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EPIDEMIOLOGY

# Baseline characteristics and first-line treatment patterns in patients with HER2-positive metastatic breast cancer in the SystHERs registry

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## Abstract

**Background** Systemic Therapies for HER2-Positive Metastatic Breast Cancer Study (SystHERs, NCT01615068) was a prospective, observational disease registry designed to identify treatment patterns and clinical outcomes in patients with HER2-positive metastatic breast cancer (MBC) in real-world treatment settings.

**Methods** SystHERs enrolled patients aged ≥ 18 years with recently diagnosed HER2-positive MBC. Treatment regimens and clinical management were determined by the treating physician. In this analysis, patients were compared descriptively by first-line treatment, age, or race. Multivariate logistic regression was used to examine the associations between baseline variables and treatment selections. Clinical outcomes were assessed in patients treated with trastuzumab (Herceptin [H]) + pertuzumab (Perjeta [P]).

**Results** Patients were enrolled from June 2012 to June 2016. As of February 22, 2018, 948 patients from 135 US treatment sites had received first-line treatment, including HP ($n = 711$), H without P ($n = 175$), or no H ($n = 62$) (with or without chemotherapy and/or hormonal therapy). Overall, 68.7% received HP + taxane and 9.3% received H without P + taxane. Patients aged < 50 years received HP (versus H without P) more commonly than those ≥ 70 years (odds ratio 4.20; 95% CI, 1.62–10.89). Chemotherapy was less common in patients ≥ 70 years (68.2%) versus those < 50 years (88.0%) or 50–69 years (87.4%). Patients treated with HP had median overall survival of 53.8 months and median progression-free survival of 15.8 months.

**Conclusions** Our analysis of real-world data shows that most patients with HER2-positive MBC received first-line treatment with HP + taxane. However, older patients were less likely to receive dual HER2-targeted therapy and chemotherapy.

**Keywords** HER2-positive · Metastatic breast cancer · SystHERs · Baseline characteristics · First-line treatment patterns

## Abbreviations

| | |
|---|---|
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| ECOG | Eastern Cooperative Oncology Group |
| FDA | Food and Drug Administration |
| H | Trastuzumab |
| HER2 | Human epidermal growth factor receptor 2 |
| HR | Hazard ratio |
| IRB | Institutional review board |
| MBC | Metastatic breast cancer |
| OR | Odds ratio |
| OS | Overall survival |
| P | Pertuzumab |
| PFS | Progression-free survival |
| SEER | Surveillance, Epidemiology, and End Results |
| SystHERs | Systemic Therapies for HER2-Positive Metastatic Breast Cancer Study |
| T-DM1 | Trastuzumab emtansine |
| US | United States |

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## Introduction

Of the 150,000 women estimated to be living with metastatic breast cancer (MBC) in the United States (US) [1], approximately 20% have human epidermal growth factor receptor 2 (HER2)-positive disease [2]. Although HER2 was historically associated with poor clinical outcomes, the

introduction of trastuzumab (H), a HER2-targeted therapy, dramatically improved survival [3, 4]. The CLEOPATRA study showed that survival further improved with the addition of pertuzumab (P) to H + docetaxel [5, 6]. Following the 2012 US approval of P based on these results, the combination of HP + taxane became the first-line standard of care for HER2-positive MBC [7].

Limited data exist describing real-world treatment practices, and whether they reflect current guidelines for the management of HER2-positive MBC. Furthermore, prospective randomized clinical trials may underrepresent some patient subgroups common in routine clinical practice, such as older patients and minority populations [8–11]. Prior studies have suggested that these characteristics, and others, may be associated with distinct real-world treatment patterns. An analysis of first-line treatment of HER2-positive MBC in the registHER observational study, which enrolled patients from 2003 to 2006, found that older patients (≥ 75 years) were less likely to receive H and chemotherapy than younger patients [12]. Additionally, retrospective database studies suggest that minority patients with HER2-positive early breast cancer (EBC) are treated according to guidelines less commonly than white patients [13, 14]. Such observational data from real-world settings are increasingly valued as an important complement to clinical trial data, to better understand the impact of treatment guidelines and to provide external validity regarding clinical trial outcomes in the broader population of patients. In the time since registHER enrollment, however, treatments for HER2-positive MBC have evolved to incorporate P and other recently approved HER2-targeted therapies, limiting our understanding of contemporary real-world treatment patterns.

The Systemic Therapies for HER2-Positive Metastatic Breast Cancer Study (SystHERs; NCT01615068) was a disease-based observational cohort study designed to prospectively explore real-world treatment patterns and clinical outcomes over multiple lines of therapy, including a diverse patient population with recently diagnosed, HER2-positive MBC [15]. Here, we report first-line treatment patterns used in clinical practice; describe variables previously reported to influence treatment choice, including age and race; and report clinical outcomes in patients treated with HP.

## Materials and methods

### Study design and participants

The SystHERs registry protocol has been described previously [15]. Briefly, SystHERs was a US-based, prospective, multicenter, observational cohort study. The primary objective was to assess treatment patterns, treatment sequencing at disease progression, and outcomes in patients with HER2-positive MBC. There was no protocol-defined treatment regimen or patient management, as SystHERs was a disease-based (rather than a treatment-based) study.

Patients aged ≥ 18 years diagnosed with HER2-positive MBC within the previous 6 months were invited to enroll. To minimize selection bias, investigators were encouraged to recruit all eligible patients in their care. All patients provided written informed consent. HER2-positivity was determined locally, based on the evaluation of the primary tumor or biopsy at recurrence, per the standards of the patients' physicians and their institutions. The study was conducted in accordance with US Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable local laws. Each participating study site obtained approval of the study protocol by the site's ethics committee or institutional review board (IRB), or a central IRB for sites that did not have an IRB.

### Evaluations and follow-up

Data for baseline patient and disease characteristics, disease history, HER2 testing method(s) used, and previous cancer-related treatment were collected at enrollment. Patients were assessed by their clinicians per normal practice/procedures at the treating institution; there was no protocol-required evaluation schedule. Data for MBC treatments, disease progression, and clinical outcomes were captured quarterly from patient charts, clinical notes, diagnostic tests, and laboratory findings. Although 5 years of follow-up was initially planned per the protocol, the SystHERs registry was terminated early due to the sponsor's decision to prioritize evaluation of new breast cancer therapies.

