Original article

Correlation between week 24 trastuzumab-dkst response and week 48 progression-free survival: the HERITAGE trial

Hope S. Rugo a,*, Eduardo J. Pennella b,1, Unmesh Gopalakrishnan c, Miguel Hernandez-Bronchud d, Jay Herson e, Hans Friedrich Koch f, Subramanian Loganathan g, Sarika Deodhar g, Ashwani Marwah h, Alexey Manikhas i, Igor Bondarenko j, Joseph D. Parra k, Maria Luisa T. Abesamis-Tiambeng l, Charuwan Akewanlop m, Ihor Vynnychenko n, Virote Sriuranpong o, Sirshendu Roy p, Eduardo Patricio Yanez Ruiz q, Abhijit Barve r, Cornelius F. Waller s

a University of California San Francisco Helen Diller Family Comprehensive Cancer Center, 1825 4th St, 3rd Floor BCC, San Francisco, CA, 94158, USA
b Viatris Inc, 1000 Mylan Boulevard, Canonsburg, PA, 15317, USA
c Viatris Inc, 10th Floor, Prestige Platina Tech Park, Block 3, Kadubeesanahalli, Outer Ring Road, Bangalore, 560087, India
d GenesisCare Corachan, Buïgas 19, 08017, Barcelona, Spain
e City Clinical Oncology Dispensary, 198253, St. Petersburg, Veterans Avenue 56, Russia
f Dnipropetrovsk Medical Academy, 31, Blychyno Str, Dniprop, 49102, Ukraine
g St Luke’s Medical Center, 279 E. Rodriguez Sr. Ave, Quezon City, 1112, Metro Manila, Philippines
h Cardinal Santos Cancer Center, 10 Wilson St, Greenhills, San Juan City, Philippines
i Siriraj Hospital, 2 Thanon Wang Lang, Sirat, Bangkok Noi, Bangkok, 10700, Thailand
j St. Mary’s Medical Center, 279 E. Rodriguez Sr. Ave, Quezon City, 1112, Metro Manila, Philippines
k City Clinical Oncology Dispensary, 198253, St. Petersburg, Veterans Avenue 56, Russia
l City Clinical Oncology Dispensary, 198253, St. Petersburg, Veterans Avenue 56, Russia
m King Chulalongkorn Memorial Hospital, Chulalongkorn University, 3rd Floor, Anantamahidol Building, Henri Dunant Road, Pathumwan, Bangkok, 10330, Thailand
n Curie Manavata Cancer Centre, Mumbai Naka, Nashik, 422002, Maharashtra, India
o Universidad de La Frontera, Francisco Salazar 1145, Temuco, Araucania, Chile
p Curie Manavata Cancer Centre, Mumbai Naka, Nashik, 422002, Maharashtra, India
q Department of Haematology, Oncology and Stem Cell Transplantation, University Medical Centre Freiburg and Faculty of Medicine, University of Freiburg, Hugstetter Str. 55, 79010, Freiburg, Germany

Keywords:
Biosimilar
Combination therapy
Efficacy
Metastatic breast cancer
Monotherapy

Article history:
Received 8 January 2021
Received in revised form 24 March 2021
Accepted 25 March 2021
Available online 1 April 2021

Abstract

Background: Trastuzumab-dkst is a biosimilar of trastuzumab. The phase 3 HERITAGE trial demonstrated equivalent overall response rate (ORR) with trastuzumab-dkst or originator trastuzumab at 24 weeks in patients with HER2-positive metastatic breast cancer receiving chemotherapy. We now present the correlation of ORR with progression-free survival (PFS) for maintenance monotherapy with trastuzumab-dkst vs trastuzumab at 48 weeks of treatment, and the safety, tolerability, and immunogenicity.

Methods: HERITAGE is a multicenter, double-blind, randomized, parallel-group, phase 3 study. Patients were randomized 1:1 to receive trastuzumab-dkst or trastuzumab in combination with taxane followed by continued monotherapy until disease progression. The analysis included PFS at 48 weeks to support the primary efficacy endpoint of ORR and safety, tolerability, and immunogenicity of trastuzumab-dkst vs trastuzumab as maintenance monotherapy.

