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Trastuzumab-based regimens beyond progression: A crucial treatment option for HER2+ advanced/metastatic breast cancer

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ABSTRACT

Upon its establishment for the treatment of metastatic breast cancer (mBC), continuing trastuzumab beyond disease progression was an important paradigm shift that became the recommendation by major guidelines. However, data supporting continuation of human epidermal growth factor receptor 2 (HER2) blockade with trastuzumab beyond the second-line setting are limited, resulting in a lack of approval of, or access to, this therapeutic strategy in many countries. This study aimed to provide additional data on the continued use of trastuzumab and trastuzumab-based therapies in combination with chemotherapy (CT) as third-line treatment for patients with mBC. This open-cohort, retrospective, observational study used deidentified patient-level data from an electronic health record–derived database that included patients with mBC who initiated third-line treatment with trastuzumab-based therapy combined with CT (Tras + CT; n = 288) or CT alone (CT; n = 49). Patients who received Tras + CT had a longer weighted median overall survival vs those who received CT only: 20.6 months (95% CI, 18.3–26.4 months) vs 10.1 months (95% CI, 7.8–12.3 months), respectively (hazard ratio [HR], 0.29; 95% CI, 0.16–0.53). This study provides additional support for maintaining trastuzumab-based therapies for patients with HER2+ mBC beyond second-line treatment. This treatment option should be available for all patients with mBC worldwide.

1. Introduction

Trastuzumab is a humanized monoclonal antibody directed against the extracellular signaling domain of human epidermal growth factor receptor 2 (HER2). Trastuzumab directly inhibits HER2-related signaling, preventing cleavage of the extracellular domain [1] and triggering an antibody-mediated immune response [2]. Trastuzumab is indicated for the treatment of patients with HER2+ early breast cancer (eBC), locally advanced breast cancer (LABC) and metastatic breast cancer (mBC) [3]. Trastuzumab and chemotherapy (CT) have synergistic effects when combined [4]. For patients with HER2+ eBC, trastuzumab-based therapy in combination with neoadjuvant or adjuvant chemotherapy is recommended [5], and trastuzumab-based therapy + CT (Tras + CT) approaches are the standard of care for first-line treatment of HER2+ LABC/mBC [4,6–11].

Pertuzumab, another monoclonal antibody that targets HER2, binds to HER2 at a different location (the dimerization domain) than trastuzumab, thus preventing formation of HER2-containing homo- and heterodimers, including the highly active HER2-HER3 heterodimer [12]. Because trastuzumab and pertuzumab target different domains of the HER2 receptor, their mechanisms of action are complementary, and their combination is synergistic and particularly effective [13]. Following the results of pivotal clinical trials [14,15], the ABC Global Alliance, European Society for Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) guidelines recommended trastuzumab + pertuzumab + CT as first-line treatment for patients with HER2+ LABC/mBC [7,16,17].

Antibody-drug conjugates (ADCs), such as trastuzumab deruxtecan (DS-8201) or trastuzumab emtansine (T-DM1; ado-trastuzumab emtansine), are recommended options for second-line treatment. These ADCs contain cytotoxic payloads, which are linked to monoclonal antibodies that bind specifically to the HER2 receptor. While T-DM1 carries the microtubule inhibitor DM1 as its cytotoxic payload, trastuzumab

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Abbreviation list

ADC	antibody-drug conjugate
aSMD	absolute standardized mean difference
CT	chemotherapy
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
LABC	locally advanced breast cancer
LOT	line of treatment
mBC	metastatic breast cancer
OS	overall survival
T-DM1	trastuzumab emtansine
Tras + CT	trastuzumab-based therapy combined with CT
eBC	early breast cancer
EHR	electronic health record
rwPFS	real-world progression-free survival

deruxtecan adopts the topoisomerase inhibitor deruxtecan as its toxic payload. Once bound, the ADC is internalized and degraded by lysosomes, enabling the release of the cytotoxic compound. ADCs are advantageous because they provide targeted delivery of highly potent cancer-killing drugs specifically to the HER2+ cancer cells. ABC [7], ESMO [16] and recently updated ASCO [17] guidelines recommend trastuzumab deruxtecan for second-line treatment where available. If it is not available, guidelines recommend T-DM1 [7].

Continuation of HER2 blockade with trastuzumab-based regimens beyond disease progression was an important paradigm change in oncology, as classically a treatment is stopped once disease progression occurs [18]. However, data supporting the use of trastuzumab-based regimens beyond the second-line setting are limited, resulting in a lack of approval of or access to this therapeutic strategy outside of the US and some European countries [19]. Several randomized trials attempted to provide a high level of evidence for trastuzumab-based regimens beyond the second-line setting but failed mostly due to insufficient accrual, in light of the clinical observation that disease progression occurs much faster when the HER2 pathway is not blocked. The only Phase 3 randomized trial that yielded sufficiently informative results was GBG-26 (NCT00148876), which evaluated the efficacy of trastuzumab + capecitabine vs capecitabine alone in patients with HER2+ LABC/mBC who progressed during treatment with Tras + CT as first-line therapy [20]. This trial was also closed prematurely due to lack of accrual and therefore was underpowered to observe significant differences between the 2 treatment arms. Final overall survival (OS) was not significantly different in patients receiving trastuzumab + capecitabine vs patients receiving capecitabine alone (24.9 vs 20.6 months; hazard ratio [HR], 0.94; 95% CI, 0.65–1.35; $P = 0.73$). However, a post hoc analysis revealed better post-progression survival in patients who received anti-HER2 treatment as third-line therapy than in those who did not receive anti-HER2 treatment (HR, 0.63; $P = 0.02$). The goal of the present study was to provide additional data to support the use of trastuzumab-based regimens beyond disease progression as third-line treatment for LABC/mBC.

2. Material and methods

2.1. Study design

This open-cohort, retrospective, observational study used deidentified patient-level data from the Flatiron Health electronic health record (EHR)–derived database. Eligible patients initiated third-line treatment with Tras + CT or CT after a HER2+ LABC/mBC diagnosis that was made on or before January 1, 2011. The start of third-line treatment was defined as the index date and ranged from January 1, 2012, to December 31, 2020. The baseline period was defined as the date of first breast cancer diagnosis to the index date. The date of first diagnosis was the date of metastatic diagnosis for patients with de novo disease or the date of eBC diagnosis for patients with recurrent disease. All patients were followed up from the index date to the last visit or death. Administration of the antineoplastic components of a regimen (ie, combination therapy) can occur on different days; therefore, a run-in period covered the first 28 days following the initiation of the first antineoplastic in a regimen. All antineoplastic treatments used over the run-in period were grouped together to define the antineoplastic regimen. A summary of the study design is shown in Fig. 1.

