Jornal de Assistência Farmacêutica e Farmacoeconomia
v.10, n.2, 2025.
Original Article

Interchangeability of Trastuzumab biosimilars in the neoadjuvant treatment of breast cancer: A real-life study

Intercambialidade dos biossimilares do Trastuzumabe no tratamento neoadjuvante do câncer de mama: Um estudo de vida real

Ana Paula Prestes[1], Monica Cristina Cambrussi[2], Ana Claudia Machado Marra[3], Isabela Marquezini Rovel[2], Marcela Bechara Carneiro[2] João Soares Nunes[2]

[1]Unimed General Hospital, Ponta Grossa, Paraná, Brazil.
[2]Erasto Gaertner Hospital, Curitiba, Paraná, Brazil.
[1]Oncoclínicas Group, Curitiba, Paraná, Brazil.

Corresponding author: Ana Paula Prestes. Unimed General Hospital, R. Carlos Osternack, 144 - Estrela, Ponta Grossa, Paraná, Brazil. Email: bidiprestes@gmail.com

How to cite: Cambrussi MC, Prestes AP, Machado Marra AC, Marquezini Rovel I, Bechara Carneiro M, Soares Nunes J. Interchangeability of Trastuzumab biosimilars in the neoadjuvant treatment of breast cancer: A real-life study. JAFF [Internet]. June 3, 2025. https://doi.org/10.22563/2525-7323.2025.v10.e00173e

Received: October 29, 2025

Accepted for publication: April 9, 2025

ABSTRACT

Introduction: Trastuzumab (Trt) is incorporated into Brazil's Public Health System (SUS) for the first-line treatment of HER 2 - positive breast cancer (CaM). The interchangeability (IC) between a comparator product and a biosimilar (BS) is a controversial topic. Post-marketing studies are needed to ensure safety and efficacy in IC situations. **Objective:** To evaluate whether IC between different manufacturers of Trt BS interferes with the rate of pathological complete response (PCR) in the neoadjuvant treatment of HER 2 – positive CaM. **Methods:** The clinical data of patients diagnosed with CaM, HER 2 – positive, clinical stage III, between 2020 and 2022 were reviewed. These patients received neoadjuvant treatment based on chemotherapy plus Trt, via SUS at an Oncology Hospital located in southern Brazil. **Results:** Between 2020 and 2022, SUS made 4 different Trt manufacturers available. one hundred thirty-eight (138) patients were eligible for analysis. Seventy eight (78) patients received only one type of Trt compound (Non-interchangeability Group – GNIC) and 60 patients received at least 2 different Trt compounds (Interchangeability Group – GCI). Both groups were clinically comparable (age, histological profile, tumor size and lymph node staging and axillary). The IC rate over time was 11%, 53%, and 33% in 2020, 2021, and 2022, respectively. The PCR was 33.33% in GNIC versus 33.33% in GCI. Both groups were comparable in terms of incidence of myelotoxicity, infusion reactions and cardiotoxicity. **Conclusion:** The present study demonstrated that the IC between BS of Trt did not interfere in a statistically significant way in the RPC.

Keywords: Trastuzumab; Biosimilars; Interchangeability.

