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ORIGINAL RESEARCH

Real-World Study of Adjuvant Biosimilar Trastuzumab-dkst for HER2-Positive Breast Cancer Treatment in a Brazilian Population

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ABSTRACT

Introduction: Biological monoclonal antibodies play a pivotal role in cancer treatment, with biosimilars significantly enhancing their accessibility. In Brazil's ethnically diverse setting, real-world evidence is crucial for assessing the effectiveness and applicability of these therapies in routine clinical practice.

Methods: We performed a multicentric, observational, prospective real-world study on biosimilar trastuzumab-dkst for adjuvant treatment of early HER2-positive breast cancer in Brazilian patients. Data were collected using a case-report form.

Results: Of the 176 recruited, we present data from the first 59 patients (mean age 51.7±12.9 years) who had completed treatment with trastuzumab-dkst. The mean time from diagnosis to the first adjuvant treatment with trastuzumab-dkst was 5.5±2.7 months. Of the patients, 59% of patients achieved at least a 30-month follow-up. The 31.7-month invasive disease-free survival rate (IDFS) was 94.5% (95% CI 83.9–98.2%) and median IDFS was not achieved, since only three patients had invasive disease recurrence. The overall survival rate was 100% until the last assessment. The observed adverse events were similar to those presented by other studies using biosimilar or reference trastuzumab. Four serious adverse events (8.5%) were observed. A reduction in left ventricular ejection fraction of at least 10% was observed in 16.9% of participants. There was no treatment interruption, and three participants (5.1%) had their trastuzumab-dkst dose reduced.

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Conclusion: Our study reinforces the existing pivotal data, underscoring the real-world efficacy and safety of biosimilar trastuzumab-dkst in the adjuvant treatment for early HER2-positive breast cancer. The preliminary long-term effectiveness and safety data we present further validate trastuzumab-dkst's role as a cost-saving alternative in oncological care. These findings have important implications for improving patient access to crucial treatments and for the more efficient use of healthcare resources.
ClinicalTrials.gov Registration: NCT03892655.

Keywords: Adjuvant breast cancer treatment; Biosimilar; Early-stage breast cancer; HER2-positive breast cancer; Trastuzumab-dkst RWD

Key Summary Points

Trastuzumab, a monoclonal antibody, has been shown to improve the survival rates of patients diagnosed with HER2-positive breast cancer (HER2+BC).

However, due to the high costs associated with biologic therapies such as trastuzumab, the development of biosimilars following patent expiration offers more affordable alternatives.

In this prospective, observational study, we assessed the effectiveness and safety of the biosimilar trastuzumab-dkst as adjuvant therapy for the first 59 Brazilian patients, out of a total of 176 enrolled. These patients represent an ethnically diverse population diagnosed with early-stage HER2+BC.

At a follow-up of 31.7 months, the invasive disease-free survival rate was 94.5%, and the overall survival rate was 100% until the latest assessment, with no new safety concerns identified.

The introduction of trastuzumab-dkst as adjuvant therapy for HER2+BC offers an opportunity to expand access to effective treatment.

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INTRODUCTION

Female breast cancer (BC) has consistently been a major health concern, evidenced by its status as the most commonly diagnosed cancer globally in 2020, with 2.3 million new cases (11.7% of total cancer cases) [1]. Long-term data from the Global Burden of Disease study highlight BC's significant impact, showing that it was a leading cause of cancer-related deaths in the female population from 1990 to 2017 [2]. In Brazil, excluding nonmelanoma skin cancer, female BC is currently the most common cancer type in all country regions [3].

Among patients with BC, approximately 20% are diagnosed with the HER2-positive subtype, characterized by the amplification or overexpression of the human epidermal growth factor receptor-2 (HER2) [4, 5]. Historically, this subtype was associated with higher recurrence rates and poorer survival compared with other BC subtypes [6, 7]. The introduction of trastuzumab, a humanized monoclonal antibody targeting HER2, revolutionized the treatment for this subtype, significantly improving patient outcomes by reducing recurrence and mortality risks [8, 9].