In this analysis, the lines of treatment (LOTs) were defined based on both exposure data (ie, antineoplastic drug use) and abstracted progression data [21]. The first LOT started on the date a new antineoplastic regimen was initiated after metastatic diagnosis and ended on the day prior to the initiation of the second LOT. The second LOT started on the date a new antineoplastic regimen was initiated following a progression event and ended on the day prior to the initiation of the third LOT. The third LOT start date was defined following the approach described for the second LOT. The regimen initiated as third LOT was used to allocate each patient to the Tras + CT or CT group.

2.2. Data source

The Flatiron Health database is a nationwide, longitudinal, demographically and geographically diverse deidentified database derived from EHR data [22,23]. It includes data from over 280 cancer clinics at over 800 sites of care in the US, representing more than 2.8 million patients with cancer available for analysis. The EHRs include structured (eg, laboratory values and prescribed drugs) and unstructured (eg, detailed biomarkers and data collected via technology-enabled chart abstraction from physician's notes) patient-level data. Patients included in the database were diagnosed with advanced or metastatic disease, had at least 2 visits in the Flatiron Health system and provided consent for the use of their data.

2.3. Inclusion and exclusion criteria

Eligible patients were adults aged ≥18 years with at least 1 visit within 90 days after their HER2+ mBC diagnosis. Patients were required to have had 2 LOTs, each with HER2-targeted therapies, and to have initiated a third LOT, with the date of initiation defined as their index date. Patients were excluded if they had other primary tumors prior to the index date, had an activity gap of >9 months prior to the index date or did not receive CT or trastuzumab-based treatment as third-line treatment.

2.4. Objectives

The objectives were to compare the effectiveness of Tras + CT vs CT in terms of OS and real-world progression-free survival (rwPFS).

2.5. Statistical analyses

Demographic and clinical characteristics were summarized by treatment subgroup at the index date using descriptive statistics, including means, standard deviations, medians, interquartile ranges and ranges for continuous variables and frequencies and proportions for categorical variables. Potential sources of confounding were identified using expert knowledge and directed acyclic graphs and included de novo status and time from eBC to mBC diagnosis for patients with recurrent disease, hormone receptor status, Eastern Cooperative Oncology Group performance status, metastatic profile (number of metastatic sites; presence of metastasis in the liver, brain, bone or lungs [each yes/no]) and use of and time on HER2 treatments (trastuzumab, pertuzumab, T-DM1).

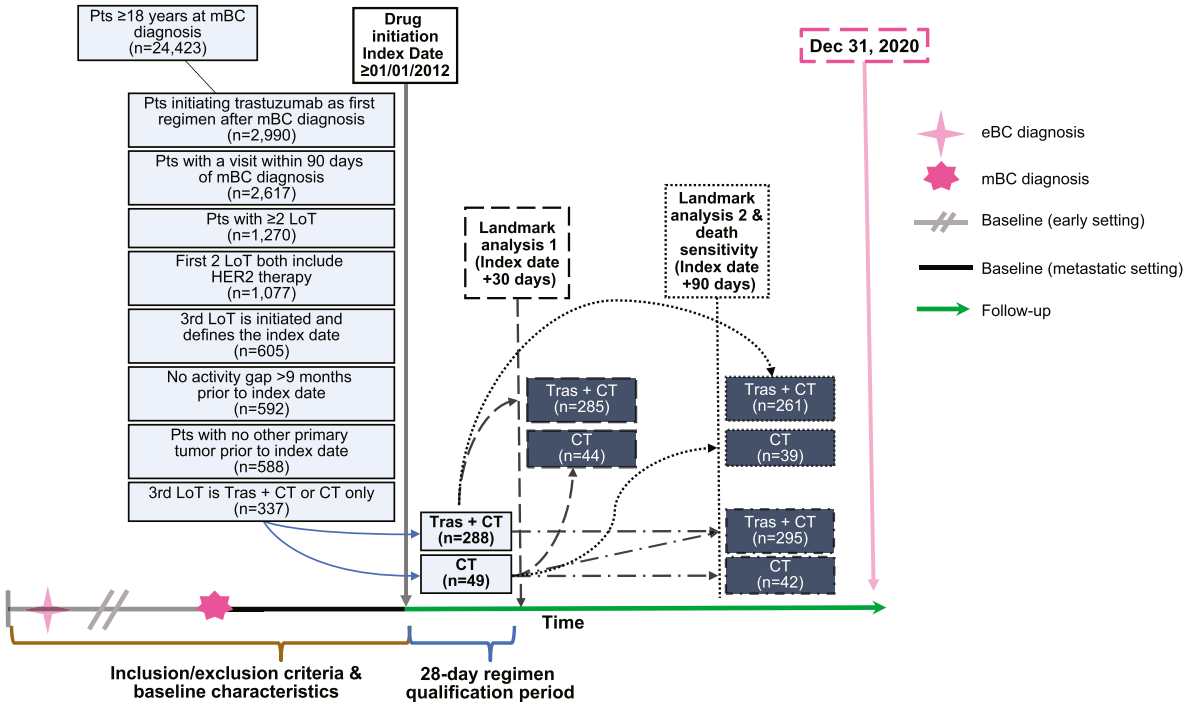

Fig. 1. Study Schematic
Abbreviations: CT, chemotherapy; eBC, early breast cancer; LoT, line of therapy; mBC, metastatic breast cancer; pts, patients; Tras, trastuzumab-based therapy.

Death date was estimated as a composite mortality variable using data from EHRs, obituaries and the Social Security Death Index [24]. Baseline differences between the treatment groups were assessed via absolute standardized mean differences (aSMDs). Based on the published literature, the pre-specified protocol and analysis plan utilized an aSMD threshold of <0.25 as an indicator of covariate imbalance between treatment groups [25–27].

OS was estimated with survival analyses and measured as the length of time (in months) from the index date to death of any cause. Patients without a death event were censored at the date of their last structured activity or an abstracted oral therapy end date, whichever occurred last. Unadjusted OS estimates were computed with Kaplan-Meier methods, and differences were assessed using the log-rank test. OS (median and 95% CI) was summarized. Adjusted OS estimates were computed with Kaplan-Meier methods in the weighted pseudo-population. Marginal Cox proportional hazards regression models were used to obtain the HRs and 95% CIs. CIs were estimated using bootstrapping [28], and E-values were calculated using the VanderWeele method [29].

Progression was defined based on clinicians' notes in EHRs referring to a distinct episode of tumor growth, as determined by radiological or pathological reporting, and/or clinician determination [21]. rwPFS was estimated with survival analyses and measured as the length of time (in months) from the index date until progression or death of any cause. Patients without a progression event were censored on the date of the last clinical note abstracted.