RESUMO

Introdução: Trastuzumabe (Trt) está incorporado no SUS para o tratamento de primeira linha do câncer de mama (CaM) HER 2 - positivo. A intercambialidade (IC) entre um produto comparador pelo biossimilar (BS) é um tema controverso. Estudos pós-comercialização são necessários para garantir a segurança e eficácia em situações de IC. **Objetivo:** Avaliar se a IC entre diferentes fabricantes de BS do Trt interfere na taxa de resposta patológica completa (RPC) no tratamento neoadjuvante do CaM HER 2 – positivo. **Métodos:** Foram revisados os dados clínicos de pacientes diagnosticadas com CaM, HER 2 – positivo, estadiamento clínico III, entre 2020 a 2022. Estas pacientes receberam tratamento neoadjuvante baseado em quimioterapia mais Trt, via SUS em um Hospital Oncológico localizado no sul do Brasil. **Resultados:** Entre 2020 e 2022 o SUS disponibilizou 4 diferentes fabricantes do Trt. Centro e trinta e oito (138) pacientes foram elegíveis para análise. Setenta e oito (78) pacientes receberam apenas um tipo de composto do Trt (Grupo não intercambialidade – GNIC) e 60 pacientes receberam pelo menos 2 compostos diferentes do Trt (Grupo de intercambialidade - GCI). Ambos os grupos foram clinicamente comparáveis (idade, perfil histológico, tamanho do tumor e estadiamento dos gânglios linfáticos e axilares). A taxa de IC ao longo do tempo foi de 11%, 53% e 33% em 2020, 2021 e 2022, respectivamente. A RPC foi de 33,33% no GNIC versus 33,33% no GCI. Ambos os grupos foram comparáveis em termos de incidência de mielotoxicidade, reações infusionais e cardiotoxicidade. **Conclusão:** O presente estudo demonstrou que a IC entre BS do Trt não interferiu de forma estatisticamente significativa na RPC.

Palavras-chave: Trastuzumabe; Biossimilares; Intercambialidade.

Introduction

in 2020, the Brazilian Health Regulatory Agency (ANVISA) approved the registration of the first trastuzumab (Trt) biosimilar in Brazil. Currently, six trastuzumab biosimilars have been approved: Zedora® (Libbs), Herzuma® (Celltrion), Kanjinti® (Amgen), Ontruzant® (Samsung Bioepis), Trazimera® (Wyeth), and Bio-Manguinhos Trastuzumab® (Fundação Oswaldo Cruz).[1] The scientific evidence supporting the approval of trastuzumab biosimilars is robust. All six biosimilars approved by ANVISA demonstrated pharmacokinetic profiles equivalent to the reference product. Phase III clinical trials confirmed the safety and efficacy of these biopharmaceuticals compared to reference trastuzumab.[2]

According to the World Health Organization (WHO), interchangeability (IC) of medicines refers to the possibility of replacing one drug with another, where the same clinical effect is expected in a given therapeutic context. In the context of biosimilar use, interchangeability may involve the substitution of the reference product with the biosimilar (or vice versa).[3] IC between medicines can occur in two ways: (1) Switching - a medical practice where the prescriber decides to change one drug for another; (2) Substitution - the dispensing of one drug instead of another, provided the medicines are considered equivalent and interchangeable.[4]

The IC between a reference product and a biosimilar (or vice versa), or even the switch between biosimilars during treatment, remains a controversial topic among different regulatory agencies. In Brazil, ANVISA's position on biosimilar interchangeability was outlined in Clarification Note No. 003/2017.[5] ANVISA states that conducting specific studies to demonstrate interchangeability is not a mandatory requirement for the approval of a biosimilar. Furthermore, ANVISA argues that IC and substitution are concepts directly related to clinical practice, recommending that the evaluation and monitoring be performed by the prescribing physician, who should be responsible for selecting the most appropriate product for each case.[6,7]

Both the American Society of Clinical Oncology (ASCO) and the Brazilian Society of Clinical Oncology (SBOC) acknowledge the need for studies evaluating interchangeability. SBOC, in particular, recommends that patients should remain on the same biological product whenever possible. If continuity of treatment with the same medicine is not feasible, SBOC advises that interchangeability should occur only under specific conditions and with the approval of the responsible physician, without pharmaceutical intervention.[8,9]

A crucial scientific and clinical concern in the use of biosimilars lies in demonstrating safety and efficacy in IC scenarios. Theoretically, switching between biosimilar products could increase the risk of immunogenicity, as well as alter safety profiles and clinical effectiveness.[10]