Trastuzumab was approved by the Brazilian Health Regulatory Agency (Anvisa) in 2000 and 2006 for the management of metastatic and locoregional BC, respectively. Despite its effectiveness, trastuzumab's high cost has been a significant barrier in Latin America, particularly in Brazil, where its use was initially limited to about 20% of the population with private health insurance [10]. The Brazilian Public Healthcare System only began incorporating trastuzumab-based chemotherapy as adjuvant therapy in 2012. Despite this progress, challenges in ensuring early diagnosis and widespread availability of trastuzumab persist across the country [10].

In response to those financial barriers and to enhance access to treatment, biosimilars offer a cost-saving alternative. Biosimilars are biological molecules that are highly similar to a reference product, displaying no relevant differences in terms of safety and clinical efficacy [11]. This class of products can be made available after the patent expiration of its originator medicine and, due to their lower development and manufacturing costs, biosimilars can be offered at prices up to 50% lower than their originator counterparts, presenting a viable solution to the cost challenges associated with biologic therapies such as trastuzumab [12].

In 2017, trastuzumab-dkst (Zedora®; Libbs Farmacêutica; São Paulo; Brazil) was approved by the Brazilian Health Regulatory Agency as the first biosimilar trastuzumab to treat HER2-positive BC. This approval was grounded in the "totality-of-the-evidence" concept within biosimilarity assessments, involving rigorous evaluations of the molecule's structural and functional characteristics, pre-clinical data, and the phase 3 HERITAGE study [13]. This study, conducted across 95 research centers in Asia, Latin America, Africa, and Europe, enrolled 500 women with metastatic HER2-positive BC and successfully demonstrated the biosimilar's therapeutic equivalence to the reference biologic, with no clinically meaningful differences in quality, safety, or efficacy [14].

While randomized clinical trials (RCTs) play a crucial role, they often have limitations, such as strict eligibility criteria and potential underestimation of real-world issues such as compliance and tolerability. As a result, the effectiveness of a treatment in clinical practice may differ from trial expectations. Real-world evidence (RWE) studies are thus increasingly important in oncology, offering insights into the long-term safety and effectiveness of treatments in broader patient populations [15, 16]. Despite extensive RCT data for the reference biological in adjuvant settings [15, 16], data for trastuzumab-dkst in non-metastatic BC were limited, especially real-world data.

Our study aimed to bridge this gap by evaluating the effectiveness and safety of trastuzumab-dkst as adjuvant therapy in HER2-positive BC in a real-world setting. Here, we present preliminary data from participants who completed adjuvant treatment with trastuzumab-dkst by February 2022.

METHODS

Study Design

We performed a multicentric, observational, prospective real-world study to assess the effectiveness and safety of adjuvant biosimilar trastuzumab-dkst in the treatment of early HER2-positive BC in Brazilian women. Participants presenting the protocol's eligibility criteria were consecutively selected. This report presents a partial analysis, reflecting outcomes from participants who completed adjuvant treatment with trastuzumab-dkst by February 2022 across 11 different Brazilian institutions. As the study is ongoing, updates on the safety outcomes and comprehensive data analysis will be provided in the final publication. ClinicalTrials.gov registration: NCT03892655.

Patients

Female participants aged 18 years or older diagnosed with early-stage HER2-positive BC as per the 2018 ASCO guidelines [17] were eligible for inclusion. A prerequisite for participation was having received at least one dose of trastuzumab-dkst as adjuvant therapy, irrespective of the chemotherapy regimen used. Exclusion criteria included the use of trastuzumab-dkst in a manner not recommended by the manufacturer, current enrollment in the Programa Vida Plena (a patient support program by Libbs that aims to enhance treatment adherence by providing tailored support and resources to patients), or the presence of cardiac dysfunction, identified as a left ventricular ejection fraction (LVEF) below the lower limit of normality, as detected by echocardiography. LVEF cutoff values were defined by laboratory reports. All participants provided signed informed consent prior to study enrollment.

