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Comprehensive Analysis of Comparison of Trastuzumab Reference with Biosimilars in the Treatment of HER2-Positive Breast Cancer: A Review

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Abstract: HER2-positive breast cancer is an aggressive subtype of breast cancer characterized by overexpression of the Human Epidermal Growth Factor Receptor-2 (HER2), which is associated with rapid tumor progression, higher metastasis rates, and poor prognosis. Trastuzumab has become one of the main targeted therapies for HER2-positive breast cancer and has significantly improved patient survival outcomes. However, the high cost of reference trastuzumab products such as Herceptin limits patient access, especially in developing countries. Therefore, trastuzumab biosimilars have emerged as more affordable therapeutic alternatives with comparable clinical performance. This review aimed to analyze and compare the efficacy, pharmacokinetic profile, safety, and cost-effectiveness of reference trastuzumab and trastuzumab biosimilars in the treatment of HER2-positive breast cancer. The method used was a systematic literature review of the PubMed and ScienceDirect databases, using keywords related to breast cancer, trastuzumab, and biosimilars. Studies published between 2014 and 2024 were included based on predetermined inclusion and exclusion criteria. The findings demonstrated that several biosimilars, including SB3 (Ontruzant), CT-P6 (Herzuma), PF-05280014 (Trazimera), ABP 980 (Kanjinti), and trastuzumab-dkst (Ogivri), exhibited equivalent efficacy to reference trastuzumab in terms of pathological complete response (pCR), progression-free survival (PFS), overall survival (OS), and disease-free survival (DFS). In addition, biosimilars showed pharmacokinetic, immunogenicity, and cardiac safety profiles comparable to those of the originator product. Biosimilars also provided significant economic advantages by reducing treatment costs and improving patient access to HER2-targeted therapy. In conclusion, trastuzumab biosimilars are effective, safe, and cost-efficient alternatives to reference trastuzumab for HER2-positive breast cancer management and may support more sustainable healthcare systems.

Keywords: Biosimilars; Breast Cancer; Trastuzumab.

Introduction

Breast cancer, also known as Carcinoma Mammae, is a type of malignant tumor (abnormal lump) that appears in the breast tissue. This tumor can develop in the milk glands, gland ducts, and supporting tissues of the breast (including the fatty tissue and connective tissue of the breast). In addition, this tumor may expand to other parts of the body, a process known as metastasis. The term "metastasis" refers to the spread of disease [1]. In addition, breast cancer is a pathological change in breast cells that grow abnormally, usually starting from the lobules (milk glands) or ducts that connect the lobules to the nipple [2]. This disease mostly affects women, with more than 1.5 million new cases each year.[3]. In 2022, Worldwide, 2.3 million women were diagnosed with breast cancer, and 670,000 lost their lives to the disease. This information comes from the World Health Organization. After reaching puberty, breast cancer can strike women of any age, and its prevalence could increase with time in any place on Earth [4]. In Indonesia, based on Globocan 2020 data, there were 68,858 new cases of breast cancer, which is 16.6% of the total new cases of cancer, and more than 22 thousand deaths occurred [5]. Multiple cellular functions are impacted by the HER2 oncogene. These functions include adhesion, motility, and HER2 receptor signalling. Excessive activation of this gene can increase breast cancer cell proliferation, leading to increased malignancy, further metastasis, and poor prognosis. Approximately 20 - 25% of breast cancers are HER2-positive [6].

One new development in the field of HER2-positive breast cancer treatment is the neoadjuvant use of monoclonal antibodies like trastuzumab for patients with early-stage disease [7]. Trastuzumab binds to the HER2 receptor, triggering antibody-dependent cytotoxicity and inhibiting signal transduction and new blood vessel formation, thereby enabling the immune system to fight cancer [6], [8]. The HER2-positive breast cancer patients who have had adjuvant, neoadjuvant, or metastatic treatment with this medicine have received approval from both the FDA and the EMA [6]. Trastuzumab plays a key role in neoadjuvant and adjuvant treatment. In neoadjuvant therapy, the pathological complete response (pCR) ratio was greater in patients with HER2-positive breast cancer who received trastuzumab in addition to chemotherapy [9]. Trastuzumab, a designed monoclonal antibody, aims to inhibit tumor development, halt cancer metastasis, and postpone disease progression by targeting the HER2 protein [10]. Trastuzumab reference, which refers to the original trastuzumab drug under the brand name herceptin, is used in the treatment of HER2-positive breast cancer [11], [12]. Given the high price of the reference

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trastuzumab, biosimilars offer a more competitive, economical alternative to other biologics for cancer treatment [13].

Biosimilars, which are a type of biological medicine, are very similar to the original authorized medicine in terms of their characteristics, but are not exact replicas. Standards, manufacturing processes, quality, security, innocence, and efficacy are all areas where these two are comparable [14]. To be approved by the FDA, a biosimilar must show that it is safe, pure, and as effective as the reference product, with no discernible variation in these areas [15]. Biosimilars are approved based on the aggregate of evidence indicating that the biological product is similar in structure, function, efficacy, and clinical safety to the reference product, and that it is as safe, pure, and effective as the reference product, with no discernible variation in clinically relevant variables [16]. Biosimilars can help reduce health care costs while still providing benefits equivalent to those of the original biologic. Biosimilar products offer levels of safety and efficacy comparable to those of their reference products, but at a more affordable price [17]. Biosimilar products are expected to compete on price with expensive chemical drugs, providing an opportunity to access cheaper biological drugs with similar benefits to the original product [14].

Although treatment with trastuzumab combined with chemotherapy has shown good results, Cancer can still spread and come back, even after metastatic breast cancer (BC) has progressed. Consequently, pertuzumab (Perjeta), another humanized antibody that targets HER2, was authorized for use in combination with trastuzumab for therapy in 2012 [9]. Based on the description above, this article aims to analyze the comparison of reference trastuzumab with biosimilar trastuzumab in the treatment of HER2-positive breast cancer.