Since 2012, the Unified Health System (SUS) has procured trastuzumab through the specialized component of pharmaceutical services. Following the National Policy for Cancer Prevention and Control (Ordinance GM/MS No. 874, May 16, 2013), the Ministry of Health (MS) centrally acquires trastuzumab using the Brazilian Common Denomination (DCB), which refers to the active pharmaceutical ingredient approved by ANVISA. After acquisition, the Ministry distributes trastuzumab every three months to High-Complexity Oncology Care Units (UNACON) and High-Complexity Oncology Centers (CACON) nationwide.[11,12]

With the incorporation of biosimilars into national and international markets, scientific societies and regulatory agencies have begun discussions regarding the feasibility, safety, and efficacy of interchangeability between biosimilars and their comparators. In 2018, three public hearings were held to debate the bidding and procurement processes, as well as interchangeability of biological products within SUS.[13] The Department of Health Logistics of the Ministry of Health evaluated the possibility of automatically replacing reference biological products with their biosimilars. At that time, no health technology assessment (HTA) studies were presented to support such decisions, with the discussions focusing mainly on economic aspects.

Interchangeability of biological products during oncology treatments – particularly among trastuzumab biosimilars – still lacks robust scientific evidence ensuring safety, efficacy, and immunogenicity, both when switching from the reference

product to a biosimilar and between biosimilars themselves. This gap must therefore be further investigated and regulated, mainly through bioequivalence clinical trials and real-world post-marketing studies.[14,15]

Objective

To evaluate whether interchangeability between different brands/manufacturers of trastuzumab biosimilars during neoadjuvant treatment of HER2-positive breast cancer interferes with the rate of pathological complete response.

Methods

Study setting, design, and randomization

This is a retrospective cohort study conducted at an oncology hospital in southern Brazil. The study population was retrospectively composed by reviewing medical records of patients referred to the institution between 2020 and 2022 with suspected and subsequently confirmed diagnosis of HER2-positive breast cancer.

Eligibility criteria included: age >18 years; histopathological and immunohistochemical confirmation of HER2-positive breast cancer; clinical stage III disease; and neoadjuvant therapeutic intent. Patients were randomized to undergo the AC-TH chemotherapy regimen.

The AC-TH regimen consists of four cycles of AC: doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2), each cycle every 21 days; followed by four cycles of TH: trastuzumab (loading dose 8 mg/kg, followed by maintenance dose 6 mg/kg) + docetaxel (75-100 mg/m^2) every 21 days for 4 cycles or paclitaxel (80 mg/m^2) weekly for 12 weeks.

After completing the four cycles of anthracycline-based chemotherapy, eligible patients were randomized into two historical cohorts: the non-interchangeability group (NICG) and the interchangeability group (ICG). Patients in the NICG cohort did not undergo interchangeability during neoadjuvant treatment, whereas patients in the ICG cohort underwent interchangeability between different trastuzumab biosimilar brands/manufacturers supplied by the Brazilian Ministry of Health (MS) during the four TH cycles.

To assess interchangeability situations, data from the Intravenous Admixture Center (CMIV) at the study institution were reviewed to determine the lot number and manufacturer of trastuzumab for each treatment cycle of each eligible patient.

Population characteristics, primary and secondary outcomes

Clinical data (age at diagnosis, clinical stage, histological profile) for each randomized patient were retrieved from medical records, covering from the first to the last clinical oncology visit. Immunohistochemical data analyzed included estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 protein, obtained from diagnostic biopsy samples.

The primary endpoint for assessing the effectiveness of AC-TH between NICG and ICG cohorts was the pathological complete response (pCR) rate. pCR was defined as the absence of invasive tumor cells upon microscopic evaluation of both the primary tumor (ypT0) and axilla (ypN0) after completion of neoadjuvant chemotherapy. This parameter was obtained through the histopathological analysis of the surgical specimen following breast surgery.