Propensity scores for having received Tras + CT vs having received CT were estimated using covariate balancing propensity score methodology, an alternative method to parametric modelling that aims to reduce bias by balancing covariates [30–32]. Average treatment effect was estimated using inverse probability of treatment weighting for Cox proportional hazards models. The 95% CIs of HRs were estimated using empirical bootstrapping [28].

Using observational data to compare the effect of initiating combination regimens (Tras + CT) vs that of initiating single-drug regimens (CT) can be prone to misclassification. For example, rapid deterioration of the patient's condition during initial CT treatment may prevent them from receiving the subsequent trastuzumab-based treatment. This would lead to bias toward assigning the rapidly deteriorating patients to the CT group and result in outcomes artificially favoring the Tras + CT group. Therefore, 3 OS sensitivity analyses were conducted to examine the impact of these potential biases. First, 2 landmark analyses were conducted, shifting the index date at 1 month (which removed 5 patients in the CT group and 3 in the Tras + CT group) and 3 months (which removed 10 patients in the CT group and 27 in the Tras + CT group), respectively. For the third sensitivity analysis, death within 3 months of the index date was used as a proxy for rapid deterioration. All patients who received CT with a death event recorded within 3 months following the index date were reclassified into the Tras + CT group, resulting in 7 patients being reallocated from the CT to the Tras + CT group (Fig. 1).

Prior to weighting, there was an imbalance in the prevalence of the most recent positive HER2 test results (Tras + CT: 88.5% vs CT: 57.1%). To examine how this may have impacted OS, we performed a fourth sensitivity analysis, which only compared those patients with a latest positive HER2 test result prior to treatment initiation.

3. Results

3.1. Demographics

Overall, 337 patients initiated either treatment strategy. Of these, 288 initiated Tras + CT: 125 (43%) received T-DM1, and 163 (57%) received another trastuzumab-based treatment without T-DM1. There were 49 patients in the CT-only arm. The median age at index date in both cohorts was 60 years. Patients in the Tras + CT group more frequently had tumors that were hormone receptor positive and had a positive result on their most recent test for HER2. These patients also had received prior pertuzumab and/or trastuzumab treatments for a longer duration than patients who received CT (Table 1).

3.2. Overall survival and real-world progression-free survival

Following inverse probability of treatment weighting, the baseline characteristics were well balanced (Table 1), with aSMDs <0.1 for all variables (Fig. 2). The unweighted median OS was 22.5 months (95% CI,

Table 1
Baseline characteristics by treatment group.

Characteristic[a]	Tras + CT (n = 288)	CT (n = 49)	aSMD[b]	Tras + CT (n = 299.6)	CT (n = 53.4)	aSMD[b]
Age in years: median (IQR)	60 (51–67)	60 (53–68)	0.02	59.6 (50.1–67.4)	60.3 (52.8–68.2)	0.03
Recurrent status						
De novo	144 (50.0)	22 (44.9)	0.05	152.5 (50.9)	27.2 (50.9)	0.00
3–24 months	31 (10.8)	10 (20.4)	0.10	33.3 (11.1)	5.9 (11.0)	0.00
24–60 months	65 (22.6)	9 (18.4)	0.04	64.4 (21.5)	11.5 (21.5)	0.00
≤60 months	48 (16.7)	8 (16.3)	0.00	49.4 (16.5)	8.9 (16.7)	0.00
Hormone receptor positive	205 (71.2)	27 (55.1)	0.13	215.4 (71.9)	38.3 (71.7)	0.00
Latest HER2 status						
Positive	255 (88.5)	28 (57.1)	0.31	241.5 (80.6)	43.0 (80.5)	0.00
Negative	26 (9.0)	16 (32.7)	0.24	47.0 (15.7)	8.4 (15.7)	0.00
Unknown	7 (2.4)	≤5 (≤10)	**	11.1 (3.7)	≤5 (≤10)	**
BMI prior to index date						
Underweight	11 (3.8)	≤5 (≤10)	**	10.8 (3.6)	≤5 (≤10)	**
Normal/healthy weight	108 (37.5)	20 (40.8)	0.05	113.2 (37.8)	26.4 (49.4)	0.12
Overweight	91 (31.6)	11 (22.4)	0.09	93.5 (31.2)	15.5 (29.0)	0.02
Obese	73 (25.3)	14 (28.6)	0.03	75.8 (25.3)	10.8 (20.2)	0.05
Missing/unknown	≤5 (≤2)	≤5 (≤10)	**	6.3 (2.1)	≤5 (≤10)	**
ECOG PS prior to index date						
0	77 (26.7)	11 (22.4)	0.04	72.2 (24.1)	12.9 (24.2)	0.00
1	118 (41.0)	17 (34.7)	0.06	120.7 (40.3)	21.5 (40.3)	0.00
≥2	28 (9.7)	9 (18.4)	0.09	33.3 (11.1)	5.9 (11.0)	0.00
Unknown	65 (22.6)	12 (24.5)	0.02	73.7 (24.6)	13.1 (24.5)	0.00
Metastatic profile						
Number of sites, mean (SD)	2.9 (1.5)	2.8 (1.4)	0.06	2.8 (0.1)	2.8 (0.2)	0.00
Bone	194 (67.4)	29 (59.2)	0.08	197.7 (66.0)	35.3 (66.1)	0.00
Distant lymph node	157 (54.5)	27 (55.1)	0.01	170.5 (56.9)	28.3 (53.0)	0.04
Lung	132 (45.8)	26 (53.1)	0.07	137.8 (46.0)	24.6 (46.1)	0.00
Liver	118 (41.0)	16 (32.7)	0.08	107.6 (35.9)	19.2 (36.0)	0.00
Brain	80 (27.8)	11 (22.4)	0.05	72.5 (24.2)	19.2 (36.0)	0.00
Practice type						
Academic	25 (8.7)	≤5 (≤10)	**	25.2 (8.4)	≤5 (≤10)	**
Community	263 (91.3)	45 (91.8)	0.01	274.4 (91.6)	49.7 (93.1)	0.02
Chemotherapy						
Taxane	226 (78.5)	35 (71.4)	0.07	234.9 (78.4)	39.8 (74.5)	0.04
Capecitabine	66 (22.9)	18 (36.7)	0.14	74.9 (25.0)	20.0 (37.5)	0.13
Anthracyclines	11 (3.8)	8 (16.3)	0.12	14.4 (4.8)	7.1 (13.3)	0.09
Other	145 (50.3)	38 (77.6)	0.27	152.8 (51.0)	42.7 (80.0)	0.29
Targeted therapy						
Trastuzumab	285 (99.0)	49 (100.0)	0.01	295.4 (98.6)	53.4 (100.0)	0.01
Pertuzumab	218 (75.7)	34 (69.4)	0.07	225.0 (75.1)	40.0 (74.9)	0.00
T-DM1			0.15			0.00

