patients who discontinued the study had the option to participate in quarterly survival follow-up.

PRO measurements quantified in this study included Functional Assessment of Cancer Therapy-Breast (FACT-B, a sum of five subscales measuring physical, social, emotional, functional, and breast cancer–related well-being on an overall scale of 0–148; ref. 15), FACT-B Trial Outcome Index (FACT-B TOI; a sum of the FACT-B physical, functional, and breast subscales on a scale of 0–96), Rotterdam Symptom Checklist–Activity Level Scale (RSC-ALS; measuring the impact of cancer on activities of daily living on a scale of 0–100; ref. 16), and the MD Anderson Symptom Inventory–Brain Tumor Module [MDASI-BT, measuring brain tumor-related symptom severity and impact on cognitive function (scale of 0–10) and interference in daily life (scale of 0–10); ref. 17].

Analyses and statistical methods

Patient characteristics were tabulated by cohorts defined by CNS metastasis observed at initial MBC diagnosis, CNS metastasis observed after MBC diagnosis, or no CNS metastasis over the study follow-up period. Calculation of P values comparing baseline characteristics between these cohorts were performed using Fisher’s exact test for categorical variables and the Kruskal–Wallis nonparametric test for continuous variables.

Multivariate and univariate logistic regression was also used to examine the association of baseline demographic and clinical characteristics in patients with CNS metastasis at any time versus those without CNS metastasis. A forest plot was prepared to present adjusted odds ratios (OR) and their 95% confidence intervals (CI) for a multivariate analysis of six variables selected on the basis of clinical significance [ethnicity, race, age, Eastern Cooperative Oncology Group (ECOG) status, MBC diagnosis type, and hormone receptor status]. The other multivariate
regression and a univariate logistic regression were carried out based on the wider collection of baseline characteristics presented in this report, with the exception of "duration from early breast cancer (EBC) diagnosis to MBC diagnosis" (as this variable is only applicable to patients with recurrent disease). The multivariate logistic regression analysis included all covariates in one regression model, and the univariate logistic regression considered each variable in the regression model separately.

First-line treatment, defined as any therapy received for MBC up to first disease progression, was analyzed in patients with versus without CNS metastasis at MBC diagnosis. Treatments administered to patients with CNS metastasis observed after diagnosis were also summarized before versus after the detection of CNS lesions, regardless of line of treatment.

PRO scores at enrollment were compared between patients with versus without CNS metastasis at MBC diagnosis. P values comparing baseline PRO scores between these groups were calculated using the Wilcoxon rank-sum nonparametric test.

Median follow-up was calculated as the median observation time in each CNS cohort and overall. PFS was defined as the time from MBC diagnosis to first investigator-assessed disease progression or death, whichever came first. OS was defined as the time from MBC diagnosis to death. PFS and OS were estimated by the Kaplan–Meier product-limit method and compared across cohorts using a log-rank test. Cox regressions were used to estimate HRs and their 95% CI.

Results

Patients

Out of a total of 1,028 patients who met the SystHERs study inclusion criteria, 1,005 patients were enrolled between June 2012 and June 2016. There were 23 refusals among patients meeting inclusion criteria over the 4-year enrollment period. Among 977 eligible patients enrolled from 135 study sites, 197 (20.2%) were from a total of 17 academic centers and 780 (79.8%) were from a total of 118 community centers. The remaining 28 patients did not meet eligibility criteria, most commonly due to lack of distant metastatic disease upon review. Eighty-seven patients (8.9%) had CNS metastasis reported at initial MBC diagnosis, 212 (21.7%) had CNS metastasis detected after MBC diagnosis, and 678 (69.4%) had no observed CNS metastasis as of the October 3, 2017, data cutoff date. Median follow-up duration was 27.8 months in patients with CNS metastasis at diagnosis in 4.3% (21/487) and 13.5% (66/490) of patients with CNS metastasis observed after diagnosis [bone: 51.3% (348/678); liver: 35.5% (241/678)], whereas lung metastasis was observed more commonly in patients with CNS metastasis at or after diagnosis [36.8% (32/87) and 38.7% (82/212), respectively] versus those without CNS metastasis [28.9% (196/678)] (Supplementary Fig. S1).