### Analyses and statistical methods

Baseline characteristics and first-line treatment regimens were summarized within patient cohorts defined by category of first-line treatment (i.e., treatment regimens that included HP, H with no P [H without P], or no H [Other]), age at enrollment (< 50 years, 50–69 years, or ≥ 70 years), and race (white or black/African American).

The association between baseline demographic, clinical, and socioeconomic characteristics and choice of first-line treatment was examined using multivariate logistic regression. Adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated and are presented as forest plots.

First-line treatment was defined as any therapy received for MBC up to first progression. Progression-free survival (PFS) was defined as time from MBC diagnosis to first investigator-assessed disease progression or death. Overall survival (OS) was defined as time from MBC diagnosis to

death. PFS and OS were estimated by the Kaplan–Meier product-limit method and compared across subgroups using a log-rank test. Cox regressions were used to estimate hazard ratios (HRs) and their 95% CIs.

## Results

### Patient disposition

Patients in SystHERs were enrolled from June 2012 to June 2016 from US academic and community practices. Out of 1028 patients who met study inclusion criteria, 1004 consented to enrollment (Supplementary Fig. 1). Of these patients, 977 from 135 treatment sites were deemed eligible for study participation; the majority of ineligible patients did not have metastatic disease or HER2-positive cancer upon review. As of the February 22, 2018, data cut-off date, 948 of the 977 eligible patients had reported first-line treatment. The remaining 29 patients did not report first-line therapy because they were undergoing a "watch-and-wait" approach until the occurrence of a subsequent progression event, or because no treatment information was available (e.g., the patient died, was lost to follow-up, or other reasons).

### Patient characteristics by first-line treatment cohort

Of the 948 patients who received first-line treatment, 75.0% ($n=711$) received HP, 18.5% ($n=175$) received H without P, and 6.5% ($n=62$) received "Other" (no H) treatment. Median follow-up from first-line treatment start was 27.8 and 29.2 months in the HP and H without P cohorts, respectively. While baseline demographics and clinical and disease characteristics were generally similar between the HP and H without P cohorts (Table 1), the HP cohort had lower median patient age at diagnosis (55 vs. 60 years) and a lower proportion of patients with prior cardiovascular disease (CVD; 11.8% vs. 17.7%). The HP cohort also had higher proportions of patients with liver metastases (42.2% vs. 27.4%) and with annual income > $50,000 (37.6% vs. 20.6%).

Among patients who received first-line treatment, 49.7% had recurrent disease. Median duration from EBC to MBC diagnoses was shorter in the HP cohort (44.0 months) than the H without P cohort (50.7 months). Among patients with recurrent disease with available information on adjuvant or neoadjuvant treatment, 63.7% (188/295) in the HP cohort and 63.9% (46/72) in the H without P cohort had prior exposure to adjuvant or neoadjuvant H.

### Association between baseline characteristics and first-line treatment choice

Among baseline characteristics assessed for possible impact on treatment choice between HP versus H without P, age had the strongest such association (Fig. 1). Use of HP (versus H without P) was more common in patients aged < 50 and 50–69 years versus ≥ 70 years (OR 4.20; 95% CI, 1.62–10.89 and OR 2.79; 95% CI, 1.26–6.19, respectively). Other baseline patient and socioeconomic characteristics did not appear to significantly impact treatment choice between HP and H without P, including race, ethnicity, Eastern Cooperative Oncology Group (ECOG) performance status, de novo/recurrent disease type, hormone receptor status, visceral/non-visceral disease type, education level, employment status, income level, type of health insurance, rural/urban/suburban location, academic versus community treatment site type, treatment region, or prior CVD.

### First-line treatment patterns and treatment exposure by treatment cohort

Of the 948 patients who received first-line treatment, 68.7% received HP + taxane, and 9.3% received H without P + taxane. The most common first-line treatment regimen across all patients was HER2-targeted therapy + chemotherapy without hormonal therapy (53.1% [$n=503$]) (Fig. 2). The second most common regimen was HER2-targeted therapy + chemotherapy + hormonal therapy (33.8% [$n=320$]); the majority of these patients received hormonal therapy that was sequential (77.5% [248/320]) rather than concurrent (22.5% [72/320]) with chemotherapy. Of the remaining 125 patients, most received HER2-targeted therapy without chemotherapy (10.5% [$n=100$], with or without hormonal therapy [$n=77$ and $n=23$, respectively]). Overall, 97.4% ($n=923$) patients received HER2-targeted therapy.

Patients in the HP cohort ($n=711$) received chemotherapy more commonly (95.1% vs. 67.4%) and hormonal therapy less commonly (40.4% vs. 54.3%) than the H without P cohort ($n=175$) (Table 2). Docetaxel was the most commonly received taxane in the HP cohort, whereas paclitaxel was the most common taxane in the H without P cohort. Median treatment duration was 23.1 months with first-line H and 17.2 months with first-line P in the HP cohort (Table 3). In the H without P cohort, median treatment duration of first-line H was 18.6 months.

In the Other (no H) treatment cohort ($n=62$), similar proportions of patients received regimens that included chemotherapy (59.7%) or hormonal therapy (56.5%). Higher proportions of patients in the Other cohort were administered lapatinib (30.6%) or trastuzumab emtansine (T-DM1; 25.8%) versus patients in the HP (1.7% and 5.3%, respectively) and H without P cohorts (5.7% and 9.7%). Antimetabolites were