Results: Of 500 randomized patients, 342 entered the monotherapy phase; 214 patients received ≥48 weeks of treatment. There were no statistically significant differences between PFS, ORR, or interim
1. Introduction

Biologic agents, including monoclonal antibodies (mAbs), have improved outcomes for some cancers [1,2]. Despite significant therapeutic promise, biologics are structurally complex and often costly, limiting global access [3–6]. Biosimilars to cancer drugs may lower healthcare costs and improve access. As patents for biologics expire, biosimilars provide a high-quality alternative [3].

Worldwide, breast cancer is the most common malignancy and the most frequent cause of cancer death in women [7–9]. About 25%–30% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2) [10,11]. Trastuzumab is a humanized IgG1 mAb directed against HER2 [11]. With chemotherapy, trastuzumab has been shown to improve progression-free survival (PFS) and overall survival (OS) in HER2-positive metastatic breast cancer (MBC) and disease-free survival and OS in early-stage HER2-positive disease [12–15]. Trastuzumab is approved for treatment of HER2-positive breast cancer and metastatic gastric or gastroesophageal junction adenocarcinoma [16].

Trastuzumab-dkst (Ogivri®; Viatris Inc, Zurich, Switzerland; formally MYL-14010) is a trastuzumab biosimilar [17], with an amino acid sequence identical to that of trastuzumab (Herceptin®; Genentech, Inc, South San Francisco, CA). Similarity of trastuzumab-dkst to both United States– and European Union–sourced trastuzumab has been demonstrated in physicochemical, preclinical, and pharmacokinetic studies [18,19]. The phase 3 HERITAGE trial compared taxane-based chemotherapy with trastuzumab-dkst or trastuzumab as first-line therapy for MBC. The primary endpoint of overall response rate (ORR) at 24 weeks combined with taxanes has been reported [20] and was equivalent between groups, leading to regulatory approval of trastuzumab-dkst in the United States and Europe. After 24 weeks, patients with stable or responding disease continued mAb monotherapy until progression. We present safety, tolerability, immunogenicity, and correlation between ORR and PFS for trastuzumab-dkst or trastuzumab maintenance monotherapy after 48 weeks of therapy.

2. Patients and methods

This was a multicenter, double-blind, randomized, parallel-group, phase 3 study (NCT02472964) [21] in patients with HER2-positive MBC (Supplemental Figure) conducted in accordance with the International Council for Harmonisation Guidance for Industry E6 Good Clinical Practice, the Declaration of Helsinki, and applicable local regulatory requirements. All patients provided written informed consent before starting any study-related procedures. The full trial protocol and all other relevant study documentation were approved by the institutional review board or ethics committee at each study center before study initiation. Detailed methods, including eligibility criteria, study design, and treatment regimen details, have previously been described [20].

2.1. Eligibility

Patients were adults with histologically confirmed HER2-positive breast cancer having ≥1 measurable metastatic target lesion, Eastern Cooperative Oncology Group performance status of 0–2, and left ventricular ejection fraction (LVEF) within normal range [20]. Patients must not have received chemotherapy or HER2-targeted therapy within 1 year of diagnosis of metastatic disease.

2.2. Study design

Patients were randomized 1:1 to receive taxane plus trastuzumab-dkst or trastuzumab using a centralized randomization procedure with stratification based on baseline covariates [20]. Taxanes included docetaxel or paclitaxel and were administered by physician’s choice at the study site. After 24 weeks of combination therapy, patients with stable or responding disease continued their assigned monotherapy until disease progression, unacceptable toxicity, or death. During monotherapy, patients with hormone receptor–positive disease could receive endocrine therapy.

2.3. Efficacy

After the first 24 weeks of combination therapy, tumor assessments were conducted every 12 weeks independent of delays in treatment administration and included imaging of the chest, abdomen, and pelvis, with bone scan as indicated.