Of patients with recurrent disease and available treatment data for EBC (n = 430), the majority of patients in all three cohorts received neoadjuvant and/or adjuvant trastuzumab [CNS metastasis at MBC diagnosis: 80.0% (48/60); CNS metastasis after MBC diagnosis: 68.4% (65/95); no CNS metastasis: 61.8% (170/275)] (Supplementary Fig. S2). Of note, among the 318 patients with known HER2 status in both primary (EBC) and metastatic tissue in the SystHERs study, 15.7% (50/318) had HER2-negative primary tumors, and 12.3% (39/318) had HER2-equivocal primary tumors. As such, these patients are not likely to have received (neo)adjuvant HER2-targeted treatment.

Association between baseline characteristics and risk of CNS metastasis

We performed a multivariate logistic analysis of baseline characteristics selected based on their clinical importance to identify risk factors associated with the development of CNS metastasis at any time. Of these characteristics, younger age showed the strongest association with CNS metastasis (OR 3.128; 95% CI, 1.852–5.284 for patients <50 vs. ≥70 years old; Fig. 1). Other characteristics associated with CNS metastasis included White race (OR 1.619; 95% CI, 1.072–2.444 vs. Black/African American race), ECOG status ≤2 (OR 1.900; 95% CI, 1.125–3.210 vs. ECOG status of 0), recurrent MBC (OR 1.650; 95% CI, 1.239–2.196 vs. de novo MBC), and hormone receptor–negative status (OR 1.841; 95% CI, 1.359–2.494 vs. hormone receptor–positive status). Multivariate and univariate logistic regression analyses considering all baseline characteristics shown in Table 1 (with the exception of “duration from EBC diagnosis to MBC diagnosis,” as this variable is only applicable to patients with recurrent disease) produced similar conclusions (Supplementary Table S2).

Treatment patterns

Among patients with CNS metastases at MBC diagnosis, 80.5% (70/87) received brain radiotherapy (local, n = 35; whole brain, n = 52) and 44.8% (39/87) received brain surgery, including 10 patients who received surgery without radiotherapy (Supplementary Table S3). In patients with CNS metastasis observed after MBC diagnosis, 79.2% (168/212) and 20.8% (44/212) had received brain radiotherapy (local, n = 60; whole brain, n = 131) and brain surgery by data cutoff, respectively, including eight patients who received surgery without radiotherapy.

At data cutoff, 97.0% of all patients (948/977) had received first-line systemic treatment for MBC, including 88.5% (77/87) of those with CNS metastasis at MBC diagnosis (of whom nine patients were still in first-line treatment) and 97.9% (871/890) of
Those without CNS metastasis at diagnosis (of whom 217 were still in first-line treatment). The most common first-line HER2-targeted agent was trastuzumab, although it was administered less frequently to patients with CNS metastasis at diagnosis [70.1% (61/87)] compared with patients without CNS metastasis at diagnosis [92.8% (82/890); Table 2]. Trastuzumab was used in combination with pertuzumab in 52.9% (46/87) of patients with and 74.8% (666/890) of patients without CNS metastasis at diagnosis. The most common first-line treatment regimen was trastuzumab + pertuzumab + taxane, with or without hormonal therapy, administered to 48.3% (42/87) and 68.3% (608/890) of patients with and without CNS metastasis at diagnosis, respectively (Supplementary Table S4).