(*continued on next page*)

Table 1 (*continued*)

Characteristic[a]	Tras + CT (n = 288)	CT (n = 49)	aSMD[b]	Tras + CT (n = 299.6)	CT (n = 53.4)	aSMD[b]
	220 (76.4)	30 (61.2)		222.9 (74.4)	39.6 (74.2)	
Lapatinib	37 (12.8)	≤5 (≤10)	**	44.6 (14.9)	≤5 (≤10)	**
Endocrine therapy	149 (51.7)	18 (36.7)	0.15	152.5 (50.9)	24.5 (45.9)	0.05
Duration of prior treatments, mean days (SD)						
Trastuzumab	525.3 (398.5)	352.8 (231.1)	0.51	484.3 (22.5)	477.0 (53.8)	0.02
Pertuzumab	372.5 (383.7)	283.6 (235.3)	0.27	346.1 (23.6)	347.1 (58.1)	0.00
T-DM1	139.2 (222.8)	103.9 (114.0)	0.26	124.0 (13.6)	122.4 (24.4)	0.01

aSMD, absolute standardized mean difference; BMI, body mass index; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; Tras + CT, trastuzumab-based therapy combined with CT.
**Data have been masked according to the Flatiron data masking policy.
[a] Values reported are No. (%) unless otherwise specified.
[b] The values reported in the aSMD column for categorical variables are the difference in percentage between the 2 groups.

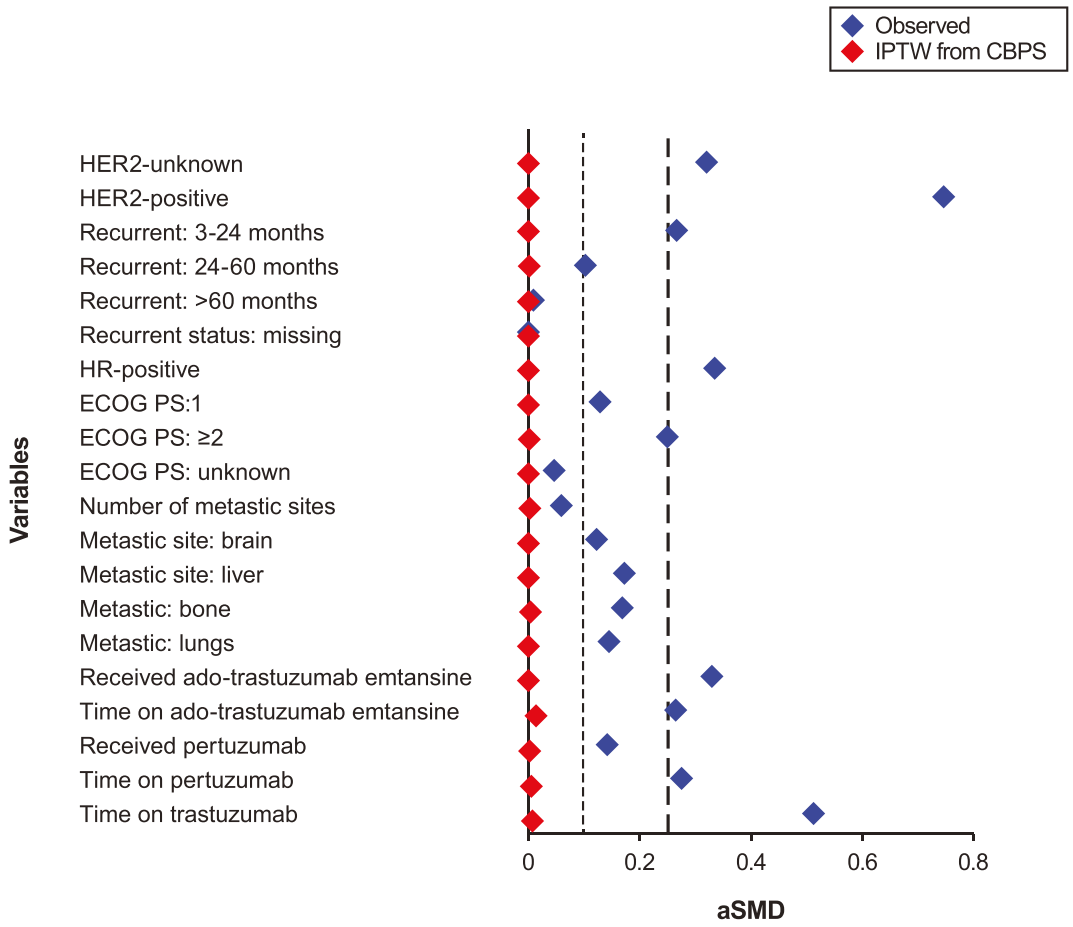

Fig. 2. aSMD Across Treatment Groups Before and After Weighting
An aSMD of <0.1 (thin dashed line) was considered an indicator of covariate balance, and an aSMD of >0.25 (thick dashed line) was considered an indicator of covariate imbalance. Abbreviations: aSMD, absolute standardized mean difference; CBPS, covariate balancing propensity score; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IPTW, inverse probability treatment weighting.

19.1–26.9 months) in patients receiving Tras + CT vs 10.1 months (95% CI, 6.8–12.3 months) in patients receiving CT alone (HR, 0.31; 95% CI, 0.19–0.50; p < 0.001) (Table 2; Fig. 3A). The weighted median OS remained over twice as long in patients receiving Tras + CT (20.6 months; 95% CI, 18.3–26.4 months) vs patients receiving CT alone (10.1 months; 95% CI, 7.8–12.3 months) (HR, 0.29; 95% CI, 0.16–0.53; p < 0.001) (Table 2; Fig. 3B).

The unweighted median rwPFS was longer in patients receiving Tras + CT (5.5 months; 95% CI, 4.6–6.7 months) vs patients receiving CT (4.3 months; 95% CI, 2.8–6.3 months) (HR, 0.65; 95% CI, 0.46–0.92; p = 0.011) (Table 2, Fig. 4A). The weighted median rwPFS was 5.2 months (95% CI, 4.1–6.3 months) in patients who received Tras + CT vs 5.0

Table 2
Unweighted and weighted survival outcomes by treatment group.