Research Methods

The method used to compile this article review is a systematic review, conducted by searching relevant literature in online databases such as PubMed and ScienceDirect. The literature search was conducted using keywords such as "Breast Cancer", "Biosimilars," and "Trastuzumab". The literature used was published between 2014 and 2024, in Indonesian or English, and addressed topics relevant to the article's main discussion, such as breast cancer treatment and the development of biosimilars in cancer therapy. Literature that was not considered for review included journals published before 2014 or had no direct relevance to the main discussion topics, such as trastuzumab biosimilar therapy and breast cancer.

Table 1. Eligibility Criteria

Information	Inclusion	Exclusion
Population	Female patients with HER2-positive breast cancer at all stages of cancer	Studies conducted on animals, in vitro studies, in silico studies and patients with HER2-negative breast cancer.
Intervention	Using biosimilar trastuzumab as breast cancer therapy either in combination with other drugs or not.	Not using biosimilar trastuzumab as breast cancer therapy
Comparison	HER2-positive female patients who received reference trastuzumab either in combination with pertuzumab or not	Patients who did not receive treatment with trastuzumab reference
Outcome	Studies assessing differences between outcomes of therapy using reference and biosimilar trastuzumab	Studies that did not explicitly compare outcomes between reference and biosimilar trastuzumab

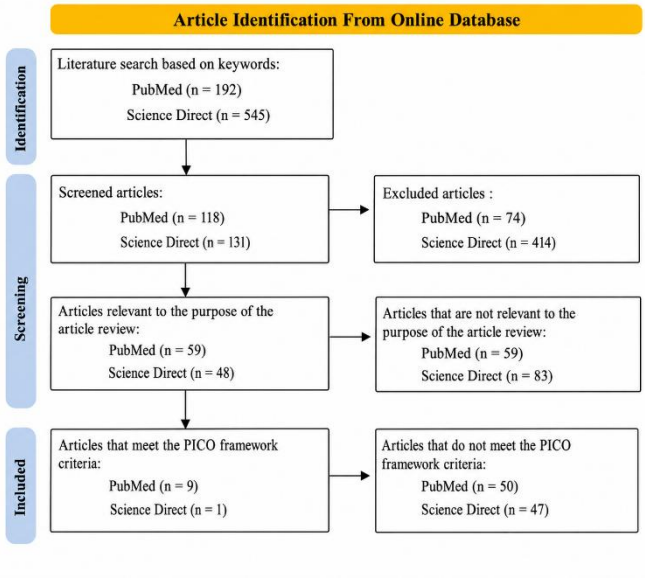

Figure 1. Search Strategy Flow

Results and Discussion

The diagram above shows the process of identifying and screening articles from online databases, which is carried out in several stages to ensure only relevant articles that meet the criteria are included in the article review. The first stage was the identification of articles using keywords in two databases, PubMed and ScienceDirect, yielding 192 articles from PubMed and 545 from ScienceDirect. Next, an initial screening was conducted to select articles worthy of further consideration. After the initial screening, 118 articles from PubMed and 131 from ScienceDirect were selected for the relevance stage, while 74 from PubMed and 414 from ScienceDirect were excluded because they did not meet the basic criteria. In the next stage, a selection was conducted to ensure the articles were relevant to the review's purpose. From this stage, 59 articles from PubMed and 48 from ScienceDirect were deemed relevant, while 59 from PubMed and 83 from ScienceDirect were considered irrelevant and excluded. The final stage was to ensure that the articles met the PICO criteria. From here, 4 articles from PubMed and 1 article from ScienceDirect were selected that met the final criteria, while 55 articles from PubMed and 47 articles from ScienceDirect did not meet the PICO criteria and were excluded.

Table 2. Research Results

Reference	Title	Drug	Results
[18]	Final overall survival analysis of the phase 3 HERITAGE study demonstrates equivalence of trastuzumab-dkst to trastuzumab in HER2-positive metastatic breast cancer	Trastuzumab-Dkst (Ogivri)	With a median OS of 35 months, the data showed that Ogivri was equally effective as the original trastuzumab, compared to 30.2 months on trastuzumab. Time to disease progression (PFS) was the same at 11.1 months.
[19]	Real-World Clinical Outcomes of Biosimilar Trastuzumab (CT-P6) in HER2-Positive Early-Stage and Metastatic Breast Cancer	CT-P6 (Herzuma)	The study results showed that CT-P6, a biosimilar of trastuzumab, had similar efficacy and risk-free rate in women diagnosed with HER2-positive breast cancer when contrasted with the gold standard trastuzumab (RTZ).
[20]	Emerging role of biosimilars: Focus on trastuzumab and metastatic human epidermal growth factor receptor 2-positive breast cancer	SB3 (Ontruzant)	When comparing SB3 (ontruzant) to the original trastuzumab, which demonstrated a CHR of 35.8% in HER2-positive breast cancer, the phase III clinical trial found that SB3 achieved a CHR of 45.8%.
[21]	Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer	PF-05280014 (Trazimera)	The results showed that PF-05280014 had PK parameters similar to those of its reference drug, with a comparable efficacy and safety profile.
[22]	Comparison of Biosimilar Trastuzumab ABP 980 with Reference Trastuzumab in Neoadjuvant Therapy for HER2-positive Breast Cancer – an Analysis of a Large University Breast Cancer Centre	ABP 980 (Kanjinti)	When it comes to treating HER2-positive breast cancer, the study's findings indicate that ABP 980 is a viable and secure alternative. The efficacy and safety profiles of both drugs are equivalent, though caution is warranted regarding the risk of cardiovascular side effects.
[23]	Real-World Study of Adjuvant Biosimilar Trastuzumab-dkst for HER2-Positive Breast Cancer Treatment in a Brazilian Population.	Trastuzumab-Dkst (Ogivri)	The results showed that trastuzumab-dkst is an effective therapy for early HER2-positive breast cancer, preventing disease progression (IDFS) and survival of 100%.
[24]	Six-Year Survival Outcomes for Patients with HER2-Positive Early Breast Cancer Treated with CT-P6 or Reference Trastuzumab: Observational Follow-Up Study of a Phase 3 Randomised Controlled Trial	CT-P6 (Herzuma)	The study results showed that CT-P6 was comparable to reference trastuzumab in terms of long-term efficacy for treating HER2-positive early breast cancer and was an effective alternative.
[25]	A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results	SB3 (Ontruzant)	The study results that SB3 demonstrated equivalent efficacy to the reference product trastuzumab (TRZ) in achieving breast pathological complete response (bPCR) rates after neoadjuvant therapy.
[26]	Long-Term Safety and Effectiveness of PF-05280014 (a Trastuzumab Biosimilar) Treatment in Patients with HER2-Positive Metastatic Breast Cancer: Updated Results of a Randomized, Double-Blind Study	PF-05280014 (Trazimera)	The study results indicate PF-05280014 is a safe and effective treatment option for metastatic HER2-positive breast cancer. There was no significant difference in effectiveness or safety compared with the reference trastuzumab.
[16]	Totality of Evidence Supporting the Use of ABP 980, a Trastuzumab Biosimilar: Practical Considerations	ABP 980 (Kanjinti)	The study results showed no clinical difference in efficacy between ABP 980 and the reference product trastuzumab (RP) with a similar safety profile between the two.