First-line lapatinib was administered to a higher proportion of patients with CNS metastasis at diagnosis [23.0% (20/87)], of whom 11 patients received lapatinib + trastuzumab compared with patients without CNS metastases at diagnosis [2.5% (22/890), of whom 12 patients received lapatinib + trastuzumab; Table 2; Supplementary Fig. S3]. Patients with CNS-only metastasis at MBC diagnosis received regimens with lapatinib more commonly, and regimens with trastuzumab + pertuzumab less commonly, than those with CNS and non-CNS metastasis at diagnosis [lapatinib: 35.7% (10/28) vs. 16.9% (10/61), respectively; trastuzumab: 17.9% (5/28) vs. 8.4% (5/61)].

### Table 1. Baseline demographics, patient characteristics, and disease characteristics

<table>
<thead>
<tr>
<th>Demographic/Characteristic</th>
<th>All eligible patients (n = 977)</th>
<th>CNS metastasis at diagnosis (n = 87)</th>
<th>CNS metastasis after diagnosis (n = 212)</th>
<th>No CNS metastasis (n = 678)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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<td><strong>Demographics</strong></td>
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<tr>
<td>Median age at MBC diagnosis, years (range)</td>
<td>56 (21–90)</td>
<td>57 (34–86)</td>
<td>53 (27–89)</td>
<td>57 (21–90)</td>
<td>&lt;0.001</td>
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<tr>
<td>Race, n (%)</td>
<td></td>
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<tr>
<td>White</td>
<td>766 (78.4)</td>
<td>71 (81.6)</td>
<td>175 (82.5)</td>
<td>520 (76.7)</td>
<td>0.288</td>
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<td>Black or African American</td>
<td>151 (15.5)</td>
<td>9 (10.3)</td>
<td>29 (13.7)</td>
<td>113 (16.7)</td>
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<tr>
<td>Asian</td>
<td>13 (1.3)</td>
<td>1 (1.2)</td>
<td>1 (0.5)</td>
<td>11 (1.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>29 (3.0)</td>
<td>5 (5.7)</td>
<td>6 (2.8)</td>
<td>18 (2.7)</td>
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</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>BMI, n (%)</td>
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<tr>
<td>&lt;30</td>
<td>581 (59.5)</td>
<td>48 (55.2)</td>
<td>137 (64.6)</td>
<td>396 (58.4)</td>
<td>0.265</td>
</tr>
<tr>
<td>≥30</td>
<td>385 (39.4)</td>
<td>38 (43.7)</td>
<td>75 (35.4)</td>
<td>272 (40.1)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>11 (11)</td>
<td>1 (1.1)</td>
<td>0</td>
<td>10 (1.5)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>460 (47.1)</td>
<td>26 (29.9)</td>
<td>106 (50.0)</td>
<td>328 (48.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>365 (37.4)</td>
<td>34 (39.1)</td>
<td>82 (38.7)</td>
<td>249 (36.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>67 (6.9)</td>
<td>15 (17.2)</td>
<td>11 (5.2)</td>
<td>41 (6.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>8 (0.8)</td>
<td>5 (5.7)</td>
<td>0</td>
<td>3 (0.4)</td>
<td></td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>77 (7.9)</td>
<td>7 (8.0)</td>
<td>15 (6.1)</td>
<td>57 (8.4)</td>
<td></td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MBC diagnosis type, n (%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>De novo</td>
<td>487 (49.8)</td>
<td>21 (24.1)</td>
<td>107 (50.5)</td>
<td>359 (52.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recurrent</td>
<td>490 (50.2)</td>
<td>66 (75.9)</td>
<td>105 (49.5)</td>
<td>319 (47.1)</td>
<td></td>
</tr>
<tr>
<td>Median duration from EBC diagnosis to MBC diagnosis, months (range)</td>
<td>43.8 (4–452)</td>
<td>39.9 (12–332)</td>
<td>40.4 (5–369)</td>
<td>48.7 (4–452)</td>
<td></td>
</tr>
<tr>
<td>Hormone receptor status, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER- and/or PR-positive</td>
<td>685 (70.1)</td>
<td>57 (65.5)</td>
<td>120 (56.3)</td>
<td>498 (73.5)</td>
<td>0.002</td>
</tr>
<tr>
<td>ER- and PR-negative</td>
<td>292 (29.9)</td>
<td>30 (34.5)</td>
<td>82 (34.7)</td>
<td>180 (26.5)</td>
<td></td>
</tr>
<tr>
<td><strong>Visceral disease, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>603 (61.7)</td>
<td>41 (47.1)</td>
<td>160 (75.5)</td>
<td>402 (59.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>302 (30.9)</td>
<td>45 (51.7)</td>
<td>86 (40.6)</td>
<td>171 (25.2)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td></td>
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</tbody>
</table>