Study Procedures

Sociodemographic and medical history data, including cancer and treatment history, were collected through a case-report form at the time of enrollment. Effectiveness and safety outcomes were assessed during regular medical appointments. Due to inconsistencies in how the number of anti-HER2 treatment cycles was recorded, we calculated this by dividing the duration of adjuvant therapy (from start to end dates) by 21 days. Adverse events (AEs) were categorized by preferred term and system organ class, using Medical Dictionary for Regulatory Activities (MedDRA) terminology. All participants who met the protocol eligibility criteria and completed adjuvant anti-HER2 treatment are included in the full analysis set (FAS), which was used for all statistical analyses.

Effectiveness Assessments

Effectiveness was evaluated using several metrics including the median invasive disease-free survival (IDFS), IDFS rate, median overall survival (OS), and OS rate.

IDFS is defined as the time from the initiation of adjuvant anti-HER2 therapy until the occurrence of any of the following events: invasive local–regional or distant recurrence, secondary primary invasive non-breast cancer, or death from any cause. This definition is aligned with the Standardized Definitions for Efficacy End Points (STEEP) version 2.0 used in Adjuvant Breast Cancer Clinical Trials [18]. IDFS was estimated using the Kaplan–Meier method, enabling the calculation of both the median IDFS and the IDFS rate throughout the study period. The median IDFS represents the time point at which 50% of patients had not yet experienced disease recurrence or other defined IDFS events. The IDFS rate provided a probability curve showing the cumulative proportion of patients who remained free from the specified IDFS events over time. Patients were censored at their last observation.

OS was defined as the time from the beginning of adjuvant anti-HER2 therapy until death from any cause. Median OS and OS rate were also calculated using Kaplan–Meier analysis.

Safety Assessments

The safety evaluation of trastuzumab-dkst involved several measures. Firstly, the Eastern

Cooperative Oncology Group (ECOG) performance scale was used to assess the functional capacity of patients on the days of administration. The frequency and details of AEs were described, including their grade of severity/intensity according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [19], seriousness (defined as grade 3 or higher), relation to study drug, and outcomes. The percentage of patients who had impairment in their LVEF was determined by comparing the baseline to follow-up echocardiograms. The test result was considered abnormal when there was a reduction of 10% or more in LVEF values compared with baseline, or LVEF was below 50%. Lastly, the number of cycles, dose reduction, and interruption were also considered.

Compliance with Ethics Guidelines

This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments, and received approval by the ethics committee at A.C. Camargo Cancer Center (CEP: 3.296.107). All participants signed an informed consent form prior to participating in the study. Participants remained anonymous and were granted the right to withdraw from the study at any time during the research period.

Data Analysis

Descriptive statistics were calculated to summarize the data according to the type of each variable [frequency, percentage, and 95% confidence interval (95% CI)]; when appropriate, they were used for categorical and ordinal numerical variables; and the number of valid observations, mean, standard deviation (SD), and median, minimum and maximum values were calculated for continuous numerical variables. For IDFS, the Kaplan–Meier estimate is presented. All statistical analyses were performed using SAS® Version 9.4.

RESULTS

Patients

Out of a total of 176 enrolled patients, we present data from the first 59 patients who met the inclusion criteria and had completed treatment with trastuzumab-dkst by February 2022. These participants represent the initial cohort of a broader ongoing study, aimed at providing early insights into the treatment's effectiveness and safety in a real-world setting. The mean age of these participants was 51.7 ± 12.9 years (range 30–84 years). Patient characteristics and medical history, other than BC, are detailed in Table 1. All 59 patients (100%) underwent surgical procedures, with the majority (91.5%) having only one surgery, while 8.5% underwent two surgeries. For the first surgical approach, 67.8% of patients underwent conservative breast surgery, and 32.2% had a mastectomy. Among those requiring a second surgery (five patients; 8.5%), one underwent conservative surgery and four underwent mastectomies. The mean time from diagnosis to initiation of neoadjuvant treatment or surgery was 3.4 ± 2.9 months (ranging from 1 day to 9.8 months). The mean time from diagnosis to first adjuvant treatment with trastuzumab-dkst was 5.5 ± 2.7 months (ranging from 1.4 to 11.5 months).