Analysis	Weighting	Treatment Group	Events, No. (%)	Censored, No. (%)	Median Mo, (95% CI)	HR (95% CI)	P-Value	E-Value
OS	Unweighted	Tras + CT (n = 288)	149 (52)	139 (48)	22.5 (19.1–26.9)	0.31 (0.19–0.50)	<0.001	3.89
		CT (n = 49)	37 (76)	12 (24)	10.1 (6.8–12.3)			
	Weighted	Tras + CT (n = 299.6)	160.4 (54)	139.2 (46)	20.6 (18.3–26.4)	0.29 (0.16–0.53)	<0.001	4.11
		CT (n = 53.4)	39.5 (74)	13.9 (26)	10.1 (7.8–12.3)			
rwPFS	Unweighted	Tras + CT (n = 288)	236 (82)	52 (18)	5.5 (4.6–6.7)	0.65 (0.46–0.92)	0.011	2.03
		CT (n = 49)	44 (90)	5 (10)	4.3 (2.8–6.3)			
	Weighted	Tras + CT (n = 299.6)	250.0 (83)	49.6 (16)	5.2 (4.1–6.3)	0.71 (0.50–1.01)	0.06	1.85
		CT (n = 53.4)	47.5 (89)	5.9 (11)	5.0 (3.9–7.8)			

CT, chemotherapy; HR, hazard ratio; OS, overall survival; rwPFS, real-world progression-free survival; Tras + CT, trastuzumab-based therapy combined with CT.

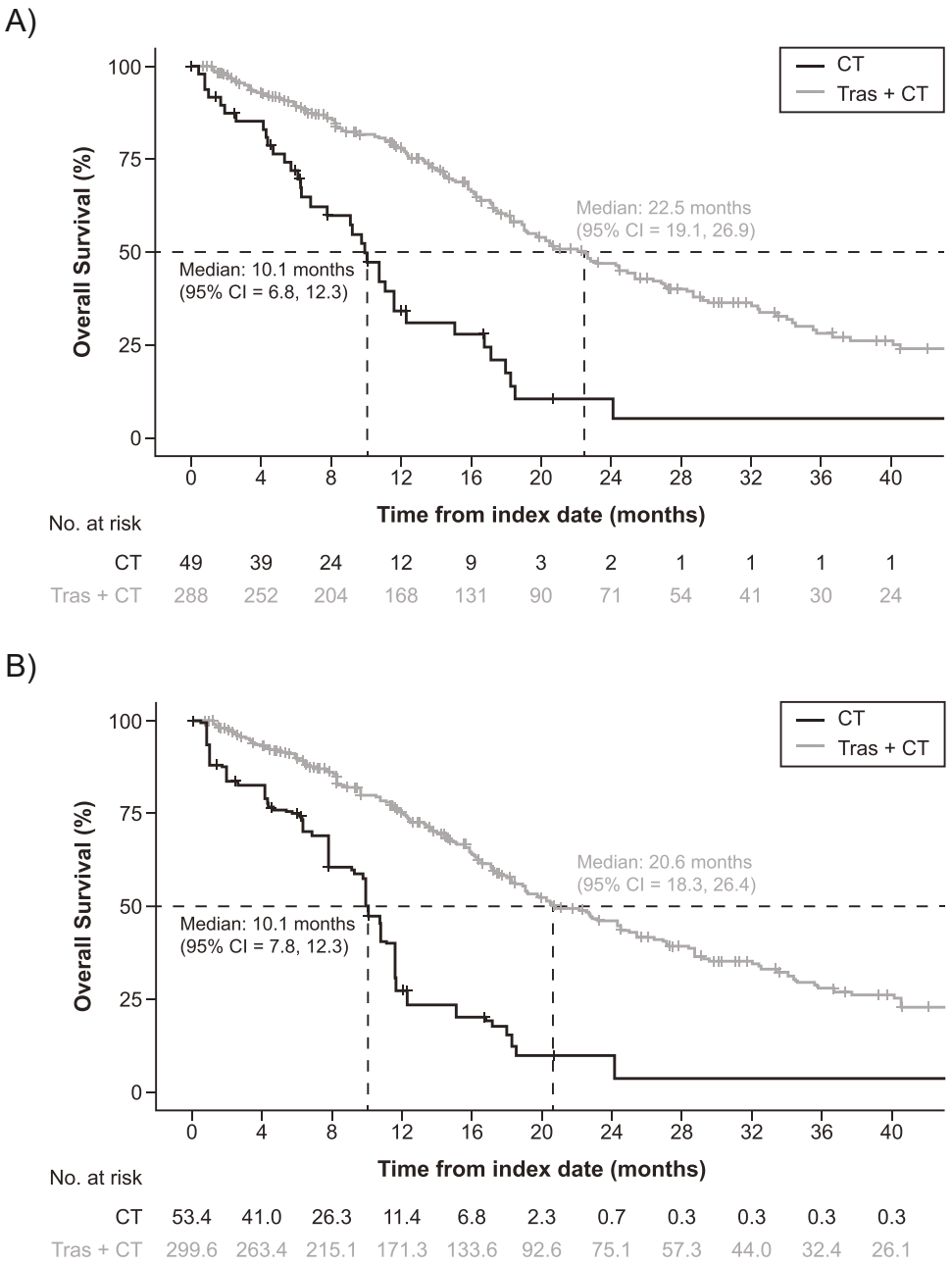

Fig. 3. Unweighted (A) and Weighted (B) Overall Survival in Patients Receiving Trastuzumab Plus Chemotherapy Compared With Patients Receiving Chemotherapy Alone
Abbreviations: CT, chemotherapy; Tras + CT, trastuzumab-based therapy combined with CT.