Abbreviations: BMI, body mass index; ER, estrogen receptor; IQR, interquartile range; PR, progesterone receptor.

Recurrent (as opposed to de novo) MBC indicates ≤90 days between EBC and MBC diagnoses.

In patients with recurrent disease.

Includes nonhepatic abdominal, ascites, liver, lung, or pleural effusion sites of metastasis (excludes CNS).
non-CNS), patients who received radiotherapy also received regimens containing lapatinib or trastuzumab + pertuzumab more commonly compared with the small group of patients who did not receive radiotherapy [lapatinib: 27.1% (19/70) vs. 5.9% (1/17), respectively; trastuzumab + pertuzumab: 55.7% (39/70) vs. 41.2% (7/17)].

In patients with CNS metastasis observed after MBC diagnosis, treatment data were available for 211 patients prior to the detection of CNS lesions and 128 patients following diagnosis of CNS metastasis. Similar to observations in patients with CNS metastasis at MBC diagnosis, administration of lapatinib in any line was more common following the detection of CNS lesions [prior to CNS metastasis: 6.2% (13/211), of whom 12 patients also received trastuzumab; following CNS metastasis: 34.4% (44/128), of whom 18 patients also received trastuzumab; Supplementary Fig. S4]. T-DM1 was administered to 26.1% (55/211) of patients receiving trastuzumab; following CNS metastasis: 34.4% (44/128). The median PFS was 9.2, 9.9, and 19.1 months in patient cohorts with CNS metastasis at diagnosis, CNS metastasis observed after diagnosis, and no CNS metastasis at diagnosis, respectively.

### Table 2. First-line HER2-targeted therapy by CNS metastasis cohort

<table>
<thead>
<tr>
<th>HER2-targeted therapy</th>
<th>CNS metastasis at diagnosis</th>
<th>No CNS metastasis at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>by patients with any first-line exposure, n (%)</td>
<td>(n = 87)</td>
<td>(n = 890)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>61 (70.1)</td>
<td>826 (92.8)</td>
</tr>
<tr>
<td>With chemotherapy</td>
<td>55 (63.2)</td>
<td>758 (82.9)</td>
</tr>
<tr>
<td>With hormonal therapy</td>
<td>20 (23.0)</td>
<td>360 (40.4)</td>
</tr>
<tr>
<td>Trastuzumab + pertuzumab</td>
<td>46 (52.9)</td>
<td>666 (74.8)</td>
</tr>
<tr>
<td>With chemotherapy</td>
<td>45 (51.7)</td>
<td>630 (70.8)</td>
</tr>
<tr>
<td>With hormonal therapy</td>
<td>13 (14.9)</td>
<td>272 (30.6)</td>
</tr>
<tr>
<td>Trastuzumab without pertuzumab</td>
<td>15 (17.2)</td>
<td>160 (18.0)</td>
</tr>
<tr>
<td>With chemotherapy</td>
<td>10 (11.5)</td>
<td>108 (12.3)</td>
</tr>
<tr>
<td>With hormonal therapy</td>
<td>7 (8.0)</td>
<td>88 (9.9)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>20 (23.0)</td>
<td>22 (2.5)</td>
</tr>
<tr>
<td>With chemotherapy</td>
<td>14 (16.1)</td>
<td>18 (2.0)</td>
</tr>
<tr>
<td>With hormonal therapy</td>
<td>7 (8.0)</td>
<td>8 (0.9)</td>
</tr>
<tr>
<td>Lapatinib + trastuzumab</td>
<td>11 (12.6)</td>
<td>12 (1.3)</td>
</tr>
<tr>
<td>T-DM1</td>
<td>10 (11.5)</td>
<td>61 (6.9)</td>
</tr>
</tbody>
</table>

*Treatments are not mutually exclusive.