The median age at first diagnosis was 50 years (range 29–83 years). Most patients (98.3%) had invasive ductal BC. The majority of patients (84.7%) had a HER2 score of 3+ in the immunohistochemistry test. In total, 14 samples (23.7%) were analyzed by fluorescence in situ hybridization (FISH), and 12 (20.3%) were HER2-positive (Table 2).

Adjuvant Treatment

The majority of participants (74.6%) received adjuvant treatment with trastuzumab-dkst only, 18.6% received trastuzumab-dkst in combination with pertuzumab, and two patients (3.4%) received reference trastuzumab (for 8 and 20 cycles each) but switched to biosimilar trastuzumab-dkst. Additionally, two patients

Table 1 Patients' characteristics and medical history

Characteristic	Patients, *n* (%)
Age, mean (SD), years	51.7 (± 12.9)
Race	
White	35 (59.3%)
Pardo	20 (33.9%)
Yellow	2 (3.4%)
Black	2 (3.4%)
Reproductive status	
Postmenopause	31 (52.5%)
Premenopause	23 (39.0%)
Perimenopause	4 (6.8%)
Unknown	1 (1.7%)
Pre-existing medical condition	
Systemic arterial hypertension	16 (27.1%)
Diabetes	8 (13.6%)
Obesity	13 (22.0%)
Dyslipidemia	12 (20.3%)
Neoadjuvant chemotherapy	
No	37 (62.7%)
Yes	22 (37.3%)
Taxane	10 (45.5%)
Anthracycline + taxane	12 (54.5%)
Neoadjuvant anti-HER2 therapy	
No	37 (62.7%)
Yes	22 (37.3%)
Trastuzumab-dkst only	4 (18.2%)
Trastuzumab-dkst + pertuzumab	17 (77.3%)
Reference trastuzumab	1 (4.5%)

SD standard deviation

Table 2 Surgical and histopathological features

Characteristic	Patients, *n* (%)
Histological type	
Ductal	58 (98.3%)
Special histologies	1 (1.7%)
Type of test for HER2	
IHC report available	59 (100.0%)
IHC positivity grade 3+	50 (84.7%)
FISH test	14 (23.7%)
Positive FISH test	12 (20.3%)
Hormone receptor positive	44 (74.6%)
ER+	40 (67.8%)
PR+	33 (55.9%)
Diameter of the first target lesion	
0–2 cm	41 (69.5%)
> 2–5 cm	16 (27.1%)
> 5 cm	2 (3.4%)
Lymph nodes resected	
0	4 (6.8%)
1–3	27 (45.8%)
4–10	20 (33.9%)
> 10	8 (13.6%)
Lymph nodes affected	
0	47 (79.7%)
1–3	9 (15.3%)
4–10	2 (3.4%)
> 10	1 (1.7%)

ER estrogen receptor, *IHC* immunohistochemistry, *PR* progesterone receptor

(3.4%) used both therapy regimens during the cycles of treatment (trastuzumab-dkst only and trastuzumab-dkst + pertuzumab; Table 3). Overall, the duration of adjuvant anti-HER2 therapy was 10.2 ± 2.2 months, ranging from 5.8 to 13.9 months. This time corresponds to, on average, 14 ± 3.2 cycles of 21 days. The maximum number of treatment cycles was 20.

