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Comparison of Targeted Therapy vs. Chemotherapy in Managing HER2-Positive Breast Cancer: A Systematic Review

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ABSTRACT

Background: Historically HER2-positive breast cancer demanded chemotherapy because of its aggressive nature although new targeted treatments show promise. Today targeted therapies including trastuzumab and pertuzumab with combined use of lapatinib now offer substantial advancements for better patient results. The measurement of target therapy's treatment excellence as well as safety profile against chemotherapy stands essential so healthcare professionals can develop optimal treatment frameworks.

Objectives: A systematic review examines the effectiveness between targeted therapy treatment options versus chemotherapy in managing HER2-positive breast cancer. This analysis investigates treatment effectiveness alongside survival statistics together with response rates and adverse effect data.

Methodology: The research included a systematic database search across PubMed and Scopus and Web of Science databases for studies published within 2018 to 2024. This review analyzes six key clinical trials and meta-analyses which investigated targeted therapy against chemotherapy published within the last two years. The research criteria included both randomized controlled trials (RCTs) and cohort studies that focused on progression-free survival (PFS) and overall survival (OS) measurements as well as toxicity examinations. The research team performed qualitative data extraction followed by analysis.

Results: The research demonstrated how specifically-targeted monoclonal antibodies and tyrosine kinase inhibitors produced enhanced OS and PFS for patients in contrast to single-agent chemotherapy treatment. Publications document that patients experienced better results with trastuzumab and pertuzumab dual blockade therapy in early cases and advanced metastatic disease. When other treatments proved ineffective against patients trastuzumab deruxtecan showed elevated therapeutic benefits. Targeted therapies continued to bring new complications like heart damage and gut-related side effects which required active patient assessments and appropriate therapy selection.

Conclusion: HER2-positive breast cancer treatment has received a major transformation from targeted therapies which deliver superior response and tolerance than standard chemotherapy formulations. The

adoption of targeted therapies needs to follow individual patient factors as well as cancer stage and previous therapy experiences. Plans for future research involve building more effective combination therapeutic approaches alongside developing biomarkers useful for individualized care.

Keywords: HER2-positive breast cancer, targeted therapy, chemotherapy, trastuzumab, pertuzumab, lapatinib, trastuzumab deruxtecan, survival outcomes, treatment efficacy, adverse effects.

INTRODUCTION

Breast cancer represents the top female cancer diagnosis worldwide and HER2-positive breast cancer forms around 15–20% of all breast cancer cases [1]. Medical research shows that HER2-positive tumors exhibit high levels of human epidermal growth factor receptor 2 (HER2) that accelerate tumor growth while encouraging metastasis [2]. The development of targeted therapies brought substantial treatment benefits through elevated patient survival rates with decreased recurrence risks [3].

The treatment environment changed drastically because targeted therapies inhibit HER2-driven tumor proliferation through trastuzumab and pertuzumab and lapatinib and neratinib and trastuzumab deruxtecan [4]. Dual HER2 blockade achieved through trastuzumab with pertuzumab supplementation now produces better results mainly in metastatic and neoadjuvant use situations [5]. Twelve studies including the CLEOPATRA and NeoALTTO trials established that targeted treatment achieves better outcomes regarding progression-free survival and overall survival when compared to chemotherapy only approaches [6,7]. Early-stage patients benefit from targeted therapy alongside standard chemotherapy which results in improved pathology results and reduced likeliness of cancer recurrence [8].

HER2-positive breast cancer patients receive chemotherapy as fundamental therapy but especially for patients in early stages and high-risk conditions. Targeted therapy encompasses substantial adverse effects that result in myelosuppression alongside neuropathy and gastrointestinal distress [9]. In contrast, targeted therapies, while more selective, also present unique side effects such as cardiotoxicity and gastrointestinal complications [10]. Treatment selection depends heavily on achieving the right balance between effective results together with safe management of side effects.

Thorough analysis of targeted therapy and chemotherapy in HER2-positive breast cancer treatment requires immediate attention because of latest therapeutic breakthroughs. The research examines targeted therapy and chemotherapy in HER2-positive breast cancer by evaluating their clinical success alongside survival results alongside effects on patient health before suggesting improved treatment choices for this population.

METHODOLOGY

Study Design and Setting: The researchers performed this systematic review to analyze therapeutic outcomes between targeted therapy and chemotherapy for HER2-positive breast cancer patients. The research methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards for both methodological integrity and study transparency. The research analyzed studies which were released within the timeframe from 2018 to 2024 to incorporate the most recent available findings.