One of the leading causes of cancer-related mortality in females globally is breast cancer, a kind of malignancy that begins in the mammary glands [27]. The term "biosimilar" refers to a class of biological agents that are structurally and functionally identical to an existing product. Biosimilars are developed under strict standards, through different regulatory pathways than the original biologic and generic drugs with the aim of providing alternatives and expanding therapeutic and treatment options [16].

A study conducted by Rugo *et al*. (2021), found that trastuzumab-dkst was just as effective as trastuzumab reference in taking care of HER2-positive breast cancer. Trastuzumab-dkst had the same overall survival (OS) rate of 35.0 months as the trastuzumab reference, compared to 30.2 months. Ogivri is expected to prolong the lives of patients with metastatic HER2-positive breast cancer by a similar amount. Regarding other metrics of therapy success, such as progression-free survival (PFS) and overall response rate (ORR), no clinically meaningful differences were observed, confirming equivalence between the two [18]. Trastuzumab-dkst was effective in increasing invasive disease-free survival (IDFS) with an IDFS rate of 94.5% for 31.7 months. The results provide credence to the theory that trastuzumab-dkst can effectively halt the progression of HER2-positive breast cancer in its early stages. During the study, no patients died, resulting in an overall survival rate of 100% [23].

In a study conducted by Bae *et al*. (2021), when it came to obtaining a pathological complete response (pCR) in patients with early-stage breast cancer having neoadjuvant treatment, CT-P6 had a clinical response rate that was nearly identical to the reference trastuzumab. In addition, in the neoadjuvant setting and supportive care, CT-P6 was used in combination with pertuzumab, docetaxel, and carboplatin. This combination is the standard of care in HER2-positive cancer therapy and supports CT-P6's flexibility across various therapeutic regimens [19]. Meanwhile, comparing CT-P6 to trastuzumab showed that it matches trastuzumab's performance in terms of OS, DFS, and PFS. Clinical trials also showed that CT-P6 was as safe as trastuzumab with respect to heart-related adverse events and left ventricular ejection fraction (LVEF). This suggests that patients treated with CT-P6 experienced fewer serious adverse events than those treated with reference trastuzumab [24].

The SB3 (Ontruzant) Study demonstrated a superior safety profile, with no cases of symptomatic heart failure or other cardiac events during long-term follow-up in 367 patients. The higher event-free interval rate (91.9% with SB3 compared to 85.2% with reference trastuzumab) indicates that this biosimilar is not only safe but also offers potential additional benefits over trastuzumab. In addition, the complete histologic response (CHR) rate of 51.7% in SB3 was higher than that with reference trastuzumab (42.0%). In addition, in combination with adjuvant chemotherapy comprising cyclophosphamide, epirubicin, and paclitaxel, SB3 achieved a CHR rate of 56%, further strengthening its potential in combination therapy settings. This effectiveness is relevant to support its use in both early-stage breast cancer (EBC) and metastatic (MBC) [20]. The SB3 study demonstrated efficacy comparable to that of the reference product, trastuzumab, in the treatment of HER2-positive breast cancer [25]. Event-free survival (EFS) and overall survival (OS) rates were 92.2% and 99.8%, respectively, for SB3, compared with 91.6% and 98.9% for reference trastuzumab. In addition, achieving a significant breast pathological complete response (bPCR) supported the clinical efficacy of both therapies. In terms of safety, the incidence of treatment-related adverse events (TEAEs) was comparable between SB3 (97.5%) and reference trastuzumab (96.1%), with low and nearly identical rates of cardiotoxicity in both groups. In this study, SB3 was used in combination with neoadjuvant and adjuvant chemotherapy. Following surgery, patients underwent an additional 10 cycles of SB3 on top of the 8 rounds of chemotherapy (5-fluorouracil, docetaxel, epirubicin, and cyclophosphamide). In cases of HER2-positive breast cancer, this combination guarantees that SB3 is effective when used in conjunction with conventional chemotherapy [25].

Research conducted by Chen *et al*. (2019), reported that PF-05280014 has pharmacokinetic properties that are almost identical to those of the reference trastuzumab in HER2-positive breast cancer patients, and that PF-05280014 demonstrates the same level of efficacy and safety as the original trastuzumab. The combination of paclitaxel therapy in both groups is intended to reflect common clinical practice and does not affect the observed PK similarities, as the combination of trastuzumab and paclitaxel is often used to treat patients with HER2-positive metastatic breast cancer [21]. In addition, research conducted by Li *et al*. (2022), PF-05280014 showed comparable results with trastuzumab, with no significant differences in efficacy and safety. These results were supported by objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) between PF-05280014 and trastuzumab in the treatment of metastatic HER2-positive breast cancer. In addition, PF-05280014 had a safety profile similar to that of trastuzumab. More patients with HER2-positive breast cancer may be able to afford the medicine they need if PF-05280014, a biosimilar of the reference trastuzumab, becomes available. Patients with HER2-positive metastatic breast cancer often get paclitaxel in conjunction with other treatments [26].