Patient-reported outcomes

PRO questionnaire completion rates at enrollment were 79.4% (776/977) for FACT-B, 80.3% (785/977) for FACT-B TOI, 77.3% (755/977) for MDASI-BT, and 77.1% (753/977) for MDASI-BT. Cognitive symptoms, and 77.3% (753/977) for MDASI-BT: interference in daily life. Rates of completion were similar between CNS cohorts. Patients with CNS metastases at MBC diagnosis reported lower quality of life at enrollment compared with patients without CNS metastasis at diagnosis, measured by FACT-B (median score 94.5 vs. 103.5 out of a possible 148, P = 0.002) and FACT-B TOI (median score 56.5 vs. 62.0 out of 96, P = 0.009; Supplementary Fig. S5A and S5B). Greater impairment in daily activities was also observed in the cohort with CNS metastases at diagnosis (versus without CNS metastases at diagnosis) per RSC-ALS (median score 77.1 vs. 87.5 out of 100, P < 0.001; brain tumor-related interference in daily life, median score 3.9 vs. 2.0 out of 10, P = 0.004; Supplementary Fig. S5E).

Clinical outcomes

Estimated median first-line PFS and OS from MBC diagnosis were markedly shorter in patients with CNS metastases at any time compared with patients with no CNS metastasis (Fig. 2). Median PFS was 9.2, 9.9, and 19.1 months in patient cohorts with CNS metastasis at diagnosis, CNS metastasis observed after diagnosis, and no CNS metastasis, respectively. By the data cutoff date, 50.6% (44/87), 49.5% (105/212), and 23.6% (160/678) patients in each cohort had died, respectively. Median OS was 30.2 months (HR 2.86; 95% CI, 2.05–4.00; P = 0.001) in patients with CNS metastasis at diagnosis, 38.3 months (HR 1.94; 95% CI, 1.52–2.49; P < 0.0001) in patients with CNS metastasis observed after diagnosis, and was not yet estimable in patients with no CNS metastasis.

Patients with CNS-only metastasis at MBC diagnosis (n = 28) had a median PFS of 9.2 months and median OS of 20.1 months.
from MBC diagnosis. In patients with CNS metastasis observed after MBC diagnosis, median time to diagnosis of CNS metastasis was 15.1 (95% CI, 13.7–16.6) months.

Among patients with CNS-only metastasis at diagnosis, 46.4% (13/28) had CNS-only progression at their next progression event, 10.7% (3/28) had non-CNS progression, and no patients had both CNS and non-CNS progression. In the 59 patients with both CNS and non-CNS metastasis at MBC diagnosis, 33.9% (20/59) had CNS-only progression at their next progression event, 35.6% (21/59) had non-CNS progression, and 5.1% (3/59) had both CNS and non-CNS progression. In each group, respectively, 42.9% (12/28) and 25.4% (15/59) of patients did not have a

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**Figure 2.** (A) Progression-free survival and (B) overall survival by CNS metastasis cohort. NE, not estimable.
progression event by the time of data cutoff, whether due to death, loss of follow-up, or study closure.

Discussion

In this real-world analysis of patients with HER2-positive MBC from the SystHERs study, we found that development of CNS metastasis was associated with race, age, hormone receptor status, and MBC diagnosis type. Patients with CNS metastasis at MBC diagnosis reported poorer quality of life at enrollment, and received first-line lapatinib more commonly and first-line trastuzumab less commonly, than patients with CNS metastasis observed after diagnosis or those with no CNS metastasis while on study. Of the three CNS metastasis cohorts, prognosis was poorest in patients with CNS metastasis at diagnosis and most favorable in patients without CNS metastasis.