**Table 1** Baseline patient and clinical characteristics by first-line MBC treatment cohort

| | HP ($n=711$) | H without P ($n=175$) | Other (No H) ($n=62$) |
|---|---|---|---|
| Median age at MBC diagnosis, years (range) | 55 (21–89) | 60 (28–90) | 62 (33–86) |
| Race, *n* (%) | | | |
| White | 565 (79.5) | 137 (78.3) | 44 (71.0) |
| Black/African American | 102 (14.3) | 26 (14.9) | 16 (25.8) |
| Asian | 8 (1.1) | 5 (2.9) | 0 |
| Other | 24 (3.4) | 4 (2.3) | 0 |
| Unknown/missing | 12 (1.7) | 3 (1.7) | 2 (3.2) |
| Ethnicity, *n* (%) | | | |
| Hispanic or Latino | 66 (9.3) | 20 (11.4) | 6 (9.7) |
| Not Hispanic or Latino | 616 (86.6) | 149 (85.1) | 55 (88.7) |
| Unknown/missing | 29 (4.1) | 6 (3.4) | 1 (1.6) |
| ECOG performance status, *n* (%) | | | |
| 0–1 | 611 (85.9) | 147 (84.0) | 45 (72.6) |
| ≥ 2 | 44 (6.2) | 18 (10.3) | 9 (14.5) |
| Unknown/missing | 56 (7.9) | 10 (5.7) | 8 (12.9) |
| Level of education, *n* (%) | | | |
| Grade school to some high school education | 44 (6.2) | 18 (10.3) | 3 (4.8) |
| High school graduate | 214 (30.1) | 58 (33.1) | 18 (29.0) |
| Some college/college graduate/postgraduate | 380 (53.4) | 77 (44.0) | 32 (51.6) |
| Unknown/missing | 73 (10.3) | 22 (12.6) | 9 (14.5) |
| Employment status, *n* (%) | | | |
| Full time or part time | 242 (34.0) | 46 (26.3) | 16 (25.8) |
| Homemaker or retired | 157 (22.1) | 50 (28.6) | 10 (16.1) |
| Not employed | 126 (17.7) | 36 (20.6) | 14 (22.6) |
| Other/missing | 186 (26.2) | 43 (24.6) | 22 (35.5) |
| Annual household income, *n* (%) | | | |
| ≤ $50,000 | 271 (38.1) | 93 (53.1) | 24 (38.7) |
| > $50,000 | 267 (37.6) | 36 (20.6) | 14 (22.6) |
| Unknown/missing | 173 (24.3) | 46 (26.3) | 24 (38.7) |
| Insurance status, *n* (%) | | | |
| Public | 137 (19.3) | 45 (25.7) | 12 (19.4) |
| Private | 298 (41.9) | 53 (30.3) | 18 (29.0) |
| Both public and private | 73 (10.3) | 32 (18.3) | 10 (16.1) |
| None | 24 (3.4) | 10 (5.7) | 1 (1.6) |
| Unknown/missing | 179 (25.2) | 35 (20.0) | 21 (33.9) |
| Treating site, *n* (%) | | | |
| Academic | 137 (19.3) | 31 (17.7) | 18 (29.0) |
| Community | 574 (80.7) | 144 (82.3) | 44 (71.0) |
| Treating site location, *n* (%) | | | |
| Midwest | 90 (12.7) | 36 (20.6) | 13 (21.0) |
| Northeast | 135 (19.0) | 18 (10.3) | 11 (17.7) |
| South | 366 (51.5) | 91 (52.0) | 27 (43.5) |
| West | 120 (16.9) | 30 (17.1) | 11 (17.7) |
| Disease type, *n* (%) | | | |
| Recurrent | 335 (47.1) | 86 (49.1) | 50 (80.6) |
| De novo | 376 (52.9) | 89 (50.9) | 12 (19.4) |
| Median time from EBC diagnosis to MBC diagnosis, months (range)[a] | 44.0 (4–392) | 50.7 (9–369) | 34.9 (7–452) |
| Hormone receptor status, *n* (%) | | | |
| ER + and/or PR + | 496 (69.8) | 126 (72.0) | 48 (77.4) |

**Table 1** (continued)

| | HP ($n=711$) | H without P ($n=175$) | Other (No H) ($n=62$) |
|---|---|---|---|
| ER– and PR– | 215 (30.2) | 49 (28.0) | 14 (22.6) |
| Visceral disease, *n* (%)[b] | 477 (67.1) | 109 (62.3) | 39 (62.9) |
| Number of metastatic sites, *n* (%) | | | |
| 1 | 284 (39.9) | 85 (48.6) | 32 (51.6) |
| 2 | 195 (27.4) | 46 (26.3) | 13 (21.0) |
| ≥3 | 232 (32.6) | 44 (25.1) | 17 (27.4) |
| Selected sites of metastasis, *n* (%) | | | |
| Bone | 375 (52.7) | 92 (52.6) | 30 (48.4) |
| Liver | 300 (42.2) | 48 (27.4) | 11 (17.7) |
| CNS | 46 (6.5) | 15 (8.6) | 16 (25.8) |
| Prior cardiovascular disease, *n* (%) | 84 (11.8) | 31 (17.7) | 16 (25.8) |

*CNS* central nervous system, *EBC* early breast cancer, *ECOG* Eastern Cooperative Oncology Group, *ER* estrogen receptor, *H* trastuzumab, *MBC* metastatic breast cancer, *P* pertuzumab, *PR* progesterone receptor

[a]In patients with recurrent MBC

[b]Includes non-hepatic abdominal, ascites, CNS, liver, lung, or pleural effusion sites of metastasis