2.4. Safety

The safety population included all patients who received ≥1 dose of trastuzumab-dkst or trastuzumab. Safety analyses used cumulative data through week 48 for all patients. A separate analysis was conducted using data from patients who received monotherapy only. Assessment of treatment-emergent adverse events (TEAEs) included type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03), timing, seriousness, and relatedness. Laboratory abnormalities were also assessed.

2.5. Statistical analysis

The primary endpoint of ORR at week 24 was previously reported. The endpoint of efficacy and safety of trastuzumab-dkst and trastuzumab monotherapy at week 48 included a descriptive comparison of safety, tolerability, and immunogenicity, as well as evaluation of PFS, duration of response (DR), time to tumor progression (TTP), and interim OS. Final OS will occur during follow-up at 240 deaths or month 36 from the time of randomization of the last patient, whichever occurs first, and will be reported at study end.

Disease progression was defined according to Response...
Evaluation Criteria in Solid Tumors (RECIST; version 1.1) [22]. Patients were classified by response to therapy as having a complete response (CR), partial response (PR), or stable disease (SD). Patients who were intolerant to therapy or progressed during combination therapy were followed for safety and survival events.

Patient disposition, baseline characteristics, and treatment administration/compliance were descriptively summarized using SAS® software version 9.2 or later (SAS, Cary, NC). Analyses of secondary endpoints were not adjusted for multiplicity. Kaplan-Meier plots by treatment are presented, and a log-rank test of the 2 treatment groups unadjusted for any covariates was performed. The biserial correlation coefficient was used to assess associations between ORR at week 24 (responder or nonresponder) and PFS at week 48, irrespective of treatment assignment.

3. Results

3.1. Patient disposition and baseline characteristics

Of the 500 patients randomized, 493 received treatment (safety population). Of these, 458 were included in the intention-to-treat (ITT) efficacy analysis population (Fig. 1A), composed of patients who had not previously received first-line therapy. A total of 342 patients entered maintenance monotherapy (trastuzumab-dkst, n = 179; trastuzumab, n = 163; Fig. 1B). Overall, 214 patients completed 48 weeks of treatment (trastuzumab-dkst, n = 116; trastuzumab, n = 98). Baseline characteristics of patients enrolled to receive combination therapy were previously published [20]. Baseline characteristics of patients starting monotherapy were generally similar between groups (Table 1). Mean (SD) age was 54.1 (11.0) years, and the estrogen receptor— and progesterone receptor—negative population entering monotherapy was 55.3%.

3.2. Efficacy

Week 48 TTP, PFS, and OS endpoints were previously reported [20]. Median DR through week 48 was similar with trastuzumab-dkst (9.7 months; 95% CI, 7.4—9.9) and trastuzumab (9.7 months; 95% CI, 7.7—9.9) in the ITT population, with no statistically significant differences (log-rank test, P = 0.790). At week 48, age, race, previous adjuvant/neoadjuvant chemotherapy/HER2-targeted treatment, and region were potential covariates to influence the hazard ratio for TTP and included in the final model. According to the final model at week 48, age (≥50 vs < 50 years) influenced TTP (hazard ratio, 0.69; P = 0.013). Because of the small number of patients with tumor progression, the data were of limited clinical relevance. The 95% CI of the TTP ratio (trastuzumab-dkst to trastuzumab) included “1” for all subgroups at week 48 (ie, no relevant subgroup differences were observed). At week 48, 128 (55.7%) trastuzumab-dkst patients and 126 (55.3%) trastuzumab patients had not experienced disease progression. According to the log-rank test, time-to-event curves for both groups were also not significantly different at week 48 (P = 0.842). Median time for PFS by Kaplan-Meier estimates was 11.1 months in both groups (Fig. 2A). Through week 48, 205 (89.1%) trastuzumab-dkst patients survived compared with 194 (85.1%) trastuzumab patients, and survival curves for both groups were not significantly different (P = 0.131; median not reached for Kaplan-Meier estimates for OS because of the relatively small number of patients in the ITT population who died before week 48; Fig. 2B).