Breast cancer is associated with a high incidence of CNS metastasis, a risk that rises significantly in patients with HER2-positive disease. Other previously identified risk factors included high tumor grade or disease burden, hormone receptor-negative MBC, and younger age. Routine magnetic resonance imaging for CNS metastasis is currently not recommended in the absence of suggestive symptoms, limiting our ability to assess whether early detection and treatment of asymptomatic CNS disease improves outcomes. In a multivariate analysis of SystHERs data, we found CNS metastasis was more common in White and younger patients, and in those with recurrent MBC and hormone receptor-negative disease. Data from SystHERs and other studies may help identify a particularly high-risk cohort of patients for further study.

Because of the presumed inability of certain pharmacologic treatments to cross the blood–brain barrier and limited historical data regarding the efficacy of these therapies against CNS lesions, management of CNS metastasis has typically involved the use of local treatments, including surgery and whole-brain or stereotactic radiotherapy. However, optimizing control of systemic disease is needed to prolong survival. As such, ASCO guidelines for patients with HER2-positive MBC and CNS metastasis recommend that in addition to local treatments, patients with progressive disease should receive systemic therapy according to standard algorithms for HER2-positive MBC. In this analysis, we found that only 68.3% of patients with CNS metastasis at MBC diagnosis were treated with the first-line standard of care, trastuzumab + pertuzumab + taxane, compared with 68.3% of patients without CNS metastasis at diagnosis, although part of this disparity could potentially be attributed to differences in CNS-independent baseline characteristics between the two groups. Patients with CNS metastasis at diagnosis preferentially received first-line regimens containing lapatinib (23.0% vs. 2.5% of patients without CNS metastasis at diagnosis), presumably due to evidence that lapatinib may have activity in the CNS. A meta-analysis of patients with HER2-positive breast cancer and brain metastasis treated with lapatinib ± capecitabine indicated an overall response rate of 21.4% in the CNS, which increased to 29.2% when lapatinib monotherapy was excluded. In the phase II LANDSCAPE study, lapatinib + capecitabine demonstrated a volumetric response rate of 65.9% against CNS lesions, although the regimen was associated with a high rate of grade 3 and 4 toxicities. However, a retrospective analysis of data from the phase III EMILIA trial showed significantly improved OS in patients with MBC and brain metastasis treated with T-DM1 versus lapatinib + capecitabine. Furthermore, a study by Gelmon and colleagues indicated that first-line lapatinib + taxane is associated with lower PFS than trastuzumab + taxane. It is possible that the use of lapatinib-based first-line treatment regimens in patients with CNS metastasis at MBC diagnosis, at the possible expense of targeting systemic disease, may contribute to the poorer outcomes observed in that cohort. The use of first-line regimens containing lapatinib versus other HER2-targeted treatments should be further examined in randomized clinical trials to assess their overall impact on survival in patients with CNS metastasis at diagnosis.

Accumulating preclinical and clinical evidence suggest that other HER2-targeted therapies can also penetrate the blood–brain barrier and delay or ameliorate CNS metastasis in patients with MBC. Preliminary results from the phase III CEREBEL study found that patients receiving lapatinib + capecitabine versus trastuzumab + capecitabine had similar incidences of CNS metastases as first detected site of relapse (3% vs. 5%, respectively), with longer PFS and OS in the trastuzumab + capecitabine arm. In the phase III CLEOPATRA trial, the addition of pertuzumab to first-line trastuzumab + docetaxel delayed observations of CNS metastasis as the first site of disease progression, from 11.9 months in the placebo arm to 15.0 months in the pertuzumab arm. Preliminary evidence from the ongoing phase III KAMILLA and phase II PATRICIA studies suggest that T-DM1 and pertuzumab + high-dose trastuzumab, respectively, have activity against CNS lesions. Finally, tucatinib, an investigational small-molecule HER2 inhibitor, has demonstrated promising CNS activity and has been granted U.S. FDA orphan drug status for patients with HER2-positive MBC with CNS metastasis. Data from these and other studies may help identify therapeutic regimens that optimize the treatment of both CNS and extracranial lesions to improve OS in patients with CNS metastasis.