In a study by Matovina et al. (2022), ABP 980, a biosimilar of trastuzumab, showed a pathological complete response (pCR) rate similar to that of the reference trastuzumab in both neoadjuvant and adjuvant therapy. In this study, patients who received ABP 980 had node-negative status, high-grade tumors and were more often receptor positive. In addition, most patients in the ABP 980 group received treatment using pertuzumab [22]. ABP 980 has efficacy and safety equivalent to the reference trastuzumab. With similar pathological complete response (pCR) rates between the two groups and side effect profiles, including cardiotoxicity and immunogenicity, also balanced without significant differences [16].

Efficacy of Biosimilar Trastuzumab in HER2-Positive Breast Cancer

Biosimilar trastuzumab has demonstrated comparable clinical efficacy to reference trastuzumab in the treatment of HER2-positive breast cancer. Several studies reported that biosimilar trastuzumab produced therapeutic responses and survival outcomes similar to those of the originator product. Comparable effectiveness between biosimilar trastuzumab and Herceptin indicates that biosimilars can maintain equivalent antitumor activity in breast cancer patients [28]. In addition, biosimilar trastuzumab demonstrated a safety

profile similar to that of reference trastuzumab, suggesting it can be safely administered in routine clinical practice. Therefore, trastuzumab biosimilars may serve as effective alternatives to the reference product for HER2-positive breast cancer therapy.

The efficacy of trastuzumab biosimilars has also been confirmed in real-world clinical settings. HLX02 demonstrated favorable efficacy and safety outcomes that were comparable with previous HLX02 studies [29]. These findings suggest that biosimilar trastuzumab can maintain consistent therapeutic performance in HER2-positive metastatic breast cancer patients. Furthermore, no clinically meaningful differences in treatment response were observed between HLX02 and the reference trastuzumab. The consistent efficacy results further support the clinical use of HLX02 as an alternative HER2-targeted therapy.

Another trastuzumab biosimilar that demonstrated promising efficacy is trastuzumab emtansine (T-DM1) biosimilar. The T-DM1 biosimilar demonstrated efficacy comparable to that of the innovator T-DM1, with a favorable safety profile and improved accessibility [30]. Comparable efficacy outcomes indicate that biosimilar T-DM1 can achieve antitumor effects similar to those of the originator product. In addition, improved accessibility may help increase patient access to HER2-targeted therapy, especially in countries with limited healthcare resources. Therefore, biosimilar T-DM1 may provide both clinical and economic benefits in the management of HER2-positive breast cancer.

Cost-effectiveness is considered a major advantage of trastuzumab biosimilars. Biosimilar formulations offer a cost-effective alternative and have demonstrated comparable efficacy and safety in metastatic HER2-positive breast cancer [31]. Lower treatment costs may help improve patient access to HER2-targeted therapy without reducing treatment quality. Moreover, biosimilars may reduce the financial burden on healthcare systems while maintaining therapeutic effectiveness. Consequently, biosimilar trastuzumab may contribute to the broader availability of targeted therapies for breast cancer patients.

The combination of trastuzumab biosimilars with chemotherapy has also demonstrated significant clinical benefits. In combination with chemotherapy, intravenous administration of both trastuzumab and its biosimilars improves overall survival (OS) and overall response rates (ORR) in patients with HER2-positive metastatic breast cancer [32]. Improvement in OS and ORR suggests that biosimilar trastuzumab can effectively enhance treatment response in metastatic disease. Combination therapy involving biosimilar trastuzumab may therefore serve as an effective therapeutic strategy in HER2-positive breast cancer treatment. These findings further strengthen the evidence supporting the therapeutic equivalence of trastuzumab biosimilars.

Several phase III studies have additionally demonstrated the equivalence of biosimilar trastuzumab in achieving pathological treatment responses. The efficacy of SB3 was equivalent to that of TRZ with respect to the risk ratio for breast pathological complete response (bpCR) [33]. Similar findings were also reported in studies that observed no differences in efficacy or adverse events between biosimilar trastuzumab and the reference product [34]. These results indicate that biosimilar trastuzumab can provide clinical benefits and tolerability similar to those of originator trastuzumab. Therefore, biosimilar trastuzumab may be considered a reliable alternative therapy for HER2-positive breast cancer patients.

The efficacy of trastuzumab biosimilars has also been demonstrated when combined with other HER2-targeted therapies such as pertuzumab. The combination of trastuzumab biosimilar HLX02, pertuzumab, and chemotherapy exhibited promising efficacy and a favorable safety profile in HER2-positive metastatic breast cancer patients [35]. Dual HER2 blockade using biosimilar trastuzumab may provide more effective disease control and improved therapeutic outcomes. In addition, the treatment regimen was generally well tolerated with manageable adverse effects during therapy administration. Overall, current evidence suggests that trastuzumab biosimilars demonstrate efficacy outcomes comparable to those of reference trastuzumab and may serve as effective therapeutic options in the management of HER2-positive breast cancer.

Pharmacokinetic and Safety Profile of Biosimilar Trastuzumab

Pharmacokinetic similarity is an important parameter in the development of biosimilar trastuzumab. Biosimilars are designed to demonstrate pharmacokinetic profiles comparable to those of the reference biologic product to ensure similar therapeutic performance. Several studies have shown that trastuzumab biosimilars exhibit pharmacokinetic profiles similar to those of the originator trastuzumab. In addition, biosimilars are considered highly similar to biologic reference products in terms of safety and efficacy outcomes. Pharmacokinetic comparability plays a major role in confirming biosimilarity between trastuzumab biosimilars and reference trastuzumab.