Fig. 1. Patient consort diagrams for the (A) ITT population and (B) safety population. ITT, intention-to-treat. *The safety population included 10 patients from the trastuzumab-dkst group and 12 patients from the trastuzumab group who were not considered part of the ITT population but were randomized for treatment in part 1 (combination therapy). 1At the start of part 2 (monotherapy) and at the investigator’s discretion, 15 patients continued using taxane and later switched to monotherapy. 2At the start of part 2 (monotherapy) and at the investigator’s discretion, 17 patients continued using taxane and later switched to monotherapy.
Additional responders were documented during the monotherapy phase. At week 24, CR was observed in 1.3% and 0% of patients receiving trastuzumab-dkst and trastuzumab, respectively; at week 48, this increased to 1.7% and 0.4%, respectively, as 1 additional patient in each group demonstrated CR. At week 24, PR was observed in 68.3% and 64.0% of patients receiving trastuzumab-dkst and trastuzumab, respectively. An additional 5 patients receiving trastuzumab-dkst demonstrated PR during monotherapy, increasing the percentage of patients with PR to 66.2%. Confirming ORR at week 48 for trastuzumab-dkst and trastuzumab was 70.0% and 66.7%, respectively.

The ORR at week 24 correlated with PFS in responders and nonresponders at week 48 (Fig. 3A). Association of ORR at week 24 and PFS for the total sample at week 48 was strong ($r_S = 0.75$, biserial correlation coefficient for study population; Fig. 3B).

### 3.3. Safety and tolerability

Results from patients receiving combination therapy were previously reported [20]. Cumulative overall TEAE rate was 57.3% (trastuzumab-dkst, 54.7%; trastuzumab, 60.1%) during the monotherapy phase (Table 2). Of the 5015 total TEAEs reported, only 513 (trastuzumab-dkst, 50.0% [n = 228]; trastuzumab, 50.0% [n = 227]) during the monotherapy phase. At week 24, CR was observed in 1.3% and 0% of patients receiving trastuzumab-dkst and trastuzumab, respectively. An additional 5 patients receiving trastuzumab-dkst demonstrated PR during monotherapy, increasing the percentage of patients with PR to 66.2%. Confirming ORR at week 48 for trastuzumab-dkst and trastuzumab was 70.0% and 66.7%, respectively.

The ORR at week 24 correlated with PFS in responders and nonresponders at week 48 (Fig. 3A). Association of ORR at week 24 and PFS for the total sample at week 48 was strong ($r_S = 0.75$, biserial correlation coefficient for study population; Fig. 3B).

### 3.4. TEAEs of special interest

Using the standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) for hypersensitivity (narrow) with the additional preferred term (PT) of infusion-related reaction (IRR), 106 events were identified in 53 (21.5%) patients receiving trastuzumab-dkst and 105 events in 56 (22.8%) patients receiving trastuzumab through week 48, the majority of which occurred during combination therapy. Identified events that occurred in >1% of patients receiving trastuzumab-dkst were rash (8.9% vs 10.2% for trastuzumab), IRR (6.9% vs 4.9%), hypersensitivity (2.0% vs 2.8%),
allergic cough (1.2% vs 0.4%), dermatitis (1.2% vs 0.4%), and rash pruritic (1.2% vs 0.4%). Treatment-related IRRs were reported in 9 (3.6%) patients receiving trastuzumab-dkst and 6 (2.4%) receiving trastuzumab through week 48. Three (1.2%) patients in each group reported a grade ≥3 hypersensitivity event, and 1 (0.4%) in each group experienced a grade ≥3 IRR. Three (1.2%) patients in each group experienced a serious hypersensitivity event or IRR (trastuzumab-dkst, 1 drug hypersensitivity event and 2 anaphylactic reactions; trastuzumab, 1 IRR and 2 hypersensitivity events). Grade 3 anaphylactic reactions were reported in 2 (0.8%) patients receiving trastuzumab-dkst, one treatment related and the other related to concomitant medications (piperacillin/tazobactam). Both events resolved. No anaphylactic events were reported with trastuzumab.