The shorter period of adjuvant trastuzumab therapy than the recommended 12 months from

Table 3 Therapy regimens

Characteristics, *n* (%)	**FAS (*N* = 59)**
Patients treated with adjuvant anti-HER2 therapy in adjuvance, *n* (%)	
Yes	59 (100.0%)
Number of valid observations	59 (100.0%)
Adjuvant anti-HER2 therapy, *n* (%)	
Trastuzumab-dkst only	44 (74.6%)
Trastuzumab-dkst + pertuzumab	11 (18.6%)
Trastuzumab-dkst + pertuzumab and trastuzumab only	2 (3.4%)
Reference trastuzumab previously and trastuzumab-dkst in the study	2 (3.4%)
Total participants	59 (100.0%)

FAS full analysis set

protocols is not due to early discontinuation, but to the fact that some patients had previously received trastuzumab in the neoadjuvant setting. Those patients had adjuvant treatment for a number of cycles sufficient to achieve an adequate time with this therapy, considering both neoadjuvant and adjuvant.

In all, 36 patients received adjuvant chemotherapy (61.0%). From these, 28 were treated with taxane (77.8%), 7 with anthracycline + taxane (19.4%), and 1 with anthracycline only (2.8%). The mean duration of adjuvant chemotherapy was 3.3 ± 1.2 months (range 1.2–6.0 months), corresponding to a mean of 4.0 ± 1.7 cycles.

Adjuvant endocrine therapy was used by 62.7% of the participants, with a mean duration of 7.8 ± 4.9 months—among them, 30.5% used an isolated aromatase inhibitor, 27.1% isolated tamoxifen, 6.8% ovarian suppression therapy associated with the aromatase inhibitor, and 3.4% ovarian suppression associated with tamoxifen. Three participants used more than one type of adjuvant endocrine therapy.

Effectiveness Assessments

Median overall follow-up was 31.7 months, with 59% of patients achieving at least 30 months of follow-up (minimum 14.2 months). At the 24-month follow-up as well as at the median follow-up (31.7 months), the IDFS rate was 94.5% (95% CI 83.9–98.2%). Since only three patients had disease recurrence, the median IDFS was not reached (Fig. 1). All these three patients had distant metastasis, and recurrence was identified at 13.0 months, 15.1 months, and 23.9 months (mean 17.3 ± 5.8 months). The OS rate was 100% at the last assessment; therefore, median OS was still not reached at the database lock of this analysis.

Safety Analysis

Regarding ECOG performance status, on the days of trastuzumab-dkst administration, 63.8% of the participants were "0—fully active" and 34.0% reported "1—restricted rigorous physical activity." Only one participant had ECOG "2—able to carry out all self-care but unable to carry out any work activities" in most treatment cycles.

Among all participants, 78.0% (46/59) experienced an AE of any intensity. Of these, 67.8% (40/59) occurred during monotherapy with trastuzumab-dkst, and 14.7% (5/34) during combined therapy with trastuzumab-dkst and chemotherapy. Details on the seriousness, intensity, and relationship to the study drug are presented in Table 4. Of the four serious AEs, two