Secondary outcomes included: incidence of myelotoxicity, infusion-related reactions, and cardiac toxicity during the TH cycles. The incidence of myelotoxicity and infusion reactions was evaluated for each patient based on neutrophil counts across TH cycles and chart records of infusion-related adverse events. These events were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, developed by the National Cancer Institute (NCI) and National Institutes of Health (NIH).[16]

Cardiovascular safety was assessed retrospectively for each patient by reviewing electronic medical record data on left ventricular ejection fraction (LVEF) measured by echocardiography before and after neoadjuvant TH chemotherapy. A cardiac safety adverse event (EDCar) was defined as any echocardiographic or clinical change justifying early suspension or delay of TH cycle administration.[1]

Statistical analysis

Data were tabulated and subjected to descriptive analysis, including frequencies, measures of central tendency, means, standard deviations, quartiles, and frequency distribution, using Microsoft Office Excel 2010® (and updated versions). Inferential statistical analyses were performed using GraphPad Prism version 9.0. Primary and secondary outcomes were compared between historical cohorts using Pearson's chi-square test or Fisher's exact test, as appropriate.

The study was approved by the Institutional Research Ethics Committee (CAAE: 75766923.8.0000.0098).

Results

Study population data

A total of 138 patients were eligible for analysis (Table 1). Seventy-eight patients received only one type of trastuzumab formulation (NICG), while 60 patients received at least two different trastuzumab formulations during treatment (ICG). Both groups were comparable in terms of clinical characteristics, including age, tumor size, histological profile, and axillary/lymph node staging

Interchangeability rate

Between January 2020 and December 2022, the Brazilian Unified Health System (SUS) supplied three trastuzumab biosimilars - ABP 980 (Amgen), CT-P6 (Celltrion), SB3 (Samsung) - in addition to the reference trastuzumab (Roche). The chemotherapy regimen consisted of cyclophosphamide + doxorubicin every 21 days for 4 cycles, followed by a taxane (docetaxel every 21 days or weekly paclitaxel) combined with trastuzumab for 4 cycles.

The distribution between the use of docetaxel and paclitaxel among NICG and ICG groups was not statistically significant ($p > 0.05$). In the NICG cohort, 33.33% (26/78) received paclitaxel, compared to 31.67% (19/60) in the ICG group. Conversely, 66.67% (52/78) of NICG patients and 68.33% (41/60) of ICG patients received docetaxel.

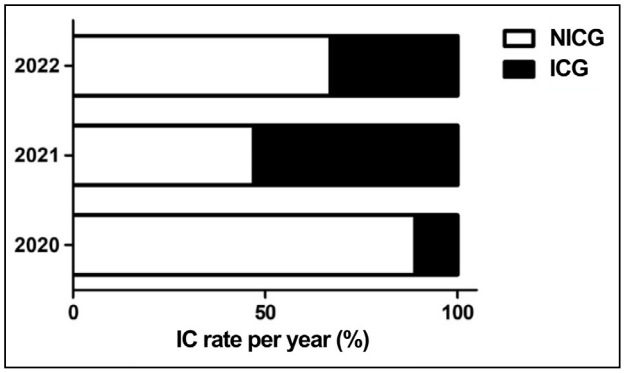
The interchangeability (IC) rates over time were 11.00% in 2020, 53.00% in 2021, and 33.00% in 2022 (Figure 1).

Table 1. Study population characteristics

Characteristics	NICG (n = 78)	ICG (n = 60)
Median age, range	52 (31 - 73)	50 (28 - 72)
Histological profile, n (%)		
IDC[a]	73 (93.59)	57 (95.00)
ILC[b]	3 (3.85)	0 (0.00)
Mixed[c]	2 (2.56)	3 (5.00)
ER Status[d], n (%)		
Positive	57 (73.08)	42 (70.00)
Negative	21 (26.92)	18 (30.00)
PR Status[e], n (%)		
Positive	43 (55.13)	34 (56.67)
Negative	35 (44.87)	26 (43.33)
Subtype, n (%)		
HR+/HER2+[f]	58 (74.36)	42 (70.00)
HR-/HER2+[g]	20 (25.64)	18 (30.00)
Ki67, n (%)		
< 14	7 (8.97)	5 (8.33)
> 14	71 (91.03)	55 (91.67)
cT[h], n (%)		
1 ou 2	67 (85.90)	25 (41.67)
3	11 (14.10)	35 (58.33)
cN[i], n (%)		
Positive	71 (91.03)	58 (96.67)
Negative	7 (8.97)	2 (3.33)