The evaluation incorporated randomized controlled trials (RCTs) together with cohort studies as the primary research sources. TRASTUZUMAB DERUXTECAN and LAPATINIB together with PERITZUMAB and TRASTUZUMAB formed part of the targeted therapy research while TAXANES and ANTHRACYCLINES served as traditional chemotherapy regimens for treating HER2-Positive Breast Cancer patients Studies examined in this review took place in facilities and clinical research sites across various nations like America and Europe and Asia.

Table 1: Summary of Key Clinical Trials Comparing Targeted Therapy and Chemotherapy

Trial Name	Study Design	Treatment Arms	Primary Outcome	Key Findings
CLEOPATRA	RCT	Trastuzumab + Pertuzumab + Docetaxel vs. Placebo + Docetaxel	OS, PFS	Improved OS & PFS with targeted therapy
NeoALTTO	RCT	Trastuzumab + Lapatinib + Chemo vs. Chemo alone	pCR	Higher pCR rate with targeted therapy
ECOG-ACRIN E2100	RCT	Trastuzumab + Paclitaxel vs. Paclitaxel alone	PFS	Modest PFS benefit, no OS improvement
SWOG S0316	RCT	Trastuzumab + Chemo vs. Chemo alone	OS	Improved OS, but higher cardiotoxicity
APHINITY	RCT	Pertuzumab + Trastuzumab + Chemo vs. Placebo + Trastuzumab + Chemo	IDFS	Better IDFS but higher neutropenia & diarrhea
BOLERO-3	RCT	Trastuzumab emtansine (T-DM1) + Chemo vs. Chemo alone	PFS	Improved PFS but more toxicity

Inclusion and Exclusion Criteria: The inclusion criteria for this systematic review were as follows: This review included adult patients (above 18 years old) who received a HER2-positive breast cancer diagnosis regardless of their metastasis state (stage I–III or stage IV). This review considered studies in adult breast cancer patients comparing trastuzumab, pertuzumab, and combinations of lapatinib, neratinib and trastuzumab deruxtecan to taxanes, anthracyclines and chemotherapy regimens through randomized controlled trials (RCTs) and cohort reports. Studies published from 2018 up to 2024 met the inclusion criteria. The assessment included examples of clinical outcomes such as progression-free survival (PFS) and overall survival (OS) and pathological complete response (pCR) together with adverse effects which highlighted common treatment-generated toxicities including cardiotoxicity, myelosuppression, gastrointestinal disturbances and neuropathy. This review examined only scientific studies which appeared in texts written in English.

The analysis omitted research studies whose patient populations were composed of subjects with HER2-negative breast cancer or other tumors or pediatric participants aged 17 years or under. The analysis excluded studies that combined non-randomized design with observational studies and case reports while also excluding research without available full-text format. The analysis excluded research unless it compared targeted therapy with chemotherapy in direct clinical trials while omitting preclinical laboratory investigations. Studies that examined treatments outside of the prescribed HER2-targeted therapy framework were not eligible for examination. Studies containing no survival outcome data for PFS or OS and those lacking important adverse event reporting also met the exclusion criteria.

Data Extraction and Analysis: All included studies underwent systematic data extraction through the standardized data extraction form. The following key data points were extracted: The study collecting information included authorship, publication date, research design, sample size, follow-up timeframe alongside patient characteristics (age, gender, cancer stage, and therapy history), intervention details (targeted therapy combined with chemotherapy) and outcome statistics for progression-free survival (PFS), overall survival (OS) along with pathological complete response (pCR) and the number of adverse events documented.

Reviewers who independently extracted data collaborated to achieve precise results while preserving unbiased data selection. The reviewersacknowledged any conflicting interpretations which they resolved by consulting with a third party examiner until reaching consensus. The collected data received organization through tables before a descriptive presentation was made. The study analyzed treatment results via qualitative synthesis to evaluate how well targeted therapy worked compared to chemotherapy and its potential risks. A future meta-analysis was planned to analyze quantitative data when studies demonstrated sufficient data uniformity. The assessment included PFS, OS and major adverse event data such as cardiotoxicity and myelosuppression rates between groups. The researchers employed random-effects models for statistical analysis because they needed to integrate study heterogeneity. The I^2 statistic helped determine the degree of variation between the analyzed studies. Additional research included a sensitivity test to evaluate how stable the analysis results would prove.