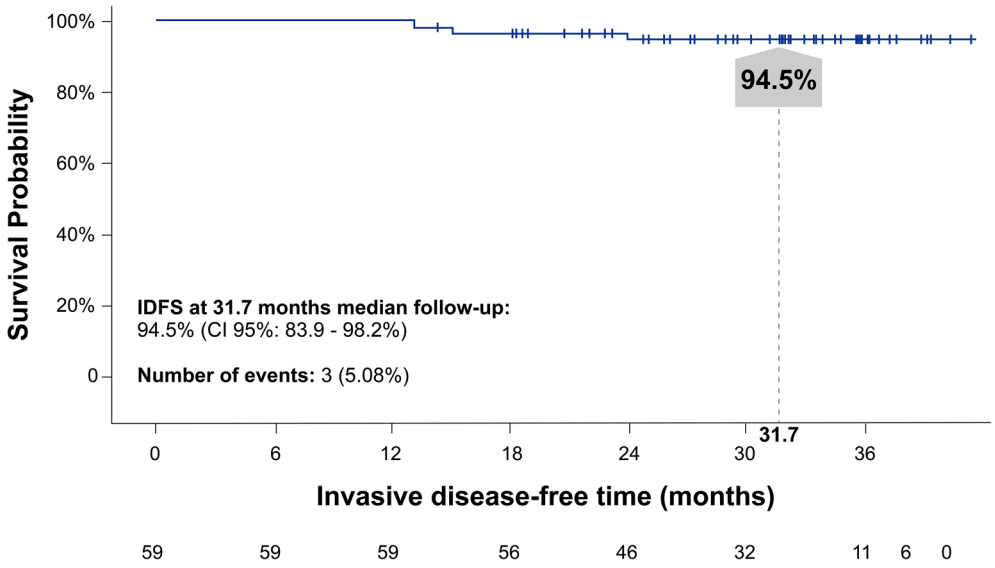

Fig. 1 Kaplan–Meier plot of invasive disease-free survival probability at the final assessment of patients treated with trastuzumab-dkst. The number of patients at risk is displayed at the bottom of the figure. *IDFS* invasive disease-free survival

occurred during treatment with trastuzumab-dkst, and two after treatment completion; these are detailed in Table 5.

Only two (3.38%) patients experienced an infusion reaction, one during cycle 6 and the other during cycle 7. AEs occurring in more than 10% of patients are detailed in Table 6, categorized by system organ class.

A reduction in LVEF of at least 10% was observed in 16.9% of participants. None of the patients had an LVEF below 50%. Two participants (3.4%) had their trastuzumab-dkst dose reduced during the study. There was no treatment interruption among participants of this study.

DISCUSSION

This ongoing RWE study on adjuvant trastuzumab-dkst for early-stage breast cancer (EBC) provides complementary insights to those offered by the HERITAGE study, which focused on metastatic HER2-positive BC. Our data feature a longer median follow-up period of over 30 months and include a diverse patient population in terms of age, ethnicity, reproductive status, comorbidity profiles, treatment regimens, and prior neoadjuvant therapies, enhancing the generalizability of the findings. Notably, 33.9% of our cohort consists of Pardo (mixed ethnic) individuals, underscoring the study's representation of a group historically known to have poorer BC outcomes in Brazil [20].

The observed effectiveness, safety, and tolerability of trastuzumab-dkst in our study align with prior data. We reported a 100% OS rate and a 94.5% IDFS rate at 31.7 months of follow-up. The median IDFS was not reached due to low recurrence rates, with only three patients experiencing disease recurrence. These results resonate with the 2-year outcomes of the HERA study, a phase 3 open-label RCT that assessed reference trastuzumab (Herceptin®, Roche Pharmaceutical) as adjuvant treatment for HER2-positive EBC, reporting a 2-year OS rate of 92.4% and a disease-free survival (DFS) rate of 80.6% [22]. Although our findings suggest potentially better outcomes compared with the HERA study, it is important to emphasize that we are reporting preliminary results from an ongoing study. Additionally, our study's IDFS endpoint specifically targets invasive malignancies, while the HERA study's DFS endpoint includes new in situ BC [18, 22].

Table 4 Adverse events by seriousness, severity, and relationship to study drug

n (%)	During adjuvant trastuzumab-dkst therapy (*n* = 59)	After treatment conclusion (*n* = 59)
Serious AEs	2 (3.4%)	2 (3.4%)
Severity of AEs		
Grade 1	30 (50.8%)	14 (23.7%)
Grade 2	20 (33.9%)	6 (10.2%)
Grade 3	1 (1.7%)	2 (3.4%)
Grade 4	1 (1.7%)	0 (0%)
Grade 5	0 (0%)	0 (0%)
Relation to study treatment		
Definite	1 (1.7%)	0 (0%)
Probable	6 (10.2%)	0 (0%)
Possible	7 (11.9%)	1 (1.7%)
Improbable/uncertain	34 (57.6%)	16 (27.1%)
Conditional/unclassified	1 (1.7%)	0 (0%)
Unaccessible/non-classifiable	3 (5.1%)	0 (0%)