Legend: (a) IDC - Invasive ductal carcinoma; (b) ILC - Invasive lobular carcinoma; (c) Mixed - Other histological types including micropapillary, apocrine, mucinous; (d) ER - Estrogen receptor; (e) PR - Progesterone receptor; (f) HR+/HER2+ - Estrogen or progesterone receptor positive / human epidermal growth factor receptor 2 positive; (g) HR-/HER2+ - Estrogen or progesterone receptor negative / human epidermal growth factor receptor 2 positive; (h) cT - Tumor size (mm); (i) cN - Number of affected lymph nodes.
Source: Elaborated by the authors.

Figure 1. Interchangeability rate between 2020 and 2022.



Source: Elaborated by the authors.

Pathological complete response rate between NICG and ICG cohorts

After completion of neoadjuvant AC-TH chemotherapy, all randomized patients underwent breast surgery. Table 2 presents the distribution of breast surgery types in both cohorts. Conservative surgery was performed in 66.67% (52/78) of NICG patients and 56.67% (34/60) of ICG patients. No statistically significant difference in breast-conserving surgery rates was found ($p > 0.05$).

Table 2. Distribution of breast surgery type and breast-conserving surgery rate

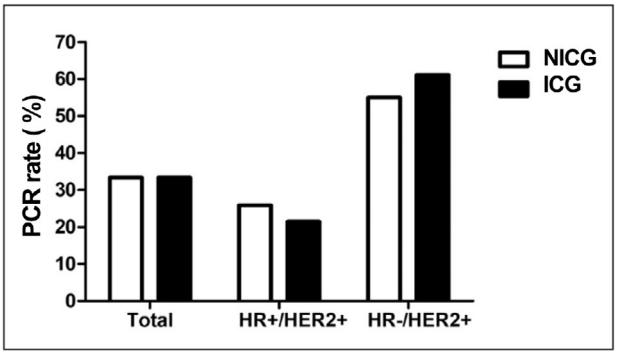
Type of surgery	NICG, n (%)	ICG, n (%)
Mastectomy	26 (33.33)	22 (36.67)
Quadrantectomy	52 (66.67)	34 (56.67)
Others[(a)]	0 (0.00)	4 (6.67)
Breast-conserving surgery rate	**52 (66.67)**	**34 (56.67)**

Source: Elaborated by the authors.

Histopathological analysis of breast tissue after oncologic surgery showed no statistically significant difference in pathological complete response (pCR) between cohorts (Figure 2). pCR was achieved by 33.33% (26/78) of NICG patients and 33.33% (20/60) of ICG patients.

Among HR+/HER2+ patients, pCR was 25.86% (15/58) in NICG and 21.43% (9/42) in ICG ($p > 0.05$). For HR-/HER2+ patients, pCR was 55.00% (11/20) in NICG and 61.11% (11/18) in ICG ($p > 0.05$).

Figure 2. PCR rate between NICG and ICG cohorts.



NICG	26/78 (33.33%)	15/58 (25.86%)	11/20 (55.00%)
ICG	20/60 (33.33%)	9/42 (21.43%)	11/18 (61.11%)

Source: Elaborated by the authors.

Adverse event rates between NICG and ICG groups

The evaluation of the incidence of myelotoxicity after TH cycles showed no statistically significant difference between the two historical cohorts (Table 3). Results demonstrated that 8.97% (7/78) of patients in the NICG group and 6.67% (4/60) of patients in the ICG group experienced one or more myelotoxic events (neutrophil count below 1500 mm^3) during the TH cycles ($p > 0.05$). A total of 10 neutropenia events were recorded in the NICG cohort and 7 neutropenia events in the ICG cohort (Table 4). According to the CTCAE - version 5.0 classification, 40.00% (4/10) of neutropenia incidents in the NICG cohort were classified as Grade 2 (neutrophil count between 1000 - 1500 mm^3). For the ICG cohort, 42.85% (3/7) of neutropenia incidents were classified as Grade 3 (neutrophil count between 500 - 1000).