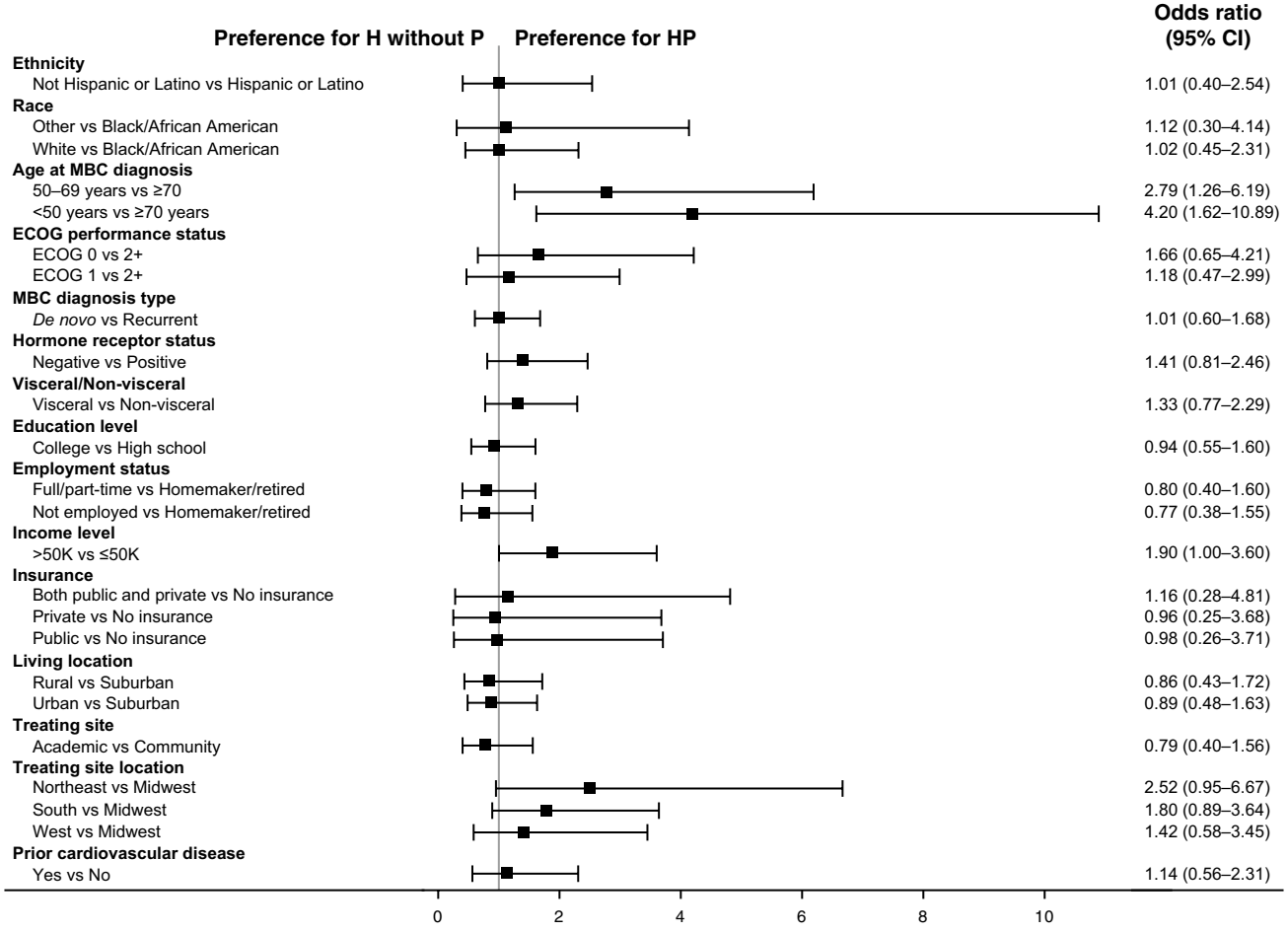


**Fig. 1** Association between first-line HP versus H without P treatment choice and baseline demographic and clinical characteristics. *CI* confidence interval, *ECOG* Eastern Cooperative Oncology Group, *H* trastuzumab, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *MBC* metastatic breast cancer, *P* pertuzumab

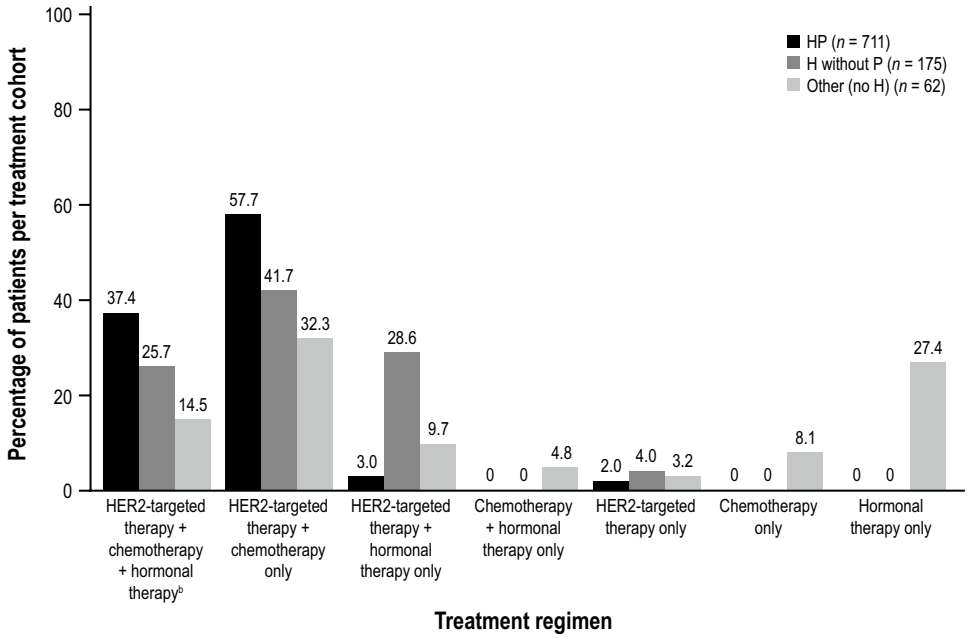


**Fig. 2** First-line treatment regimens[a] by MBC treatment cohort. [a]First-line treatment was defined as any therapy received for MBC up to first progression. [b]Most patients received hormonal therapy sequentially. Hormonal therapy was administered concurrently in 8.4%, 5.7%, and 3.2% of patients and sequentially in 29.0%, 20.0%, and 11.3% of patients in the HP, H without P, and other cohorts, respectively. *H* trastuzumab, *HER2* human epidermal growth factor receptor 2, *MBC* metastatic breast cancer, *NA* not applicable, *P* pertuzumab

**Table 2** First-line drug treatment choice by MBC treatment cohort

| Drug administration by patients with any first-line exposure[a], *n* (%) | HP (*n* = 711) | H without P (*n* = 175) | Other (No H)[b] (*n* = 62) |
|---|---|---|---|
| With chemotherapy | 676 (95.1) | 118 (67.4) | 37 (59.7) |
| Any taxane or epothilone | 651 (91.6) | 88 (50.3) | 12 (19.4) |
| Docetaxel | 479 (67.4) | 35 (20.0) | 4 (6.5) |
| Paclitaxel | 198 (27.8) | 51 (29.1) | 7 (11.3) |
| Other taxanes[c] | 28 (3.9) | 8 (4.6) | 2 (3.2) |
| Platinum | 67 (9.4) | 41 (23.4) | 1 (1.6) |
| Antimetabolite | 19 (2.7) | 11 (6.3) | 13 (21.0) |
| Vinca derivative | 23 (3.2) | 16 (9.1) | 0 (0) |
| Alkylating agent | 15 (2.1) | 10 (5.7) | 3 (4.8) |
| Anthracycline | 14 (2.0) | 10 (5.7) | 2 (3.2) |
| Nucleoside analog | 9 (1.3) | 5 (2.9) | 1 (1.6) |
| With hormonal therapy | 287 (40.4) | 95 (54.3) | 35 (56.5) |
| Aromatase inhibitor | 225 (31.6) | 76 (43.4) | 26 (41.9) |
| Tamoxifen | 62 (8.7) | 13 (7.4) | 4 (6.5) |
| Fulvestrant | 28 (3.9) | 13 (7.4) | 6 (9.7) |
| Goserelin | 23 (3.2) | 3 (1.7) | 0 (0) |
| Other hormonal agents | 21 (3.0) | 4 (2.3) | 3 (4.8) |
| With other HER2-targeted therapies | | | |
| T-DM1 | 38 (5.3) | 17 (9.7) | 16 (25.8) |
| Lapatinib | 12 (1.7) | 10 (5.7) | 19 (30.6) |