One important indicator of pharmacokinetic equivalence is the evaluation of serum concentration parameters such as AUC and Cmax. A study demonstrated that the 90% confidence intervals for AUC0-inf, AUC0-t, and Cmax ratios were within the predefined equivalence margin of 80% to 125% for all pairwise comparisons [36]. These findings indicate that the biosimilar product achieved pharmacokinetic equivalence with the reference trastuzumab. Similar serum concentration profiles suggest that both products may provide comparable therapeutic exposure in patients. As a result, biosimilar trastuzumab may deliver clinical effectiveness similar to that of the originator biologic.

Comparable pharmacokinetic profiles were also demonstrated by MYL-1401O biosimilar trastuzumab. MYL-1401O demonstrated pharmacokinetic bioequivalence to reference trastuzumab in clinical studies [37]. The study further showed that secondary pharmacokinetic parameters, such as elimination half-life and time to maximum concentration, were comparable between treatment groups. Similar pharmacokinetic characteristics indicate that MYL-1401O can achieve systemic exposure equivalent to that of trastuzumab. This evidence supports the potential use of MYL-1401O as a reliable biosimilar alternative for HER2-positive breast cancer treatment.

Another biosimilar that demonstrated comparable pharmacokinetic characteristics is CT-P6. The overall pharmacokinetic profile of trastuzumab was similar in both the CT-P6 and reference trastuzumab groups [38].

Comparable pharmacokinetic parameters between CT-P6 and trastuzumab further support the biosimilarity of the two products. In addition, no clinically meaningful differences in drug exposure or elimination were observed during treatment evaluation. These findings suggest that CT-P6 may provide outcomes and treatment consistency similar to those of reference trastuzumab.

The pharmacokinetic equivalence of biosimilar trastuzumab was also supported by geometric mean ratio analysis. A study reported that the geometric mean ratios for Cmax, AUC0-t, and AUCinf remained within acceptable bioequivalence ranges between the biosimilar and reference trastuzumab groups [39]. The results demonstrated that the biosimilar achieved systemic drug exposure comparable to that of the reference product. Similar pharmacokinetic behavior indicates that the biosimilar can maintain equivalent drug concentrations during therapy administration. In this regard, biosimilar trastuzumab may achieve efficacy and tolerability comparable to those of the reference product in HER2-positive breast cancer patients.

Safety profiles are another essential consideration in evaluating trastuzumab biosimilars. Clinical studies demonstrated that biosimilar trastuzumab can safely replace reference trastuzumab in HER2-positive cancer treatment without increasing adverse events [40]. Similar incidences of treatment-related adverse events and cardiotoxicity were reported between biosimilar and reference trastuzumab groups. Furthermore, no clinically significant decline in left ventricular ejection fraction (LVEF) was observed in most studies. These findings indicate that trastuzumab biosimilars have cardiac safety profiles comparable to those of the originator trastuzumab.

Additional evidence of pharmacokinetic similarity was also reported for the PF-05280014 biosimilar of trastuzumab. PF-05280014 and trastuzumab-EU demonstrated similar pharmacokinetic parameters and influential pharmacokinetic covariates in patients with HER2-positive metastatic breast cancer [41]. Similar pharmacokinetic profiles suggest that the biosimilar can maintain equivalent therapeutic drug exposure during treatment. In addition, comparable safety and immunogenicity outcomes were observed between the two products. This supports the use of PF-05280014 as a biosimilar to reference trastuzumab, with clinical performance and tolerability similar to those of reference trastuzumab.

Another trastuzumab biosimilar that demonstrated comparable pharmacokinetic and safety outcomes is BCD-022. BCD-022 was shown to be equivalent to reference trastuzumab through extensive physicochemical and preclinical evaluations conducted both in vitro and in vivo [42]. Clinical studies also confirmed that BCD-022 exhibited efficacy, safety, and pharmacokinetic profiles comparable to those of the originator trastuzumab. Moreover, no unexpected adverse reactions or significant differences in immunogenicity were observed between the treatment groups. Overall, current evidence suggests that trastuzumab biosimilars have pharmacokinetic and safety profiles highly comparable to those of reference trastuzumab, supporting their clinical use in HER2-positive breast cancer therapy.

Clinical Benefits and Cost-Effectiveness of Biosimilars

Biosimilars have become an important innovation in modern healthcare because they provide outcomes comparable to those of originator biologic drugs at lower cost. These agents are increasingly used in the management of chronic diseases, including cancer, autoimmune diseases, and respiratory disorders. Studies have shown that biosimilars closely resemble reference biologics in terms of efficacy, safety, and quality standards [43]. The availability of biosimilars has also expanded treatment options for patients who previously had limited access to biologic therapies. As a result, biosimilars are considered valuable alternatives in improving both clinical outcomes and healthcare affordability.

Clinical evidence consistently demonstrates that biosimilars provide therapeutic effects comparable to reference biologic products. Biosimilars of rituximab, bevacizumab, and trastuzumab showed clinical benefits similar to those observed with the originator drugs in several studies [44]. Comparable efficacy outcomes support the reliability of biosimilars in maintaining disease control among patients with chronic and malignant conditions. In addition, studies have reported no clinically meaningful differences in safety or immunogenicity between biosimilars and reference biologics. These findings strengthen confidence in the clinical use of biosimilars across various therapeutic areas.

The growing use of biosimilars is also supported by increasing evidence from real-world clinical practice. Real-world data continue to demonstrate favorable outcomes associated with biosimilar treatment in routine healthcare settings [45]. The accumulation of real-world evidence has increased physician and patient confidence in the efficacy and safety of biosimilars. Moreover, observational studies and post-marketing surveillance have confirmed consistent treatment responses after switching from reference biologics to biosimilars. This evidence suggests that biosimilars can maintain long-term therapeutic effectiveness in clinical practice.

Another important advantage of biosimilars is their contribution to the sustainability of the healthcare system. Biosimilars can maintain the therapeutic benefits of biologic therapy while simultaneously reducing treatment costs [46]. Lower biologic costs improve treatment affordability and increase patient access to advanced therapies. Reduced healthcare spending may also help healthcare systems allocate resources more efficiently for other medical services. Consequently, biosimilars play an essential role in supporting sustainable and equitable healthcare delivery.