Table 3. Adverse event rates between NICG and ICG cohorts

Adverse event type	NICG	ICG
Incidence of myelotoxicity	7 (8.97%)	4 (5.13%)
Incidence of infusion reaction	5 (6.41%)	3 (5.00%)

Source: Elaborated by the authors.

The incidence of infusion reactions during the four TH cycles showed no statistically significant difference between the two historical cohorts (Table 3). Results demonstrated that 5.13% (4/78) of pa-

tients in the NICG cohort and 5.00% (3/60) of patients in the ICG cohort experienced one or more infusion reaction episodes. A total of 8 infusion reaction events were recorded in the NICG cohort and 5 episodes in the ICG cohort (Table 4). According to the CTCAE - version 5.0 classification, 62.50% (5/8) of infusion reactions in the NICG cohort and 66.67% (3/5) in the ICG cohort were classified as Grade 2 (requiring interruption of infusion or treatment; rapid response to symptomatic treatment).

Table 4. CTCAE - version 5.0 classification of myelotoxicity and infusion reaction incidents

Myelotoxicity incidence			Infusion reaction incidence		
Cohort	**NICG**	**ICG**	**Cohort**	**NICG**	**ICG**
Grade 1[(a)]	–	1	Grade 1[(e)]	1	–
Grade 2[(b)]	1	1	Grade 2[(f)]	5	2
Grade 3[(c)]	4	1	Grade 3[(g)]	2	1
Grade 4[(d)]	0	1	Grade 4[(h)]	–	–

Legend: (a) Neutrophils < 1500 mm^3; (b) Neutrophils between 1000 - 1500 mm^3; (c) Neutrophils between 500 - 1000 mm^3; (d) Neutrophils < 500 mm^3; (e) Mild and transient reaction; no need to interrupt infusion or intervene; (f) Infusion interruption or treatment discontinuation required; rapid response to symptomatic treatment; (g) Prolonged reaction; recurrence of symptoms after initial improvement; hospitalization required; (h) Fatal consequences; urgent intervention required.
Source: Elaborated by the authors

The evaluation of cardiovascular safety was based on the analysis of EDCar events defined as any echocardiographic or clinical alterations that justified early discontinuation or delay of applications during the TH antineoplastic cycle. Two EDCar episodes were observed in the NICG cohort and one in the ICG cohort, with no statistically significant difference between NICG versus ICG ($p > 0.05$). The three EDCar episodes in both cohorts resulted in treatment delays and subsequent definitive discontinuation of the neoadjuvant TH regimen.

Discussion

The interchangeability (IC) guidance developed by the U.S. Food and Drug Administration (FDA) recommends that, within the scope of a clinical study aimed at demonstrating the safety of IC practice, at least three switches between biosimilars per patient should be included over the established treatment period.19 The main elements of an ideal study related to this type of investigation include: adequate randomization; an appropriate control group; assessment of immunogenicity; and the proper choice of study endpoints. The follow-up period must also be sufficient to assess the impact of potential distortions in clinical pharmacokinetics and pharmacodynamics resulting from IC practice.20 Although retrospective in nature, the present study applies the parameters required by the FDA's IC guidance to investigate the post-marketing impact of IC with trastuzumab supplied by the Brazilian Ministry of Health (MS) between 2020 and 2022.