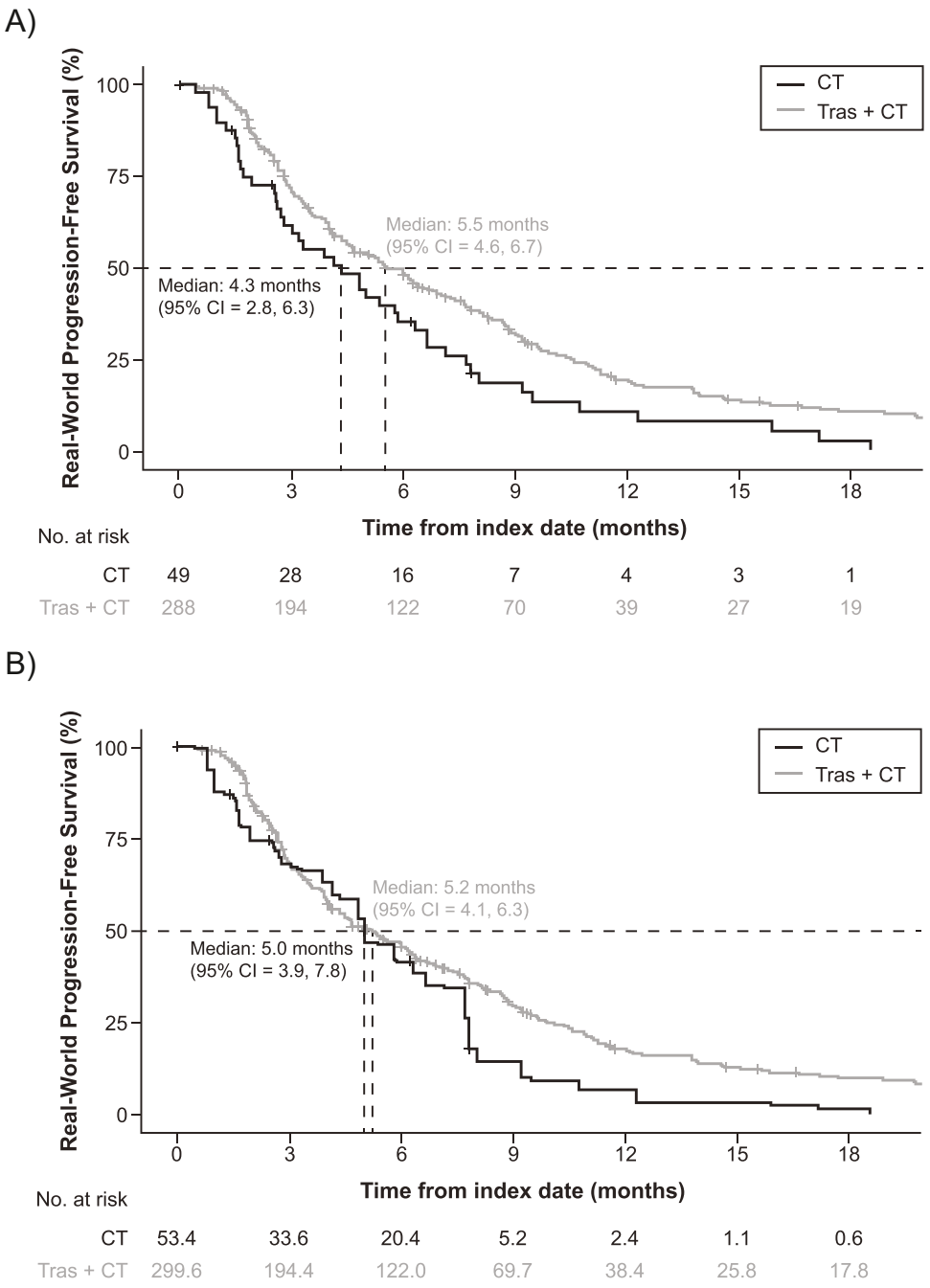

Fig. 4. Unweighted (A) and Weighted (B) Real-World Progression-Free Survival in Patients Receiving Trastuzumab Plus Chemotherapy Compared With Patients Receiving With Chemotherapy Alone
Abbreviations: CT, chemotherapy; Tras + CT, trastuzumab-based therapy combined with CT.

months (95% CI, 3.9–7.8 months) in those who received CT (HR, 0.71; 95% CI, 0.50–1.01; p = 0.06) (Table 2, Fig. 4B).

3.3. Sensitivity analyses

The first 2 landmark analyses, which shifted the index dates by 1 and 3 months, respectively, yielded similar treatment effect estimates for OS, with HRs of 0.34 (95% CI, 0.21–0.55; p < 0.001) and 0.31 (95% CI, 0.18–0.53; p < 0.001), respectively. The third sensitivity analysis, which re-allocated patients from the CT to the Tras + CT arm if they had a death event in the first 3 months, marginally impacted the estimated OS (HR, 0.40; 95% CI, 0.26–0.63; p < 0.001). Finally, the fourth sensitivity analysis, which examined only patients with a most recent positive HER2 test result (Tras + CT, n = 255; CT, n = 28), resulted in an HR of 0.29 (95% CI, 0.15–0.58; p < 0.001).

Both treatment groups initiated a variety of regimens as third-line treatments; therefore, heterogeneity of treatment effect was expected [33]. For instance, the 125 patients in the Tras + CT group who initiated T-DM1 in the third-line setting (n = 125) had an unweighted median OS of 29.2 months (95% CI, 24.3–40.1 months). The other 163 patients in the Tras + CT group initiated 1 of 49 trastuzumab-based regimens, the most frequent being trastuzumab + vinorelbine (n = 24), thus precluding comparison of individual subgroups and resulting in heterogeneity of treatment effect.

4. Discussion

The results of this study show that treatment with Tras + CT in the third-line setting is associated with markedly improved survival outcomes (≈1-year increase in OS) compared with CT alone. With newer anti-HER2 therapies being used in clinical practice for HER2+ mBC, the treatment effect estimate may vary, but it is expected to increase in view of the OS results with T-DM1, trastuzumab deruxtecan and tucatinib.

For third-line treatment and beyond, 4 new agents/regimens have been recently approved by the US Food and Drug Administration, including tucatinib + capecitabine + trastuzumab, trastuzumab deruxtecan, margetuximab + CT, and neratinib + capecitabine [34]. In Europe, the European Medicines Agency has approved tucatinib [35] and trastuzumab deruxtecan [11]. The results for neratinib and margetuximab were only borderline statistically significant and were not clinically meaningful; therefore, the ABC consensus guidelines recommend against the use of these agents [7,34].

For patients receiving third-line treatment (n = 498) in the observational PANHER study, the most frequently used regimen was lapatinib + capecitabine (29.3%), followed by trastuzumab-based CT (28.3%) and T-DM1 (20.5%) [36]. The overall median rwPFS in the third-line setting was 7 months (95% CI, 6.3–7.7 months), with no significant differences by treatments received [36], which is similar to the rwPFS results reported here. Evaluation of rwPFS is complex and limited by the heterogenous definition of this endpoint in clinical practice, and homogenous measures of disease response such as Response Evaluation Criteria in Solid Tumors version 1.1 [37] are not usually used outside clinical trials. Due to its homogenous definition, OS could be a more reliable endpoint in these types of studies.