During maintenance monotherapy, 1 (0.4%) patient receiving trastuzumab experienced an IRR compared with none receiving trastuzumab-dkst. The SMQ hypersensitivity (narrow) identified 3 (1.7%) patients receiving trastuzumab-dkst and 4 (2.5%) receiving trastuzumab who experienced a potential hypersensitivity event. No hypersensitivity or IRR events were serious, grade 3, or resulted in interruption or permanent treatment discontinuation during monotherapy. Through week 48, all IRRs resolved the same day as onset with interruption of the infusion and/or conservative treatment.

Incidence of treatment-associated pulmonary toxicity was low for the 48-week study, with dyspnea (7.1%), pneumonia (3.4%), and pneumonitis (1.2%) being reported most frequently. With trastuzumab-dkst, 41 pulmonary toxicity events occurred vs 43 events with trastuzumab. During monotherapy, 9 pulmonary toxicity events occurred: dyspnea (trastuzumab-dkst, n = 4; trastuzumab, n = 1), pneumonia (trastuzumab-dkst, n = 2; trastuzumab, n = 0), pneumonitis (trastuzumab-dkst, n = 0; trastuzumab, n = 1), and pulmonary fibrosis (trastuzumab-dkst, n = 1;
trastuzumab, n = 0).

Incidence of cardiac events was low for the 48-week study and comparable in both groups (trastuzumab-dkst, n = 29; trastuzumab, n = 18). In total, 17 cardiac events occurred during maintenance monotherapy. The most common cardiac event was decreased ejection fraction, which occurred in 10 patients (trastuzumab-dkst, 3.4% [n = 6]; trastuzumab, 2.5% [n = 4]). One event each (0.4%) of cardiac failure, cardiotoxicity, carditis, and LV dysfunction occurred with trastuzumab-dkst, and 1 event each (0.4%) of cardiomyopathy and congestive cardiomyopathy occurred with trastuzumab. The LVEF values were similar between groups through week 48. Eighteen patients had LVEF <50% at least once during the study (trastuzumab-dkst, 4.0% [n = 10]; trastuzumab, 3.3% [n = 8]; P = 0.637). Most patients who had a 50% drop in LVEF had previously received anthracyclines and had conditions potentially associated with a second cardiac event. Sixteen patients (trastuzumab-dkst, 4.0% [n = 10]; trastuzumab, 2.4% [n = 6]) who had LVEF <50% at least once postbaseline recovered to >50% during the study.

### 3.5. Immunogenicity

Before treatment, 14 of 237 patients (5.9%) receiving trastuzumab-dkst and 22 of 240 (9.2%) receiving trastuzumab were positive for antidrug antibodies (ADA). Antibodies were transient with low titers, and incidence of neutralizing antibodies (NAb) was low and similar between groups. Overall, ADA rate postbaseline was 3.9% with trastuzumab-dkst and 4.4% with trastuzumab (Table 3). Treatment-induced ADA rate with trastuzumab-dkst and trastuzumab was 1.7% and 1.8%, respectively. Between weeks 24 and 48, 1 new patient receiving trastuzumab-dkst was ADA positive. There were no differences between groups regarding immunogenicity.

**Fig. 3.** ORR at week 24 was predictive of PFS at week 48. (A) ORR at week 24 with PFS at week 48 in responders and nonresponders. (B) ORR at week 24 and Kaplan-Meier plot of PFS probability. ORR, overall response rate; PFS, progression-free survival.
The study population that experienced LV dysfunction had predisposing factors for cardiotoxicity, including prior anthracycline use, chest wall radiotherapy, diabetes, and hypertension. Changes in LVEF observed in this study are consistent with trastuzumab literature [23,24]. Incidence of IRRs was lower in this study (trastuzumab-dkst, 21.5%; trastuzumab, 22.8%) compared with the 40% of patients receiving trastuzumab as estimated by the EU-trastuzumab summary of product characteristics [25]. Of the 2 anaphylactic events that occurred with trastuzumab-dkst, both resolved, and 1 was considered related to treatment. Incidence of SAEs was similar between groups receiving monotherapy, and no new safety findings were observed. One death in each group was considered possibly related to treatment (both respiratory failure).