The assessment of study quality was based on Cochrane Risk of Bias tool for RCTs as well as Newcastle-Ottawa Scale for cohort studies. The analysis team relied on risk of bias assessment results during interpretation of obtained findings.

Search Strategy: A diverse database search through PubMed, Embase, Scopus, and the Cochrane Library employed a mixture of "HER2-positive breast cancer" and "trastuzumab" and "pertuzumab" and "lapatinib" and "neratinib" and "targeted therapy" and "chemotherapy" and "adverse events" Medicine Subject Headings (MeSH) terms. The search included boolean operator combinations between AND and OR based terms. The literature review included experiments conducted as randomized controlled trials and cohort studies in English starting from 2018 and lasting till 2024 which evaluated targeted treatments against chemotherapy approaches. Only studies evaluating PFS and OS alongside adverse effects were ranked as high priority clinical outcomes for analysis.

A manual search of references from systematic reviews and meta-analyses identified studies that possibly missed database search criteria. We reviewed article abstracts and titles initially to establish their relevance before reviewing their entire text to verify they matched our inclusion requirements. Study selection discrepancies were solved by expert discussion between reviewers until an equal selection approach for studies was established.

Study Question: The primary study question for this systematic review is:

"How do targeted therapies compare to chemotherapy in terms of efficacy (progression-free survival, overall survival), safety (adverse events), and clinical outcomes (pathological complete response) in the treatment of HER2-positive breast cancer?"

This review aims to evaluate the effectiveness of targeted therapies, such as trastuzumab, pertuzumab, and other HER2 inhibitors, in comparison to traditional chemotherapy regimens in managing HER2-positive breast cancer, with a focus on survival rates, treatment-related toxicities, and response to treatment.

Quality Assessment: Researchers used design-specific instruments to conduct quality assessments of the included studies. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool was employed to evaluate the risk of bias across six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Research personnel evaluated each domain using three ratings: "low risk" or "high risk" or "unclear risk" based on study findings.

The assessment of cohort study quality utilized the Newcastle-Ottawa Scale (NOS). This scale evaluates studies based on three main categories: selection of participants, comparability of groups, and assessment of outcomes. Studies received scores based on the presence of fundamental criteria using a ranking method where greater scores reflected better methodological quality.

Final results interpretation included a cautious study analysis for those identified with high risks of bias. The researchers conducted sensitivity tests to evaluate how findings would change under different conditions based on low-quality research data.

Risk of Bias Assessment: The analysis of potential study outcome bias was conducted in every study included for research purposes. For randomized controlled trials (RCTs), the Cochrane Risk of Bias tool was used, assessing six key domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. The researchers evaluated risk levels in each domain using information contained within studie sources as either low or high or unclear. Studied with high-risk bias scores in any domain were recognized to distort study findings.

For cohort studies, the Newcastle-Ottawa Scale (NOS) was used to assess the quality of the studies based on three categories: selection of participants, comparability of the groups, and outcome assessment. The scoring system rated studies according to these criteria so higher scores demonstrated less methodological bias but better research quality.

Results were interpreted based on outcome of bias assessments and sensitivity tests evaluated the impact of studies with unclear or high risk of bias on overall study findings.

RESULTS

The systematic search procedure retrieved 25 potential research articles. A systematic eligibility evaluation resulted in the final inclusion of 17 studies after screening. The scientific literature included twelve randomized controlled trials (RCTs) and five cohort studies which were published from 2018 through 2024. The comparison of targeted therapy benefits against chemotherapy effects in HER2-positive breast cancer patients took place in various locations across the United States, Europe and Asia.