*H* trastuzumab, *MBC* metastatic breast cancer, *P* pertuzumab, *T-DM1* trastuzumab emtansine

[a]First-line treatment was defined as any therapy received for MBC up to first progression. Treatments are not mutually exclusive and may have been received concurrently or sequentially with other treatments in the first line

[b]Patients received first-line MBC treatment regimens that did not include H, including four patients who receive P without H

[c]Includes nab-paclitaxel

**Table 3** First-line MBC treatment durations by first-line MBC treatment cohort

| | HP | | H without P | |
|---|---|---|---|---|
| | *N* | Treatment duration, median months (IQR) | *N* | Treatment duration, median months (IQR) |
| Trastuzumab | 711 | 23.1 (9.5–36.1) | 175 | 18.6 (6.9–34.3) |
| Pertuzumab | 711 | 17.2 (5.6–33.6) | N/A | N/A |
| Docetaxel | 479 | 3.5 (3.4–4.9) | 35 | 3.5 (2.1–3.9) |
| Paclitaxel | 198 | 3.7 (2.6–6.7) | 51 | 4.6 (2.6–8.6) |

*H* trastuzumab, *IQR* interquartile range, *MBC* metastatic breast cancer, *N/A* not applicable, *P* pertuzumab

used by 21.0% of patients in the Other cohort, compared with 2.7% and 6.3% of patients in the HP and H without P cohorts, respectively (Table 2).

## First-line treatment patterns and treatment exposure by age cohort

At enrollment, 29.0% ($n=283$) of the 977 eligible patients were aged < 50 years, 57.8% ($n=565$) were 50–69 years, and 13.2% ($n=129$) were ≥ 70 years (Supplementary Table 1). Compared with the < 50 years age cohort, the ≥ 70 years cohort had higher proportions of patients who were white (73.1% vs. 86.0%, respectively), had recurrent (versus de novo) disease (45.2% vs. 58.9%), and had prior CVD (5.3% vs. 38.0%). Bone and liver metastases at MBC diagnosis were more common in patients aged < 50 years than in those ≥ 70 years (bone: 58.0% vs. 44.2%; liver: 40.6% vs. 25.6%, respectively).

HER2-targeted therapy with chemotherapy alone (i.e., without hormonal therapy) was the most common first-line treatment regimen among all age cohorts, but was administered more frequently to patients < 50 years (52.7% [$n=149$]) and 50–69 years (54.0% [$n=305$]) than to patients ≥ 70 years (38.0% [$n=49$]) (Supplementary Fig. 2). HER2-targeted therapy + chemotherapy + hormonal therapy was the second most common treatment regimen and was used by similar proportions in each age cohort, with hormonal therapy generally given sequentially (rather than concurrently) after chemotherapy.

HP administration was more common than H without P across all age cohorts (Supplementary Table 2), although patients ≥ 70 years received H without P more commonly than the other age cohorts (78.8% vs. 13.1% [< 50 years]; 74.0% vs. 16.6% [50–69 years]; 54.3% vs. 34.1% [≥ 70 years]). Median treatment durations for H and P were longer in the < 50 age cohort (23.8 and 22.6 months, respectively) versus the ≥ 70 age cohort (18.8 and 12.1 months) (Supplementary Table 3).

Across age cohorts, most patients received HP with taxane (with or without first-line hormonal therapy), although patients ≥ 70 received this combination less frequently than the other age cohorts. Docetaxel was the most common chemotherapy administered to patients aged < 50 and 50–69 years. In patients aged ≥ 70 years, approximately equal proportions received docetaxel and paclitaxel. Patients aged ≥ 70 years received first-line hormonal therapy without chemotherapy (with or without HER2-targeted therapy) more commonly (23.3%) than patients aged < 50 years (4.6%) and 50–69 years (9.0%). Notably, use of hormonal therapy was likely underestimated due to limited follow-up time.

## First-line treatment patterns and treatment exposure by race cohort

In SystHERs, the two largest race cohorts among the 977 eligible patients were white (78.4% [$n=766$]) and black/African American (15.5% [$n=151$]) (Supplementary Table 4). A higher proportion of white patients, compared with black/African American patients, had college-level education (53.8% vs. 40.4%), annual income > $50,000 (36.4% vs. 16.6%), and private insurance (41.5% vs. 29.1%).

HER2-targeted therapy + chemotherapy alone was the most common first-line treatment regimen for patients in both white and black/African American cohorts (51.4% [$n=394$] and 53.0% [$n=80$], respectively), and HER2-targeted therapy + chemotherapy and hormonal therapy (with hormonal therapy typically administered after discontinuation of chemotherapy) was the second most common treatment regimen (32.6% [$n=250$] and 32.5% [$n=49$]) (Supplementary Fig. 3).

Overall use of first-line HER2-targeted therapy was similar between both race cohorts (Supplementary Table 5). HP administration was slightly higher in white (73.8%) versus black/African American patients (67.5%), but the OR 95% CI (0.45–2.31) did not cross unity in the multivariate analysis of baseline characteristics and treatment choice (Fig. 1). Use of H without P was similar in both cohorts. Median treatment durations for H and P were shorter in white (21.5 and 16.8 months, respectively) versus black/African American (25.8 and 20.5 months) patients (Supplementary Table 6). Most patients in both cohorts received a taxane with HP (with or without first-line hormonal therapy), most commonly docetaxel. The proportions of patients who received first-line hormonal therapy without chemotherapy (with or without HER2-targeted therapy) was similar for both white and black/African American patients (10.2% and 7.9%, respectively). Similar to the treatment and age cohort data, use of hormonal therapy by race may also have been underestimated due to limited follow-up time.