A retrospective chart review of >3000 cases of mBC from Spain, Italy, the Netherlands and the UK showed that fewer patients than expected transitioned from one LOT to the next [38]. Treatment in the first- and second-line setting was generally consistent with the European guidelines in place at the time of the study [38], which highlights the need for data to support third-line treatment regimens and the importance of specific guidelines for patient subgroups (eg, age, performance status). In line with this observation, a report combining input from 3 studies commissioned by Breast Cancer Foundation NZ showed that patients with HER2+ mBC have a median survival of 13.3 months after metastatic diagnosis, which is considerably shorter than that in comparable countries [39]. The authors suggested that restrictions on existing drugs (eg, lapatinib) should be removed and that oncologists should have the ability to continue or restart therapy (eg, trastuzumab) following progression to provide additional treatment options for later lines of therapy [39]. Faster access to newer therapies, which have been shown to delay breast cancer progression, is warranted in New Zealand and other countries that lack access to such therapies. In addition, the option to continue trastuzumab-based regimens beyond the second-line setting must be made possible in countries where it is not currently available.

The current study adds to growing evidence that CT alone has limited efficacy in HER2+ LABC/mBC, and therefore patients whose tumors continue to be sensitive to HER2-targeted therapy should always receive it with or without CT. Despite multiple approaches now available for treatment in later lines of therapy [34], HER2 blockade with trastuzumab-based regimens remains an important component of treatment for patients with HER2+ LABC/mBC. The availability of anti-HER2 agents is limited in many areas due to the high cost of these agents. The only anti-HER2 agent that has approved biosimilars is trastuzumab, which is the least costly of all anti-HER agents and has excellent tolerability [40]. Additional indirect evidence of benefit with Tras + CT after disease progression is provided by the results in the Tras + CT comparator arm of studies evaluating newer anti-HER2 agents as second, third or later lines of treatment for HER2+ LABC/mBC. It is therefore imperative that all regulatory agencies consider approving the use of trastuzumab-based regimens beyond disease progression as soon as possible, and that these regimens are reimbursed by funding bodies, to substantially increase the survival of patients with HER2+ LABC/mBC.

One potential limitation of our study is the possible presence of unmeasured confounders. For instance, prior to weighting, analysis of baseline characteristics suggested that patients treated with CT alone tended to have more characteristics associated with poor prognosis (eg, were less likely to have a positive hormone receptor test result, had a shorter duration of prior treatment). Weighting allowed for balancing of numerous baseline characteristics associated with survival, but it is possible that some residual or unmeasured confounding remained. For example, the CT cohort may have contained more patients with lower socioeconomic status (and therefore reduced access to anti-HER2 agents) or more patients with comorbidities, which may have impacted the estimated treatment effect. Other limitations include the modest sample size of the CT cohort, difficulty in estimating and therefore misclassification of LOTs and patient treatment preference. The estimated treatment effect is influenced by the regimen initiated as third LOT, which has implications for the generalizability of these results outside of the US. Since prior cardiac toxicity or cardiac frailty could impede the initiation of CT as well as trastuzumab-based regimens, indication bias due to cardiac frailty is unlikely to have affected our analysis; however, as the study used real-world data, we cannot completely rule out this possibility.

This study also has several strengths. Analyses are based on recent data, with a cutoff date of December 2020. The results reflect the procedures of community practices as opposed to large academic centers, which have published many of the previous studies. We used a propensity score method that adjusted for potential differences across comparison groups. This weighting adjusted for prior exposure to trastuzumab-based regimens and duration of each specific therapy (trastuzumab, pertuzumab and T-DM1). Therefore, these measures acted as proxies for disease indolence and level of control achieved with prior treatment, which would otherwise have acted as an unmeasured confounder.

The different sensitivity analyses support that our findings are not explained by treatment misclassification or an imbalance in the prevalence of patients with a latest positive HER2 test result. The first 2 OS sensitivity analyses, which shifted the index dates by 1 and 3 months, respectively, only marginally impacted the treatment effect (HRs, 0.34 and 0.31, respectively; HR with no sensitivity analyses, 0.31). The third sensitivity analysis re-allocated 7 patients who died within 3 months of starting CT into the Tras + CT group. As expected, this resulted in a weaker effect of the trastuzumab-based regimen on OS (HR, 0.40), but does not change the interpretation of a superior OS outcome with Tras + CT compared with CT. Finally, the fourth sensitivity analysis, which only analyzed data from patients whose most recent HER2 test result was positive, also only marginally impacted the OS treatment effect (HR, 0.29). Together, these analyses suggest that these types of bias in the data do not explain the OS study results.

5. Conclusions

The main goal of this manuscript is to present further data showing that blocking the HER2 pathway is essential for the management of HER2+ metastatic breast cancer and may lead to better OS. In high-income countries and for patients with good healthcare coverage, other anti-HER2 agents are available and should be used to provide the continuous HER2 pathway blockade, as recommended by the major guidelines. However, in low- and middle-income countries and for patients with insufficient health coverage, the only available anti-HER2 therapy is often trastuzumab or its biosimilars. Even these are often available only for eBC or as first-line therapy for metastatic breast cancer, and in many countries, they are not available at all. In such countries, patients only have access to anti-HER2 therapy in the first line and afterwards are treated with CT alone. In some of these countries, the

justification given by payers is the lack of strong post-progression data to support that the use of Tras + CT is better than CT alone. The main goal of the current work is to generate additional evidence to support the use of trastuzumab-based regimens as a treatment option in the third-line setting, specifically for countries or patients without access to the newer anti-HER2 agents.

The ABC Global Alliance, with almost 200 members worldwide, advocates for access to multiple lines of anti-HER2 therapy, including access to trastuzumab beyond progression, for all patients with HER2+ LABC/mBC [41]. These treatments are also recommended by all major national and international guidelines. We plan to further evaluate the magnitude of the benefit of continuing trastuzumab-based therapy beyond progression using additional real-world datasets from different countries.

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Data sharing statement

The data that support the findings of this study have been originated by Flatiron Health and Foundation Medicine. These deidentified data may be made available upon request and are subject to a license agreement with Flatiron Health and Foundation Medicine; interested researchers should contact dataaccess@flatiron.com to determine licensing terms.

Author contribution statements

Study design: TSa, RR, TS, JM, SS, FC. Data collection: TSa, RR. Analysis and interpretation of data: TSa, RR, TS, JM, SS, FC. Writing of report: TSa, RR, TS, JM, SS, FC. Decision to submit article for publication: TSa, RR, TS, JM, SS, FC.

Declaration of competing interest

TSa, RR, TS and JM are employed by and own stock in Roche. FC has received advisory/consultancy fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, IQVIA, Macrogenics, Medscape, MSD, Merus B.V., Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva Pharmaceuticals and touchIME. SMS has received advisory/consultancy fees from AstraZeneca, Genentech/Roche, Molecular Therapeutics, Merck, Daiichi Sankyo, Lilly, Athenex, Exact Sciences and Natura; in-kind third-party writing assistance from AstraZeneca and Genentech/Roche; and research funding to institution from Genentech and Kailos Genetics.