The accumulated experience over the last decade and the results of comparative studies completed to date have not demonstrated evidence of safety issues associated with IC between biosimilars. As of December 31, 2023, a total of 31 observational studies had been published, including 6,081 patients who underwent IC from one biosimilar to another of the same reference biologic. The majority of these studies evaluated infliximab, while a smaller number assessed adalimumab, rituximab, or etanercept.21 A systematic review conducted by Declerck et al. (2018) evaluated eight IC studies involving monoclonal antibodies, including rituximab and trastuzumab biosimilars. Among these, two studies related to oncological indications and six to the use of rituximab in rheumatoid arthritis.22

More recently, the phase 3 clinical trial known as the "LILAC Study" provided clinical safety and efficacy data for the biosimilar Kanjinti® (Amgen) versus reference trastuzumab in women with HER2-positive breast cancer.23 This double-blind, randomized, multinational, multicenter trial involved 827 women with early-stage HER2-positive breast cancer. Initially, patients received anthracycline-based chemotherapy and were subsequently randomized 1:1 to receive either Kanjinti® (Amgen) or reference trastuzumab as anti-HER2 therapy. After surgical resection of the breast tumor, patients were again randomized to continue adjuvant therapy with Kanjinti® (Amgen) or to switch to the reference trastuzumab, and vice versa.

The results of the LILAC Study demonstrat-

ed that safety and immunogenicity profiles were comparable among patients who underwent IC and those who did not undergo any switching during the adjuvant phase of treatment.24 In line with these findings, the present study is the first real-world analysis in a Brazilian setting to demonstrate that IC between trastuzumab biosimilars during neoadjuvant treatment of HER2-positive breast cancer does not impact the pathological complete response (pCR) rate. In this study, pCR was chosen as the primary endpoint because this pathological parameter is widely recognized as a surrogate marker for predicting long-term clinical benefits such as progression-free survival and overall survival. Thus, its use allows an objective evaluation of possible therapeutic discrepancies between the NICG and ICG historical cohorts.25

In the LILAC Study, the frequency, type, and severity of adverse events were comparable between treatment groups and consistent with the established safety profile of trastuzumab.23,24 The immunogenicity analysis showed that the incidence of anti-drug antibodies was low and similar in both treatment arms. In agreement, the present work demonstrates that IC between trastuzumab biosimilars, in this specific clinical setting and in a retrospective analysis, did not impact cardiac safety, the incidence of infusion-related reactions, or myelotoxicity associated with antineoplastic therapy. Additional prospective studies are warranted to further characterize immunogenicity profiles in IC scenarios involving trastuzumab biosimilars in the neoadjuvant treatment of HER2-positive breast cancer.

Although IC between biosimilars is globally accepted, its clinical practice has not been extensively evaluated in the context of oncology treatment.26 The Brazilian Ministry of Health (MS), the sole supplier of trastuzumab for patients treated under the Unified Health System (SUS), follows a procurement policy based on lowest cost, leading to constant changes in brands and manufacturers of biosimilars throughout treatment. In this context, Brazil has great potential to conduct large-scale prospective and retrospective multicenter IC studies in thousands of patients over the coming years, particularly addressing IC in oncology, including HER2-positive breast cancer.

Conclusions

The present study demonstrated that interchangeability between trastuzumab compounds does not significantly interfere with the pathological complete response (pCR) rate in the neoadjuvant treatment of HER2-positive breast cancer. In this analysis, the practice of interchangeability did not affect the frequency, type, or severity of adverse events related to myelotoxicity, cardiotoxicity, or infusion reactions. Additional studies addressing safety, toxicity, and immunogenicity in scenarios of trastuzumab compound interchangeability should be conducted in different clinical contexts. Multicenter strategies involving both retrospective and prospective evaluations have the potential to provide robust scientific evidence on the clinical impacts and safety of incorporating interchangeability practices among biosimilars.

Authors' Contributions
APP, MCC, MBC, JSN: Conception, investigation, formal analysis, review.
APP, ACMM, IMR, JSN: Methodology, investigation.
ACMM, IMR: Data curation.
APP, JSN: Administration, planning, and editing.
JSN: Supervision and validation.

Conflicts of Interest
The authors declare no conflicts of interest.

Funding
The research that originated the work submitted for publication was not funded.

Data Availability Statement
All underlying data are already available within the article.

Responsible editor
Lindemberg Assunção Costa.

Acknowledgments
The authors thank the Erasto Gaertner Hospital for fostering patient-centered oncology care based on Science, Humanism, and Compassion.

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