## Clinical outcomes in patients treated with first-line HP

Among all patients treated with first-line HP, median OS was 53.8 months and median PFS was 15.8 months, although the OS data were constrained by the small number of patients in the "at risk" population at the median timepoint due to limited follow-up time. Patients with non-visceral metastasis generally had longer survival than those with visceral metastasis (OS: HR 0.65, 95% CI 0.48–0.88, $p = 0.0062$; PFS: HR 0.77, 95% CI 0.63–0.93, $p = 0.0092$) (Fig. 3). Similar results were observed in patients with bone-only versus visceral metastasis (OS: HR 0.55, 95% CI 0.35–0.87, $p = 0.0094$; PFS: HR 0.76, 95% CI 0.58–1.00, $p = 0.0490$). However, clinically meaningful differences in survival were not observed in patients without versus with liver metastasis (OS: HR 0.91, 95% CI 0.70–1.19, $p = 0.5061$; PFS: HR 0.89, 95% CI 0.75–1.06, $p = 0.2037$). Compared with patients with ≥ 3 metastatic sites, patients with one metastatic site had higher median OS (HR 0.51, 95% CI 0.38–0.70) and PFS (HR 0.61, 95% CI 0.49–0.75) (Fig. 4). White and black/African American patients had similar median survival (OS: HR 0.93, 95% CI 0.64–1.34; PFS: HR 0.98, 95% CI 0.76–1.27).

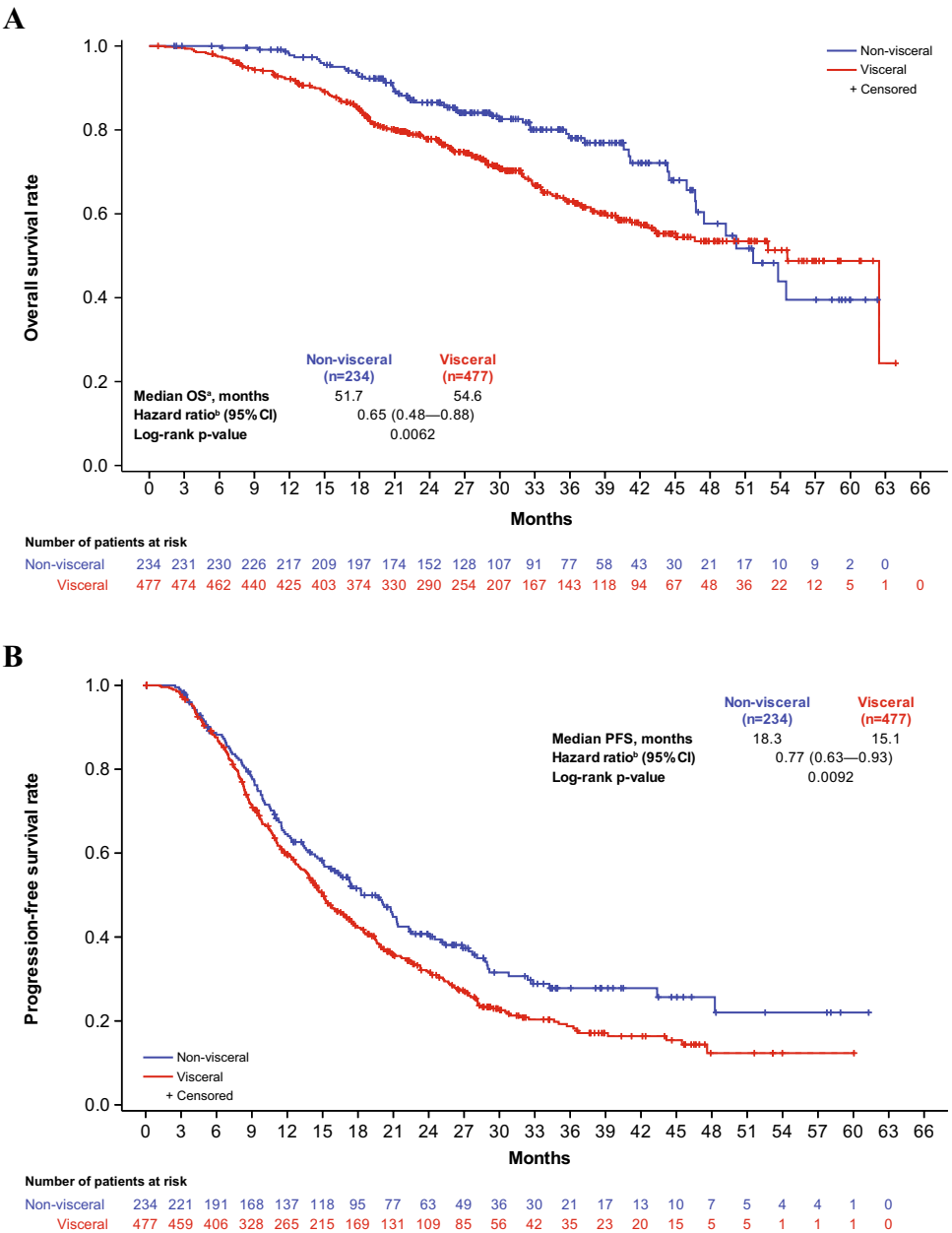


**Fig. 3** OS (**A**) and PFS (**B**) by non-visceral versus visceral metastasis in patients treated with HP. [a]Median OS values may have been impacted by patient censoring due to limited follow-up time. [b]Patients with visceral disease used as reference group. *CI* confidence interval, *H* trastuzumab, *P* pertuzumab, *PFS* progression-free survival, *OS* overall survival