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References

[1] Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, Baselga J. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. Cancer Res 2001;61(12):4744–9.

[2] Clynes RA, Towers TL, Presta LG, Ravetch JV. Inhibitory Fc receptors modulate in vivo cytotoxicity against tumor targets. Nat Med 2000 Apr;6(4):443–6.

[3] Herceptin (trastuzumab) [US prescribing information]. https://www.gene.com/download/pdf/herceptin_prescribing.pdf. Accessed April 4, 2022.

[4] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344(11):783–92.

[5] Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30(8):1194–220.

[6] Martínez-Sáez O, Prat A. Current and future management of HER2-positive metastatic breast cancer. JCO Oncol Pract 2021;17(10):594–604.

[7] Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31(12):1623–49.

[8] FDA Approval Letter. Trastuzumab. FDA; 1998. September 25, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/1998/trasgen092598L.pdf. [Accessed 4 April 2022].

[9] FDA Approval Letter. Trastuzumab. FDA; 2006. November 16; https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/103792%205150ltr.pdfAccessed April 4, 2022.

[10] European Medicines Agency. Herceptin (trastuzumab). https://www.ema.europa.eu/en/medicines/human/EPAR/herceptin#authorisation-details-section. Accessed April 4, 2022.

[11] European Medicines Agency. Enhertu (trastuzumab deruxtecan). https://www.ema.europa.eu/en/medicines/human/EPAR/enhertu. Accessed April 8, 2022.

[12] Franklin MC, Carey KD, Vajdos FF, Leahy DJ, De Vos AM, Sliwkowski MX. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. Cancer Cell 2004;5(4):317–28.

[13] Nami B, Maadi H, Wang Z. Mechanisms underlying the action and synergism of trastuzumab and pertuzumab in targeting HER2-positive breast cancer. Cancers 2018;10(10):342.

[14] Swain SM, Miles D, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol 2020;21(4):519–30.

[15] Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol 2016;17(6):791–800.

[16] Gennari A, André F, Barrios CH, et al. ESMO clinical practice guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12):1475–95.

[17] Giordano SH, Franzoi MAB, Temin S, et al. Systemic therapy for advanced human epidermal growth factor receptor 2–positive breast cancer: ASCO guideline update. J Clin Oncol. Publ Online May 31, 2022. doi:10.1200/JCO.22.00519.

[18] Han Y, Wang J, Liu W, et al. Trastuzumab treatment after progression in HER2-positive metastatic breast cancer following relapse of trastuzumab-based regimens: a meta-analysis. Cancer Manag Res 2019;11:4699–706.

[19] Blackwell K, Gligorov J, Jacobs I, Twelves C. The global need for a trastuzumab biosimilar for patients with HER2-positive breast cancer. Clin Breast Cancer 2018;18(2):95–113.

[20] von Minckwitz G, Schwedler K, Schmidt M, et al. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. Eur J Cancer 2011;47(15):2273–81.

[21] Griffith SD, Tucker M, Bowser B, et al. Generating real-world tumor burden endpoints from electronic health record data: comparison of RECIST, radiology-anchored, and clinician-anchored approaches for abstracting real-world progression in non-small cell lung cancer. Adv Ther 2019;36(8):2122–36.

[22] Ma X, Bellomo L, Magee K, et al. Characterization of a real-world response variable and comparison with RECIST-based response rates from clinical trials in advanced NSCLC. Adv Ther 2021;38(4):1843–59.

[23] Birnbaum B, Nussbaum N, Seidl-Rathkopf K, et al. Model-assisted cohort selection with bias analysis for generating large-scale cohorts from the EHR for oncology research. arXiv preprint 2020.

[24] Zhang Q, Gossai A, Monroe S, Nussbaum NC, Parrinello CM. Validation analysis of a composite real-world mortality endpoint for patients with cancer in the United States. Health Serv Res 2021;56(6):1281–7.

[25] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28(25):3083–107.

[26] Stuart EA, Lee BK, Leacy FP. Prognostic score-based balance measures can be a useful diagnostic for propensity score methods in comparative effectiveness research. J Clin Epidemiol 2013;66(8 Suppl):S84–90.e1.

[27] Harder VS, Stuart EA, Anthony JC. Propensity score techniques and the assessment of measured covariate balance to test causal associations in psychological research. Psychol Methods 2010;15(3):234–49.

[28] Austin PC. Variance estimation when using inverse probability of treatment weighting (IPTW) with survival analysis. Stat Med 2016;35(30):5642–55.

[29] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017;167(4):268–74.

[30] Imai K, Ratkovic M. Covariate balancing propensity score. J Roy Stat Soc B 2014;76(1):243–63.

[31] Ross RD, Shi X, Caram MEV, et al. Veridical causal inference using propensity score methods for comparative effectiveness research with medical claims. Health Serv Outcome Res Methodol 2021;21(2):206–28.

[32] Wyss R, Ellis AR, Brookhart MA, et al. The role of prediction modeling in propensity score estimation: an evaluation of logistic regression, bCART, and the covariate-balancing propensity score. Am J Epidemiol 2014;180(6):645–55.
[33] Varadhan R, Seeger JD. Estimation and reporting of heterogeneity of treatment effects. In: Developing a protocol for observational comparative effectiveness research: a user's guide. Rockville, MD: Agency for Healthcare Research and Quality; 2013. 35–44.29.
[34] Martínez-Sáez O, Prat A. Current and future management of HER2-positive metastatic breast cancer. JCO Oncol Pract 2021;17(10):594–604.
[35] European Medicines Agency. Tukysa (tucatinib). https://www.ema.europa.eu/en/medicines/human/EPAR/tukysa. Accessed April 8, 2022.
[36] Pizzuti L, Krasniqi E, Sperduti I, et al. PANHER study: a 20-year treatment outcome analysis from a multicentre observational study of HER2-positive advanced breast cancer patients from the real-world setting. Ther Adv Med Oncol 2021;13:17588359211059873.
[37] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47.
[38] Colomer R, Hall P, Szkultecka-Debek M, et al. Real-world treatment in patients with HER2+ metastatic breast cancer. Breast Cancer Res Treat 2018;168(1):197–205.
[39] Breast Cancer Foundation NZ. "I'm Still Here"; insights into living - and dying - with advanced breast cancer in New Zealand 2018; https://www.breastcancerfoundation.org.nz/images/assets/21894/1/bcfnz-abc-report-2018-executive-summary.pdf. Accessed May 10, 2022.
[40] Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol 2002;20(3):719–26.
[41] ABC Global Alliance. 2022. https://www.abcglobalalliance.org/. [Accessed 10 May 2022].