Cost-effectiveness analyses have demonstrated significant economic benefits associated with biosimilar use. Patients with immune-mediated inflammatory diseases (IMIDs) who use biosimilars could save $874-$2,184 per month in treatment costs compared with reference biologics [47]. These substantial savings may reduce the financial burden experienced by both patients and healthcare institutions. Lower treatment costs may also encourage wider adoption of biologic therapy among eligible patients. Therefore, biosimilars represent an economically beneficial strategy for long-term disease management.

The economic value of biosimilars has also been observed in rheumatologic diseases. Biologic therapies were considered cost-effective for patients with axial spondyloarthritis, particularly among individuals who did

not achieve treatment targets using conventional therapies [48]. Biosimilar use may further enhance the cost-effectiveness of biologic treatment by reducing acquisition costs. In addition, improved disease control may decrease indirect costs associated with hospitalization, disability, and productivity loss. These outcomes demonstrate that biosimilars may provide both clinical and economic advantages in chronic inflammatory diseases.

In oncology, trastuzumab biosimilars have received increasing attention because of their potential to improve access to HER2-targeted therapy. The introduction of lower-cost trastuzumab biosimilars, combined with their substantial clinical benefits, has raised important considerations regarding their financial feasibility and cost-effectiveness in healthcare systems [49]. Biosimilar trastuzumab may help reduce the economic burden associated with long-term cancer treatment. Furthermore, lower drug prices may allow more patients to receive targeted therapy earlier in the course of disease management. This situation highlights the important role of biosimilars in expanding access to high-cost cancer therapies.

Several pharmacoeconomic studies have further confirmed the value of biosimilars in clinical practice. Treatment sequences initiated with biosimilar disease-modifying antirheumatic drugs (DMARDs) were shown to be more cost-effective than treatment strategies initiated with leflunomide [50]. Biosimilar treatment strategies were associated with lower healthcare costs while also providing greater quality-adjusted life years (QALYs). These findings indicate that biosimilars may improve patient outcomes while simultaneously reducing overall healthcare expenditures. Overall, current evidence supports the clinical benefits and cost-effectiveness of biosimilars as sustainable therapeutic options in modern healthcare systems.

Conclusion

Based on the reviewed studies, trastuzumab biosimilars such as SB3 (Ontruzant), CT-P6 (Herzuma), PF-05280014 (Trazimera), ABP 980 (Kanjinti), and trastuzumab-dkst (Ogivri) demonstrated comparable efficacy, pharmacokinetic profiles, and safety outcomes to reference trastuzumab in the treatment of HER2-positive breast cancer. Clinical outcomes, including pathological complete response (pCR), progression-free survival (PFS), overall survival (OS), and disease-free survival (DFS), showed no clinically meaningful differences between biosimilars and the originator product. In addition, biosimilars exhibited immunogenicity and cardiotoxicity profiles similar to those of the reference products, indicating that they can be safely administered in both early-stage and metastatic HER2-positive breast cancer therapy. The use of trastuzumab biosimilars also offers significant economic benefits by reducing treatment costs and increasing patient access to HER2-targeted therapy, particularly in healthcare systems with limited resources. Therefore, trastuzumab biosimilars can be considered effective, safe, and cost-efficient alternatives to reference trastuzumab in routine clinical practice. However, further long-term studies are still needed to evaluate their effectiveness and safety in broader patient populations and in combination with newer therapeutic agents

Author's Contribution

A. Kasasiah: supervised the development of the review article, provided conceptual guidance, and contributed critical revisions and suggestions to improve the quality of the manuscript. A. Khaerunisa, M. D. Ananda, N. Y. Fadhillah, and S. R. H. Herlaesa: conducted literature search, performed selection and analysis of relevant references, prepared the discussion, and contributed to the writing of the review article. All authors read and approved the final version of the manuscript.

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References

[1] L. O. Iqmy, S. Setiawati, and D. E. Yanti, "Faktor risiko yang berhubungan dengan kanker payudara," *JKM (Jurnal Kebidanan Malahayati)*, vol. 7, no. 1, pp. 32–36, 2021.

[2] N. Y. RAtnasari and R. R. N. Aysyah, "Efektivitas Penyuluhan Kesehatan Pemeriksaan Payudara Sendiri (SADARI) Terhadap Tingkat Pengetahuan Remaja Putri," *Jurnal Keperawatan GSH*, vol. 12, no. 2, pp. 34–39, 2023.

[3] I. Rona and N. Swastika, "Penyuluhan Kesehatan Tentang Periksa Payudara Sendiri (Sadari) Sebagai Upaya Deteksi Dini Kanker Payudara Di MAN 2 Sigli Kabupaten Pidie," *BAKTIMAS: Jurnal Pengabdian pada Masyarakat*, vol. 4, no. 3, pp. 156–165, 2022.

[4] WHO, "Breast Cancer," World Health Organization.

[5] Kemenkes RI, "Kanker Payudara Paling Banyak di Indonesia, Kemenkes Targetkan Pemerataan Layanan Kesehatan," Redaksi Sehat Negeriku.

[6] A. Rahma and N. B. Khairun, "Peran Human Epidermal Growth Factor Receptor-2 pada Kanker Payudara," *Agromedicine Unila*, vol. 5, no. 2, pp. 644–647, 2018.

[7] O. Tredan *et al.*, "Innovative approach for a typology of treatment sequences in early stage HER2 positive breast cancer patients treated with trastuzumab in the French national hospital database," *Cancer Inform.*, vol. 21, p. 11769351221135134, 2022.

[8] B. Nami, H. Maadi, and Z. Wang, "Mechanisms underlying the action and synergism of trastuzumab and pertuzumab in targeting HER2-positive breast cancer," *Cancers (Basel).*, vol. 10, no. 10, p. 342, 2018.

[9] S. M. Swain *et al.*, "Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer," *New England journal of medicine*, vol. 372, no. 8, pp. 724–734, 2015.