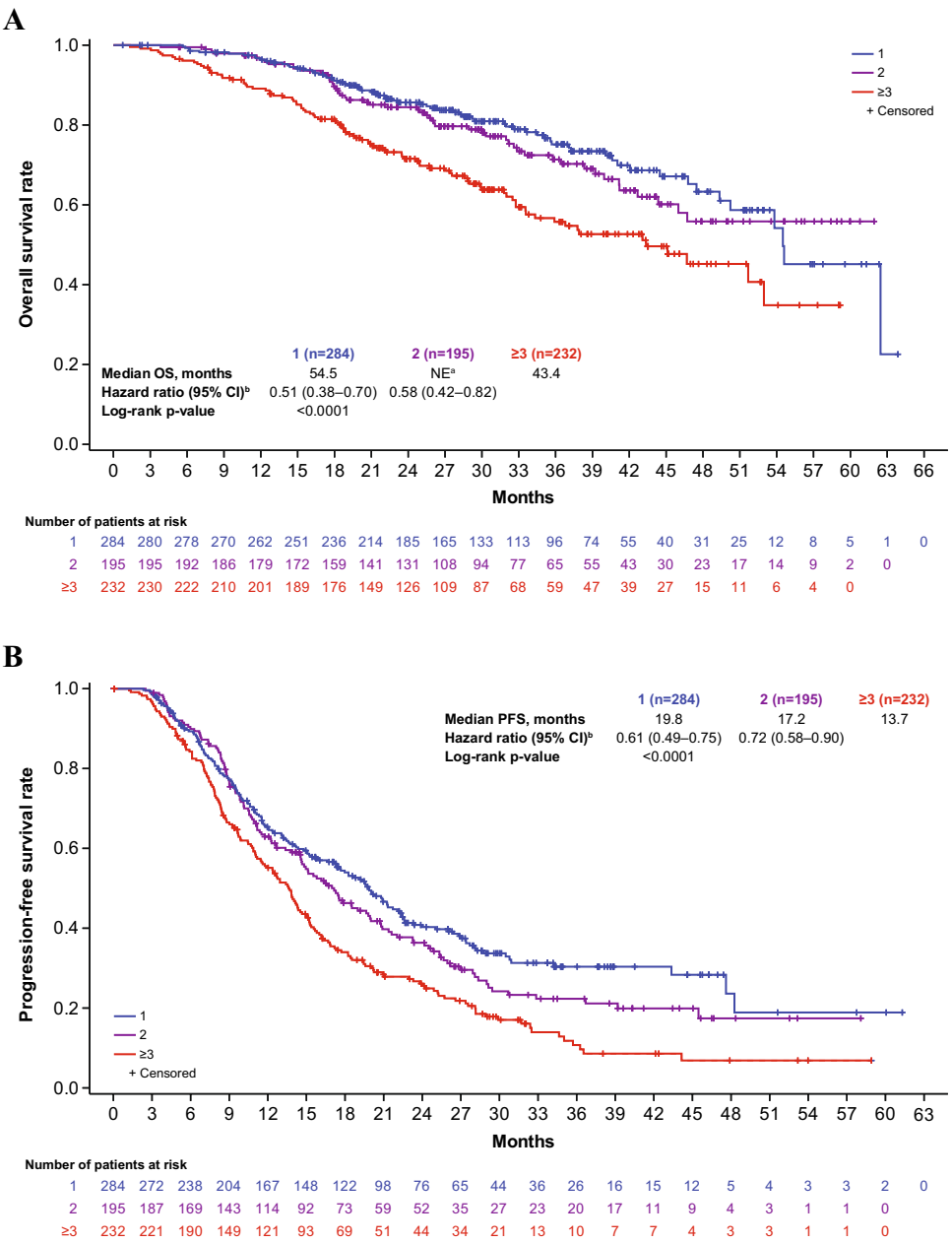


**Fig. 4** OS (**A**) and PFS (**B**) by number of metastatic sites in patients treated with HP. [a]Due to limited follow-up time, median OS for patients with two metastatic sites was not estimable. [b]Patients with ≥ 3 metastatic sites used as reference group. *CI* confidence interval, *H* trastuzumab, *P* pertuzumab, *PFS* progression-free survival, *NE* not estimable, *OS* overall survival

## Discussion

In this real-world analysis of patients with HER2-positive MBC from the SystHERs registry, 68.7% of patients enrolled from 2012 to 2016 who received first-line therapy were treated with first-line HP + taxane, consistent with current clinical practice guidelines [7, 16]. HP + taxane has been shown to improve survival over H + taxane alone, with an OS rate of 37% at 8 years [17]. Among patients who did not receive HP + taxane, most received H without P + taxane (9.3% overall) or HER2-targeted therapy without chemotherapy (10.5% overall). Patients treated with first-line HP received chemotherapy more commonly and hormonal therapy less commonly than those who received H without P. Compared with patients who received HP, those treated with H without P were older, suggesting that age may have influenced treatment choice during the SystHERs study period.

Across all age cohorts, HP administration was more common than H without P; however, younger patients more commonly received HP (including HP + taxane) than patients aged ≥ 70 years. Our findings reflect those reported from registHER, which found that patients ≥ 75 years old received modestly lower rates of first-line H, including H + chemotherapy, than younger patients [12]. The use of P was not reported in registHER, which was fully enrolled before the US FDA approval of P. In SystHERs and registHER,

patients ≥ 70 and ≥ 75 years old, respectively, were less likely to receive chemotherapy and more likely to receive hormonal therapy alone or with HER2-targeted therapy. These disparities could be due to a higher incidence of comorbidities in older patients, including a higher incidence of prior CVD, or physician biases concerning therapy tolerability (benefit/risk) in these patients. Data from registHER additionally found that patients aged ≥ 75 years have poor clinical outcomes relative to younger patients, but that H improved PFS across all age cohorts after adjusting for first-line treatment patterns, ECOG performance status, underlying CVD, and other comorbidities [12]. Further studies will be needed to assess whether greater adherence to current standard of care treatments, including HP + taxane, can improve outcomes in patients ≥ 70 years old.

Prior studies have indicated that black/African American patients with both EBC and MBC have poorer survival outcomes than white patients independent of socioeconomic factors and disease characteristics [18, 19], suggesting that other variables such as treatment disparities may impact outcomes. Retrospective analyses of stage I to III HER2-positive breast cancer from the Surveillance, Epidemiology, and End Results (SEER) database found that black/African American patients were less likely to receive treatments concordant with guidelines, including H, relative to white patients [13, 14]. In contrast, treatment patterns for HER2-positive MBC from registHER indicated that first-line H administration was comparable between white and black patients [18]. Our analysis of patients in SystHERs, in the modern era of HER2-targeted therapy, similarly found that white and black/African American patients received first-line HER2-targeted therapy at comparable rates. Although use of P was slightly less common in black/African American patients, treatment choice between HP and H without P did not significantly differ in white versus black/African American patients in a multivariate analysis. Furthermore, we found that survival outcomes in patients treated with first-line HP were similar between white and black/African American subgroups. These results contrast with findings from registHER, prior to the approval of pertuzumab, which found that black versus white patients had significantly higher risk of disease progression and death [18]. Future studies should explore additional variables that may be prognostic for survival in HER2-positive MBC in white and black/African American patients in the current treatment setting.