CNS metastasis in patients with breast cancer has historically been associated with decreased quality of life and a poor prognosis. As management of MBC is often considered palliative, PRO-assessed quality of life is an important consideration in this population. In this study, PRO measures captured at enrollment suggested that patients with CNS metastases at MBC diagnosis may carry a greater disease burden than those without CNS metastases at diagnosis. Patients with CNS metastases at MBC diagnosis reported poorer quality of life and higher impairment in functional measures of cognition and daily activities, although these measures may reflect composite effects of disease and treatments initiated prior to enrollment. Furthermore, patients with CNS metastasis at or after MBC diagnosis had markedly shorter median PFS (9.2 and 9.9 months, respectively) and median OS (30.2 and 38.3 months, respectively) compared with patients who did not develop CNS metastasis on study (median PFS, 19.1 months; median OS, not yet estimable). Despite these differences, OS observed in patients with CNS metastasis notably exceeds that reported prior to the approval of lapatinib, pertuzumab, and T-DM1 in registHER, which enrolled patients from 2003 to 2006, patients with CNS metastasis at MBC diagnosis had a median OS of 20.3 months. In patients with CNS metastasis observed after MBC diagnosis, median time to diagnosis of CNS metastasis was 15.1 months in SystHERs versus 13.3 months in registHER after similar follow-up durations for both studies. Data from both registHER and SystHERs...
represent substantial improvements in clinical outcomes relative to the pre-trastuzumab era, when median survival following brain metastasis was only 4 months (33). Among other variables, future studies should assess the contribution of different systemic treatments (e.g., regimens including trastuzumab + pertuzumab vs. lapatinib) on PROs and clinical outcomes in patients with CNS metastasis.

In the SystHERs study, CNS metastasis at MBC diagnosis was observed in 8.9% of patients. With a median follow-up of 27.8 months from MBC diagnosis in SystHERs, CNS metastasis was detected in an additional 21.7% of patients (i.e., a total of 30.6% of patients with CNS metastasis). Of note, this number would be expected to increase with longer follow-up. Additionally, screening for CNS metastasis in SystHERs was not required at enrollment and was conducted at the investigator’s discretion. As previous studies have suggested a high incidence of asymptomatic CNS lesions (34), the reported prevalence of CNS metastasis in SystHERs may be underestimated due to undetected CNS disease. Our analysis was also constrained by limitations inherent to registry studies. For example, because EBC data were collected retrospectively, some data were missing, and prospectively collected data may have been impacted by attrition or reporting bias. Finally, similar to the methodological caveats common to other reports of real-world studies, clinical response data were based on investigator assessments with variable assessment intervals across patients in accordance with institutional practice norms, which may be less reliable than standardized criteria used in randomized clinical trials.

In summary, data from the SystHERs registry study suggest that while patients with CNS metastasis continue to experience lower quality of life and a poorer prognosis than patients without CNS metastasis, key clinical outcomes, including time to CNS progression and OS, have improved in this population over time. Recent interest in the use of HER2-targeted therapies against CNS lesions, along with promising preliminary results from the LANDSCAPE, KAMILLA, PATRICIA, and other studies, may lead to further improvements in the treatment, management, and prognosis of patients with HER2-positive MBC and CNS metastasis.

Disclosure of Potential Conflicts of Interest
S.A. Hurvitz reports receiving commercial research grants from Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Lilly, MacroGenics, Merck, Novartis, Pfizer, Roche, Seattle Genetics, and Svion Therapeutics; serves on advisory boards for AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Genentech, GlaxoSmithKline, Lilly, MacroGenics, Medimmune, Merck, Novartis, Pfizer, Roche, Seattle Genetics, and Svion Therapeutics; and holds patents in Roche.

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