[10] R. Kongsakon, S. Lochid-Amnuay, N. Kapol, and O. Pattanaprateep, "From research to policy

implementation: trastuzumab in early-stage breast cancer treatment in Thailand," *Value Health Reg. Issues*, vol. 18, pp. 47–53, 2019.
[11] S. M. Alexeev *et al.*, "Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-022 with reference trastuzumab," *BMC Cancer*, vol. 20, pp. 1–10, 2020.
[12] F. Cardoso *et al.*, "Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up," *Annals of oncology*, vol. 30, no. 8, pp. 1194–1220, 2019.
[13] Z. Nahleh *et al.*, "Use of biosimilar medications in oncology," *JCO Oncol. Pract.*, vol. 18, no. 3, pp. 177–186, 2022.
[14] N. Herawati, "Biosimilar: Trend Obat Masa Kini," *Biotrends*, vol. 7, no. 1, pp. 14–19, 2016.
[15] U.S. Food and Drug Administration, "Scientific Considerations in Demonstrating Biosimilarity to a Reference Product," Food and Drug Administration.
[16] H.-C. Kolberg, G. S. Demetriou, and V. Hanes, "Totality of evidence supporting the use of ABP 980, a trastuzumab biosimilar: Practical considerations," *Oncol. Ther.*, vol. 9, pp. 225–238, 2021.
[17] T. K. Kvien, K. Patel, and V. Strand, "The cost savings of biosimilars can help increase patient access and lift the financial burden of health care systems," in *Seminars in arthritis and rheumatism*, Elsevier, 2022, p. 151939.
[18] H. S. Rugo *et al.*, "Final overall survival analysis of the phase 3 HERITAGE study demonstrates equivalence of trastuzumab-dkst to trastuzumab in HER2-positive metastatic breast cancer," *Breast Cancer Res. Treat.*, vol. 188, no. 2, pp. 369–377, 2021.
[19] S. J. Bae *et al.*, "Real-world clinical outcomes of biosimilar trastuzumab (CT-P6) in HER2-positive early-stage and metastatic breast cancer," *Front. Oncol.*, vol. 11, p. 689587, 2021.
[20] L. U. Sarder and S. Ahmad, "Emerging role of biosimilars: Focus on trastuzumab and metastatic human epidermal growth factor receptor 2-positive breast cancer," *Results Chem.*, vol. 6, p. 101055, 2023.
[21] X. Chen, C. Li, R. Ewesuedo, and D. Yin, "Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer," *Cancer Chemother. Pharmacol.*, vol. 84, pp. 83–92, 2019.
[22] S. Matovina *et al.*, "Comparison of Biosimilar Trastuzumab ABP 980 with Reference Trastuzumab in Neoadjuvant Therapy for HER2-positive Breast Cancer–an Analysis of a Large University Breast Cancer Centre," *Geburtshilfe Frauenheilkd.*, vol. 83, no. 06, pp. 694–701, 2023.
[23] D. Gagliato *et al.*, "Real-World Study of Adjuvant Biosimilar Trastuzumab-dkst for HER2-Positive Breast Cancer Treatment in a Brazilian Population," *Oncol. Ther.*, pp. 1–13, 2024.
[24] J. Stebbing *et al.*, "Six-year survival outcomes for patients with HER2-positive early breast cancer treated with CT-P6 or reference trastuzumab: observational follow-up study of a phase 3 randomised controlled trial," *BioDrugs*, vol. 37, no. 3, pp. 433–440, 2023.
[25] X. Pivot *et al.*, "A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: final safety, immunogenicity and survival results," *Eur. J. Cancer*, vol. 93, pp. 19–27, 2018.
[26] R. K. Li *et al.*, "Long-term safety and effectiveness of PF-05280014 (a trastuzumab biosimilar) treatment in patients with HER2-positive metastatic breast cancer: updated results of a randomized, double-blind study," *BioDrugs*, vol. 36, no. 1, pp. 55–69, 2022.
[27] Y. Huang *et al.*, "Longitudinal MRI-based fusion novel model predicts pathological complete response in breast cancer treated with neoadjuvant chemotherapy: a multicenter, retrospective study," *EClinicalMedicine*, vol. 58, 2023.
[28] C. Muñoz *et al.*, "Comparative Effectiveness and Safety of Trastuzumab Biosimilars to Herceptin for Adjuvant Treatment of HER2+ Breast Cancer," *Current Oncology*, vol. 31, no. 3, pp. 1633–1644, Mar. 2024, doi: 10.3390/curroncol31030124.
[29] X. Ye *et al.*, "Efficacy and safety of biosimilar trastuzumab (HLX02) in patients with HER2-positive advanced breast cancer: a retrospective real-world analysis," *Front. Oncol.*, vol. 15, 2025, doi: 10.3389/fonc.2025.1622854.
[30] M. Masse, "382P FES PET/CT predictive value of late hormone therapy rechallenge efficacy in metastatic breast cancer," *ESMO Open*, vol. 10, p. 104953, May 2025, doi: 10.1016/j.esmoop.2025.104953.
[31] K. Kaushal, V. Thummar, and P. Mehta, "Real-World Evaluation of Trastuzumab Emtansine Biosimilar in Early-Stage HER2-Positive Breast Cancer: Results from a Single-Center Retrospective Study in India," *Archives of Breast Cancer*, vol. 13, no. 2, pp. 182–189, Apr. 2026, doi: 10.32768/abc.2906718345-529.
[32] E. Triantafyllidi and J. K. Triantafillidis, "Systematic Review on the Use of Biosimilars of Trastuzumab in HER2+ Breast Cancer," Aug. 01, 2022, *MDPI*. doi: 10.3390/biomedicines10082045.
[33] X. Pivot *et al.*, "Cardiac Safety and Efficacy of SB3 Trastuzumab Biosimilar for ERBB2-Positive Early Breast Cancer: Secondary Analysis of a Randomized Clinical Trial," *JAMA Netw. Open*, vol. 6, no. 4, p. E235822, Apr. 2023, doi: 10.1001/jamanetworkopen.2023.5822.
[34] A. Bernat-Peguera *et al.*, "Efficacy of CT-P6 (trastuzumab biosimilar) versus reference trastuzumab in combination with pertuzumab in HER2-positive early-stage breast cancer: Preclinical and real-life clinical data," *Breast*, vol. 62, pp. 1–9, Apr. 2022, doi: 10.1016/j.breast.2022.01.007.
[35] R. Zhang, X. Liu, G. Song, Y. Zhang, and H. Li, "Trastuzumab Biosimilar (HLX02), Pertuzumab Plus Chemotherapy in Patients with HER2-Positive Metastatic Breast Cancer after Progression of Trastuzumab: A Prospective, Phase II Study," *Cancer Res. Treat.*, vol. 56, no. 3, pp. 795–801, Jul. 2024, doi: 10.4143/crt.2023.1151.
[36] C. Schwabe, C. Wynne, D. R. Dyapa, A. Prajapati, and D. Dadke, "Pharmacokinetics, Safety, Tolerability, and Immunogenicity of BP02 (Trastuzumab Biosimilar) Compared to EU- and US-Approved