AE adverse event

Table 5 Characteristics of serious adverse events

	AE recovery status	Relationship to study medication
Papillary thyroid cancer	Recovering	Improbable/uncertain
Hypertension	Fully recovered	Possible
Hypoglycemia	Fully recovered	Not available/not classified
Diarrhea	Unchanged	Possible

AE adverse event

The HERA study's extended follow-up of up to 11 years revealed a DFS rate of 69% and an OS rate of 79% [16]. Given the demonstrated therapeutic equivalence of trastuzumab-dkst [15], it is reasonable to anticipate that patients treated with this anti-HER2 biosimilar will experience comparable long-term benefits. Other studies with the reference trastuzumab, such as NSABP B-31, NCCTG N9831, and the BCIRG-006 trials, also demonstrated similar OS and DFS findings [23, 24].

Regarding distant recurrences, both our study and the HERA study reported low percentages at the 2-year follow-up mark. In our cohort, 5.1% (3 out of 59) of patients experienced a distant recurrence at intervals of 13.0, 15.1, and 23.9 months, respectively. The HERA study, in turn, observed a 5.0% distant recurrence rate

Table 6 Number of adverse events by system organ classes

System organ class	Total AEs *n* (%)	During adjuvant trastuzumab-dkst therapy, *n* (%)
Musculoskeletal and connective tissue disorders	22 (37.3%)	12 (20.3%)
General disorders and administration site conditions	16 (27.1%)	11 (18.6%)
Gastrointestinal disorders	14 (23.7%)	11 (18.6%)
Infections and infestations	13 (22.0%)	9 (15.3%)
Nervous system disorders	13 (22.0%)	8 (13.6%)
Metabolism and nutrition disorders	8 (13.6%)	4 (6.8%)
Skin and subcutaneous tissue disorders	8 (13.6%)	6 (10.2%)
Psychiatric disorders	7 (11.9%)	4 (6.8%)
Reproductive system and breast disorders	6 (10.2%)	3 (5.1%)

AE adverse event

within the first year, which increased to 9.0% by the end of the second year [15, 22].

The AEs observed with trastuzumab-dkst in our study align with those reported with other biosimilar or reference trastuzumab treatments [15, 21, 25, 26]. The incidence of serious AEs in this study (6.8%) was comparable to that reported in the HERA study (9.0%) [22]. However, for grade 3 or 4 AEs, the HERA study observed them in 18% of patients after 1 year and 22% after 2 years [18]. In contrast, in our study, only 3.4% of patients experienced grade 3 or 4 AEs during treatment, and the same percentage (3.4%) was observed post-treatment. Furthermore, 67.8% of AEs in our study were considered unrelated or likely unrelated to the treatment, with no patients withdrawing due to AEs. In the HERA trial, 11% of patients discontinued treatment due to AEs, including 5% due to cardiac events [26].

Previous studies have shown that 4.5% of patients treated with trastuzumab-dkst for metastatic BC experienced LVEF values below 50% at least once [21]. In our study, while 16.9% of patients experienced a decrease in LVEF of ≥ 10%, none had LVEF values drop below 50%. In the HERA study, 3% of patients presented a confirmed significant LVEF drop at the 2-year follow-up. Notably, during the extended evaluation period of up to 10 years, the HERA study did not observe new safety concerns, specifically no late cardiac issues, even as the patient cohort aged over a decade. Most of the cardiac events in the HERA study occurred during the treatment phase and were predominantly reversible [15, 16]. Therefore, our findings suggest that trastuzumab-dkst does not compromise cardiac function or the risk of cardiac events any differently than the reference trastuzumab.

The low incidence of acute infusional reactions in our study (3.38%) underscores trastuzumab-dkst's tolerability in a real-world setting, compared with a 6.9% incidence in the phase 3 HERITAGE study [21].

Importantly, real-world data, such as that from our study, enriche our understanding of how medications perform outside the controlled conditions of clinical trials. It provides comprehensive insights into treatment effectiveness and clinical applicability across diverse patient populations, including those with conditions such as obesity and hypertension [27].