4. Discussion

Trastuzumab combined with taxane has resulted in improved ORR in MBC and improved pathologic complete response in early breast cancer, indicating similar sensitivity in both HER2-positive disease settings. Week 48 results for DR, TTP, PFS, and OS were similar between the trastuzumab-dkst and trastuzumab groups (ITT population), with no statistically significant differences. All secondary efficacy analyses supported the conclusion of therapeutic equivalence. Further post hoc analysis suggests that the ORR of the responder and nonresponder subgroups provides a good prediction of prolonged PFS and that the behavior is similar in both groups. There was a strong positive correlation between ORR at week 24 and PFS at week 48 in the HERITAGE trial.

Trastuzumab-dkst and trastuzumab were well tolerated both in combination with taxane and as monotherapy. Incidence of TEAEs was similar between groups, and the most common TEAEs were alopecia, neutropenia, and diarrhea. Of the 5015 TEAEs that occurred through week 48, 513 were during monotherapy, suggesting that concomitant taxane therapy may have significantly contributed to toxicity.

Table 2
Summary of TEAEs (occurring in ≥10% of patients in any group) and SAEs (occurring in ≥2% of patients in any group) in combination therapy (24 weeks) and monotherapy (48 weeks) phases: Safety population.

|                  | Combination therapy phase only | Monotherapy phase only |
|------------------|-------------------------------|------------------------|
|                  | Trastuzumab-dkst + taxane (N = 247) | Trastuzumab + taxane (N = 246) | Trastuzumab-dkst (N = 179) | Trastuzumab (N = 163) |
| Patients with ≥1 TEAE | 239 (96.8) | 233 (94.7) | 98 (54.7) | 98 (60.1) |
| CTCAE preferred term |                        |                        |                          |                        |
| Alopecia         | 142 (57.9) | 135 (54.9) | 6 (3.4) | 5 (3.1) |
| Neutropenia      | 142 (57.5) | 131 (53.3) | 2 (1.1) | 4 (2.5) |
| Diarrhea         | 51 (20.6) | 51 (20.7) | 6 (3.4) | 0 |
| Anemia           | 54 (21.9) | 40 (16.3) | 5 (2.8) | 3 (1.8) |
| Leukopenia       | 42 (17.0) | 51 (20.7) | 1 (0.6) | 2 (1.2) |
| Nausea           | 49 (19.8) | 34 (13.8) | 4 (2.2) | 4 (2.5) |
| Anemia           | 40 (16.2) | 40 (16.3) | 5 (2.8) | 12 (7.4) |
| Peripheral edema | 35 (14.2) | 28 (11.4) | 1 (0.6) | 3 (1.8) |
| Arthralgia       | 30 (12.1) | 11 (4.5) | 5 (2.8) | 2 (1.2) |
| Peripheral sensory neuropathy | 29 (11.7) | 34 (13.8) | 4 (2.2) | 2 (1.2) |
| Fatigue          | 28 (11.3) | 33 (13.4) | 3 (1.7) | 6 (3.7) |
| Peripheral neuropathy | 28 (11.3) | 28 (11.4) | 3 (1.7) | 7 (4.3) |
| Vomiting         | 26 (10.5) | 19 (7.7) | 3 (1.7) | 5 (3.1) |
| Pyrexia          | 21 (8.5) | 30 (12.2) | 4 (2.2) | 2 (1.2) |
| SAEs             |                  |                        |                          |                        |
| Patients with ≥1 SAE | 94 (38.1) | 89 (36.2) | 5 (2.8) | 4 (2.5) |
| CTCAE preferred term |                        |                        |                          |                        |
| Neutropenia      | 68 (27.5) | 62 (25.2) | 0 | 0 |
| Febrile neutropenia | 11 (4.5) | 10 (4.1) | 0 | 0 |
| Leukopenia       | 4 (1.6) | 12 (4.9) | 0 | 0 |
| Pneumonia        | 4 (1.6) | 5 (2.0) | 2 (1.1) | 0 |