Patients treated in the real-world setting with first-line HP in SystHERs had a median OS of 53.8 months and PFS of 15.8 months, numerically slightly lower than the 57.1 and 18.7 month OS and PFS values reported in patients treated with HP + taxane in the CLEOPATRA clinical trial [6, 17]. However, our data indicate that 8.4% of patients in the HP cohort did not receive first-line taxane and, further, that the median treatment duration of first-line P (17.2 months) was numerically shorter than that of H (23.1 months) in patients treated with HP. P was FDA-approved for MBC in June 2012, coinciding with the first month of SystHERs enrollment, which potentially impacted the choice and duration of P administration prior to the establishment of HP + taxane as the standard of care. For example, clinicians may have discontinued P alongside chemotherapy discontinuation, while continuing maintenance therapy with first-line H. Additionally, clinicians may have preferentially administered P to patients with more aggressive disease. Although we did not observe a significant statistical association between any individual baseline disease characteristic with treatment choice of HP versus H without P, unfavorable disease characteristics overall (including visceral disease and higher number of metastatic sites) were numerically overrepresented in patients who received HP versus H without P in SystHERs versus CLEOPATRA. Altogether, these variables may contribute to differences in OS and PFS observed in patients who received HP between the two studies.

SystHERs was designed with broad inclusion criteria and relatively few exclusion criteria and did not specify any particular disease management protocols. Notably, there was a very low refusal rate during the 4-year enrollment period. As such, SystHERs includes a broad patient population treated in a real-world setting, complementing findings from more restrictive clinical trial populations. Our analysis was limited by follow-up duration due to early study termination, potentially impacting clinical outcomes data and the completeness of reported patient treatments. For example, patients who received sequential hormonal therapy following chemotherapy may be underrepresented since SystHERs may have been terminated before initiation of hormonal treatment for some patients. Furthermore, given the short time frame between initiation of SystHERs enrollment and FDA approval of P, our treatment data may not accurately represent the current real-world frequency of P administration.

In conclusion, our analysis of first-line treatment patterns in patients with HER2-positive MBC from SystHERs found that 68.7% of patients received the current first-line standard of care, HP + taxane. However, differences were observed in patient characteristics and the treatments administered among patient cohorts defined by first-line treatment and age in this real-world clinical practice setting. Younger patients received HP versus H without P more commonly than older patients, and older patients were also less likely to receive treatment regimens with chemotherapy. Future studies exploring real-world breast cancer treatments should assess reasons for treatment choice and their impact on breast cancer-specific survival in various patient cohorts.

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**Author contributions** All authors contributed to the study conception, design, oversight, and data interpretation. Statistical analysis was performed by HL. The first draft of the manuscript was written by PAK and all authors participated in revisions on subsequent versions of the manuscript. All authors read and approved the final manuscript.

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**Data availability** Qualified researchers may request access to de-identified patient level data through the Clinical Study Data Request platform (www.clinicalstudydatarequest.com) and will be provided with accompanying clinical study documentation (protocol and any associated amendments, annotated case report form, reporting and analysis plan, dataset specifications, and the clinical study report). Researchers requesting access to clinical study documentation only can do so via the following link: http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing/clinical_study_documents_request_form.htm. Documents are made available on application, per scope and timing criteria as published on the Clinical Study Data Request platform.

## Compliance with ethical standards

**Conflict of interest** P.A. Kaufman has received consulting fees and research funding from F. Hoffmann-La Roche/Genentech, Lilly, Celgene, Eisai, Amgen, Novartis, Macrogenics, and Puma Biotechnology. S.A. Hurvitz has received travel support from Novartis, Lilly, and OBI Pharma; and research funding from F. Hoffmann-La Roche/Genentech, Novartis, GlaxoSmithKline, Boehringer Ingelheim, Sanofi, Pfizer, Amgen, OBI Pharma, Puma Biotechnology, Dignitana, Bayer, BioMarin, Lilly, Merrimack, Daiichi-Sankyo, Immunomedics, Macrogenics, Pieris, and Seattle Genetics. J. O'Shaughnessy has received consulting fees from AbbVie Inc., Agendia, Amgen Biotechnology, AstraZeneca, Bristol-Myers Squibb, Celgene Corporation, Eisai, Genentech, Genomic Health, GRAIL, Immunomedics, Heron Therapeutics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad, Novartis, Ondonate Therapeutics, Pfizer, Puma Biotechnology, Roche, Seattle Genetics, and Syndax Pharmaceuticals. G. Mason has no additional disclosures. D.A. Yardley has received consulting/advisory fees from Novartis and Genentech; and research funding from F. Hoffmann-La Roche/Genentech and Novartis. A. Brufsky has received consulting fees and travel support from F. Hoffmann-La Roche/Genentech, Novartis, Pfizer, Sandoz, AstraZeneca, Amgen, and Lilly. H.S. Rugo has received travel support from Merck, Mylan, Puma, Lilly, and Pfizer; and research funding from F. Hoffmann-La Roche/Genentech, Pfizer, Novartis, Lilly, OBI Pharma, Macrogenics, and Merck. M. Cobleigh has received consulting fees and research funding from F. Hoffmann-La Roche/Genentech. S.M. Swain has received consulting fees from AstraZeneca, Athenex, Daiichi-Sanyo, Eli Lilly and Company, F. Hoffmann-La Roche/Genentech, Genomic Health, Inivata, Ltd., Molecular Therapeutics, Novartis, Pieris Pharmaceuticals, Silverback Therapeutics, and Tocagen; research funding from F. Hoffmann-La Roche/Genentech and Kailos Genetics; non-financial support from Athenex, Daiichi-Sanyo, Eli Lilly and Company, F. Hoffmann-La Roche/Genentech, Inivata, Ltd., Novartis, Pieris Pharmaceuticals, Caris Life Sciences, AstraZeneca, Bristol-Myers Squibb; and is on an Independent Data Monitoring Committee for AstraZeneca. D. Tripathy has received consulting fees from Pfizer and Novartis, and research funding from Novartis. A. Morris was a contract employee of Genentech. V. Antao is an employee of Genentech and owns stock in F. Hoffmann-La Roche/Genentech. H. Li is an employee of F. Hoffmann-La Roche/Genentech. M. Jahanzeb has received consulting fees from F. Hoffmann-La Roche/Genentech, and served on a Scientific Advisory Board and Data and Safety Monitoring Board for Puma. All authors received non-financial support from F. Hoffmann-La Roche in the form of medical writing support for this manuscript.

**Ethical approval** SystHERs was conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonisation E6 Guidelines for Good Clinical Practice, the Declaration of Helsinki, and applicable local laws. Each participating site obtained approval of the study protocol by the site's ethics committee or institutional review board (IRB), or a central IRB for sites that did not have an IRB.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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