Trastuzumab in Healthy Adult Male Volunteers: A Phase 1, Randomized, Double-Blind Study," *Oncol. Ther.*, vol. 12, no. 3, pp. 477–490, Sep. 2024, doi: 10.1007/s40487-024-00289-0.

[37] C. F. Waller *et al.*, "A pharmacokinetics phase 1 bioequivalence study of the trastuzumab biosimilar MYL-1401O vs. EU-trastuzumab and US-trastuzumab," *Br. J. Clin. Pharmacol.*, vol. 84, no. 10, pp. 2336–2343, Oct. 2018, doi: 10.1111/bcp.13689.

[38] F. J. Esteva, J. Stebbing, R. N. Wood-Horrall, P. J. Winkle, S. Y. Lee, and S. J. Lee, "A randomised trial comparing the pharmacokinetics and safety of the biosimilar CT-P6 with reference trastuzumab," *Cancer Chemother. Pharmacol.*, vol. 81, no. 3, pp. 505–514, Mar. 2018, doi: 10.1007/s00280-017-3510-7.

[39] H. Zhou *et al.*, "A randomized Phase I pharmacokinetic trial comparing the potential biosimilar trastuzumab (SIBP-01) with the reference product (Herceptin®) in healthy Chinese male volunteers," *Expert Opin. Drug Metab. Toxicol.*, vol. 16, no. 10, pp. 997–1003, Oct. 2020, doi: 10.1080/17425255.2020.1807935.

[40] J. H. Park *et al.*, "Efficacy and Safety of Trastuzumab Biosimilar (CT-P6) Compared With Reference Trastuzumab in Patients With HER2-positive Advanced Gastric Cancer A Retrospective Analysis," *American Journal of Clinical Oncology: Cancer Clinical Trials*, vol. 45, no. 2, Feb. 2022, doi: 10.1097/COC.0000000000000887.

[41] X. Chen, C. Li, R. Ewesuedo, and D. Yin, "Population pharmacokinetics of PF-05280014 (a trastuzumab biosimilar) and reference trastuzumab (Herceptin®) in patients with HER2-positive metastatic breast cancer," *Cancer Chemother. Pharmacol.*, vol. 84, no. 1, pp. 83–92, Jul. 2019, doi: 10.1007/s00280-019-03850-1.

[42] S. M. Alexeev *et al.*, "Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-022 with reference trastuzumab," *BMC Cancer*, vol. 20, no. 1, Aug. 2020, doi: 10.1186/s12885-020-07247-9.

[43] C. A. Ferrara and P. L. Ferrara, "Cost-effectiveness and efficacy analysis of biosimilar drugs for lung diseases: a systematic review," Dec. 15, 2025, *Emerald Publishing*. doi: 10.1108/JES-01-2025-0059.

[44] X. Luo *et al.*, "Clinical Benefit, Price, and Uptake for Cancer Biosimilars vs Reference Drugs in China: A Systematic Review and Meta-Analysis," *JAMA Netw. Open*, vol. 6, no. 10, p. E2337348, Oct. 2023, doi: 10.1001/jamanetworkopen.2023.37348.

[45] H. U. Kim *et al.*, "The Future of Biosimilars: Maximizing Benefits Across Immune-Mediated Inflammatory Diseases," *Drugs*, vol. 80, no. 2, pp. 99–113, Feb. 2020, doi: 10.1007/s40265-020-01256-5.

[46] T. K. Kvien *et al.*, "Beyond Cost: Observations on Clinical and Patient Benefits of Biosimilars in Real-World Settings," Jul. 01, 2025, *Adis*. doi: 10.1007/s40259-025-00727-z.

[47] X. Du *et al.*, "Assessment of clinical benefit, cost and uptake of biosimilars versus reference biologics in immune-mediated inflammatory diseases in China," *Front. Public Health*, vol. 12, 2024, doi: 10.3389/fpubh.2024.1476213.

[48] J. Al-Saleh, A. A. Negm, A. Almarzooqi, N. E. E. Elsidig, and N. Zamani, "Analysis of Cost-Effectiveness of Biologic Therapies in Axial Spondyloarthritis Based on Real-World Data," *ClinicoEconomics and Outcomes Research* , vol. 17, pp. 915–930, 2025, doi: 10.2147/CEOR.S556012.

[49] S. Lochid-Amnuay and R. Kongsakon, "Economic Evaluation and Budget Impact of Biosimilar Trastuzumab for HER2-Positive Metastatic Breast Cancer in Thailand: Policy Implications for Access and Affordability." [Online]. Available: www.elsevier.com/locate/vhri

[50] K. Peng *et al.*, "Cost-Effectiveness of Biosimilars vs Leflunomide in Patients with Rheumatoid Arthritis," *JAMA Netw. Open*, vol. 7, no. 6, p. e2418800, Jun. 2024, doi: 10.1001/jamanetworkopen.2024.18800.