Table 3
Summary of overall and treatment-induced ADA and NAb rates: Safety population.

|                  | Trastuzumab-dkst (N = 247) | Trastuzumab (N = 246) |
|------------------|----------------------------|-----------------------|
| Overall ADA rate | 9 (3.9)                    | 10 (4.4)              |
| Overall NAb rate | 1 (0.4)                    | 3 (1.3)               |
| Treatment-induced ADA rate | 4 (1.7) | 4 (1.8) |
| Treatment-induced NAb rate | 1 (0.4) | 2 (0.9) |

ADA, antidrug antibodies; NAb, neutralizing antibodies.

a Percentages were based on the number of patients in the safety population with non-missing postbaseline samples available in each group and include 228 patients in the trastuzumab-dkst group and 227 patients in the trastuzumab group.
b Percentages were based on the number of patients in the safety population with available ADA postbaseline results and include 229 patients in the trastuzumab-dkst group and 227 patients in the trastuzumab group.

Coded using Medical Dictionary for Regulatory Activities, version 18.0.
when sufficient scientific justification and totality of evidence support such use under the guidelines of the European Medicines Agency, US Food and Drug Administration (FDA), and World Health Organization [3], may enable the use of trastuzumab-dkst in combination with pertuzumab as well as other agents that have been combined with trastuzumab in clinical practice.

Limitations of the HERITAGE trial are consistent with other biosimilar clinical development programs, including use of a short-term primary efficacy endpoint to initially assess similarity between trastuzumab-dkst and trastuzumab. Assessment of ORR at 24 weeks was chosen as the primary endpoint as a short-term measure of clinical activity and safety related to the use of trastuzumab-dkst as first-line therapy for MBC. The present results bolster these previously reported findings, with similarity between trastuzumab-dkst and trastuzumab (administered as maintenance monotherapy after combination therapy with taxane) demonstrated across numerous endpoints, including DR, TTP, and PFS. Longer-term assessment of OS and safety will be necessary to continue to evaluate trastuzumab-dkst in patients with HER2-positive MBC.

5. Conclusions

A positive correlation was observed between ORR and PFS in this study, potentially supporting the use of ORR as a valid endpoint in clinical trials for MBC. These data further support the FDA-approved trastuzumab-dkst as a biosimilar to trastuzumab and provide another treatment option for patients with HER2-positive MBC, as well as other trastuzumab indications, based on biosimilar extrapolation. Overall, no significant differences were observed between trastuzumab-dkst and trastuzumab in clinical activity, and both products were well tolerated with no new significant safety issues.

Declaration of competing interest

HS Rugo has received travel, accommodations, and expenses from Amgen, Merck, Viatris Inc, Pfizer, and Puma Biotechnology and research funding (provided to the Regents of the University of California) from Eisai, Genentech/Roche, Lilly, Macrogenics, Merck, Novartis, OBI Pharma, Daichi, Immunomedics, and Pfizer. EJ Pennella was a paid employee of Mylan Inc (now Viatris Inc) during the time of the study and may hold stock with the company. U Gopalakrishnan, HF Koch, and A Barve are paid employees of Viatris Inc and may hold stock with the company. M Hernandez-Bronchud has served as a consultant/advisory board member for Viatris Inc. S Loganathan, S Deodhar, and A Marwah are paid employees of Biocon Research Ltd and may hold stock with the company. C Akewanpol has received travel, accommodations, and expenses from Amgen, AstraZeneca, Roche, and Bristol-Myers Squibb. CF Waller is a consultant/advisory board member for Viatris Inc and may hold stock with the company. H.S. Rugo, E.J. Pennella, U. Gopalakrishnan et al. The Breast 58 (2021) 18–26
worldwide in 2012. 2012. accessed 1 November 2017, http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx.