The evidence supports biosimilar monoclonal antibodies as cost-reducing options in oncology, potentially improving patient access to these important treatments without a detrimental effect on efficacy or safety [28]. However, challenges in biosimilar adoption remain,

largely due to gaps in knowledge about biosimilar development, equivalence, regulatory requirements for their approval, and concerns related to their safety and efficacy [11]. By demonstrating these attributes, our findings contribute to increasing confidence in the use of biosimilars and add valuable evidence toward the broader acceptance and implementation of biosimilars in clinical settings, reinforcing their role in reducing oncology treatment costs while maintaining high standards of care [28].

This research builds upon the findings of the HERITAGE phase 3 trial, expanding trastuzumab-dkst therapeutic equivalence data beyond metastatic BC settings [14, 21].

Lastly, the recruitment from all five Brazilian regions enriches the diversity of our study population, broadening the applicability of our findings to various medical conditions and patient profiles. However, the limited sample size is a constraint of our analysis. Future analysis with our complete and larger cohort will further solidify these findings, thereby enhancing the generalizability of our conclusions.

CONCLUSIONS

Our study bolsters the existing pivotal data concerning the biosimilar trastuzumab-dkst, underscoring its real-world efficacy and safety in the adjuvant treatment of early HER2-positive BC. The comprehensive long-term efficacy and safety data we provide further establish trastuzumab-dkst as a cost-saving alternative in oncological care. These findings carry important implications for enhancing patient access to essential therapies and optimizing the efficiency of healthcare resource utilization.

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Author Contributions. The study design was performed by Debora Gagliato, Érida Magaton, Natália Brito, Ana Carolina Cardoso, and Vivienne Castilho. Patient material preparation and data collection were performed by Debora Gagliato, Tomás Reinert, Cláudio Rocha, Monique Tavares, Sâmio Pimentel, William Fuzita, Márcia Araújo, Danielli Matias, Sabina Aleixo, and Bruno França. Analysis and interpretation of data were performed by Debora Gagliato, Natália Brito and Ana Carolina Cardoso. All authors participated in writing and/or reviewing the manuscript and approved the final version.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Conflict of Interest. Debora Gagliato reports receiving consulting honoraries from Libbs Farmacêutica, AstraZeneca, Daichii-Sankyo, Lilly, Novartis, Gilead, and Roche. Tomás Reinert reports receiving consulting honoraries from AstraZeneca, Daichii-Sankyo, Lilly, Novartis, MSD, and Pfizer; speaker honoraries from AstraZeneca, Daichii-Sankyo, Lilly, Novartis, MSD, Pfizer, and Libbs Farmacêutica; and research funding from AstraZeneca and Libbs Farmacêutica. William Fuzita reported having received honoraries for participation in clinical trials in the name of Instituto Sensumed de Ensino e Pesquisa—Ruy França. Danielli Matias declared receiving speaker honoraries from MSD, Janssen, AstraZeneca, and BMS; manuscript honoraries from MSD and Libbs Farmacêutica; consultory honoraries from MSD, Daichii-Sankyo, and AstraZeneca; event supporting fees from Janssen, MSD, and AstraZeneca; being a member of committees in Grupo Brasileiro de Oncologia Torácica (GBOT) and Sociedade Brasileira de Oncologia Clínica (SBOC). Cláudio Rocha, Monique Tavares, Sâmio Pimentel,

Sabina Aleixo, Marcia Araujo and Bruno França declared that they have no conflicts of interest. Érida Magaton, Natália Brito, Ana Carolina Cardoso, and Vivienne Castilho report being current full-time employees of Libbs Farmacêutica.

Ethical Approval. This study was conducted in accordance with Good Clinical Practice Guidelines and the provisions of the Declaration of Helsinki and its later amendments. Protocol approval was obtained at Fundação Antônio Prudente—A.C. Camargo Cancer Center number 5432 (CAAE: 11576919.0.1001.5432) and from an independent ethics committee at each site. All participants signed informed consent.

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