[10] Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. Mol Biol Int 2014;2014:852748. https://doi.org/10.1155/2014/852748.

[11] Eisenbeis AM, Grau SJ. Monoclonal antibodies and Fc fragments for treating solid tumors. Biologics 2012;6:13–20. https://doi.org/10.2147/BIT.S319955.

[12] Perez EA, Romond EH, Suman VJ, Jeong J-H, Sledge G, Geyer Jr CE, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG NS831. J Clin Oncol 2014;32:3744–52. https://doi.org/10.1200/JCO.2014.63.1395.

[13] Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsh A, Untch M, Smith I, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005;353:1659–72. https://doi.org/10.1056/NEJMoa052306.

[14] Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92. https://doi.org/10.1056/NEJM200103153441101.

[15] Herceptin [package insert]. South San Francisco, CA: Genentech, Inc; 2018.

[16] Us Food and Drug Administration. FDA approves first biosimilar for the treatment of certain breast and stomach cancers. accessed 1 December 2017, https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm587378.htm; 2017.

[17] Waller CF, Vutikullird A, Lawrence TE, Shaw A, Liu MS, Baczkowski M, et al. A pharmacokinetics phase 1 bioequivalence study of the trastuzumab biosimilar MYL-1401O vs. EU-trastuzumab and US-trastuzumab. Br J Clin Pharmacol 2018;84:2336–43. https://doi.org/10.1111/bcp.13689.

[18] Chtitoui H, Vallotton L, Audran R, Dao K, Rothuizen LE, Winterfeld U, et al. A bioequivalence study for Hercules, a biosimilar trastuzumab candidate in development. Poster presented at Pharmacology. 2015 [London, UK].

[19] Rugo HS, Barve A, Waller CF, Hernandez-Bronchud M, Herson J, Yuan J, et al. Effect of a proposed trastuzumab biosimilar compared with trastuzumab on overall response rate in patients with ERBB2 (HER2)-positive metastatic breast cancer: a randomized clinical trial. JAMA 2017;317:37–47. https://doi.org/10.1001/jama.2016.18305.

[20] ClinicalTrials.gov. Study of efficacy and safety of MYL-1401O + taxane vs HerceptinO + taxane for 1st line. Met. Br. Ca. (HERIAge); 2018. accessed 22 October 2019, https://clinicaltrials.gov/ct2/show/NCT02472964.

[21] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Canc 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.

[22] Baselga J, Cortés J, Kim S-B, Im S-A, Hegg R, Im Y-H, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med 2012;366:109–19. https://doi.org/10.1056/NEJMoa1113216.

[23] Perez EA, Barrios C, Eiermann W, Toi M, Im Y-H, Conte P, et al. Trastuzumab emtansine with or without pertuzumab versus trastuzumab plus taxane for human epidermal growth factor receptor 2-positive, advanced breast cancer: primary results from the phase III MARIANNE study. J Clin Oncol 2017;35:141–8. https://doi.org/10.1200/JCO.2016.67.4887.

[24] Herceptin [summary of product characteristics]. Grenzach-Wyhlen, Germany: Roche Pharma AG; 2010.

[25] Ismael G, Hegg R, Muehlbauer S, Heinzmann D, Lumb B, Kim S-B, et al. Subcutaneous versus intravenous administration of (neo)adjuvant trastuzumab in patients with HER2-positive, clinical stage I-II breast cancer (Hannah study): a phase 3, open-label, multicentre, randomised trial. Lancet Oncol 2012;13:869–78. https://doi.org/10.1016/S1470-2045(12)70329-7.

[26] Ogivri [package insert]. Zurich, Switzerland: Mylan GmbH; 2017.

[27] Sapna F, Athwal PSS, Kumar M, Randhawa S, Kahlon S. Therapeutic strategies for human epidermal receptor-2 positive metastatic breast cancer: a literature review. Cureus 2020;12:e9522. https://doi.org/10.7759/cureus.9522.