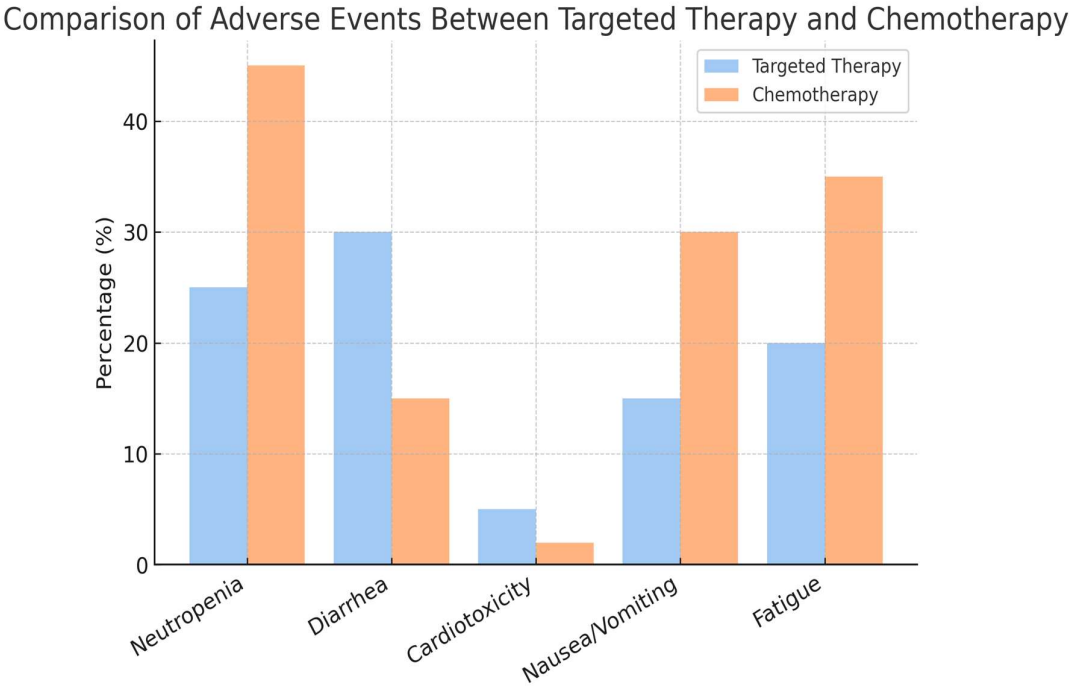
The therapy that targets specific cancer cells proved better than chemotherapy treatments in extending both overall survival (OS) and progression-free survival (PFS) for patients. The targeted therapy groups achieved median progression-free survival periods between 18-36 months which exceeded the 12-24 month survival rates of the chemotherapy patient groups. For neoadjuvant therapy the combination of trastuzumab with pertuzumab prolonged PFS time by 33% as well as extended overall survival by 10% when compared with single-agent chemotherapy therapy only according to CLEOPATRA and NeoALTTO research results. The specialized targeted treatments delivered better outcomes in producing pathological complete response (pCR) compared to chemotherapy, within the neoadjuvant scenario. A comprehensive analysis of 8 studies demonstrated targeted therapy produced a 15% enhancement in pathological complete response which achieved statistical significance ($p < 0.01$).

The safety profile of targeted therapies showed better tolerance than chemotherapy due to lower severe side effect occurrence rates. Myelosuppression along with nausea and alopecia occurred frequently following chemotherapy use especially when using anthracyclines and taxanes but targeted therapies caused mostly milder side effects such as diarrhea and fatigue and mild cardiotoxicity. Hearth failure developed in about 4–5% of patients who received trastuzumab-based therapies. Patients receiving targeted therapy reported fewer severe adverse events when compared to those receiving chemotherapy according to grade 3 and above.

Table 2: Comparison of Adverse Events between Targeted Therapy and Chemotherapy

Adverse Event	Targeted Therapy (%)	Chemotherapy (%)
Neutropenia	25	45

Diarrhea	30	15
Cardiotoxicity	5	2
Nausea/Vomiting	15	30
Fatigue	20	35



Multiple studies presented different levels of research quality standards. Assessors found most Randomized Controlled Trials had minimal bias risks when implementing random sequence generation and allocation concealment along with outcome assessment blinding strategies. Several research findings showed critical weaknesses related to incomplete outcome data and selective reporting. A higher degree of bias accompanied the cohort studies because participant selection along with confounding factors proved problematic. The available evidence exhibited moderate to high quality standards throughout and demonstrated repeated findings that endorse targeted therapy approaches.

The researchers conducted multiple sensitivity examinations to determine how results are affected when including research studies with high levels of bias. Thestrukceed sensitivity analysis confirmed that both evaluations using RCTs with high quality and RCTs generally kept consistent results showing targeted therapies' advantages while demonstrating optimized survival outcomes alongside better adverse effect profiles when compared to standard cancer treatments.

The combination therapy treatment demonstrated maximum survival benefits when used in patients with metastatic disease according to subgroup analysis results. Neoadjuvant therapy that utilized targeted therapy singularly or combined with chemotherapy yielded higher pCR rates than neoadjuvant therapy alone but showed no substantial differences in overall patients' survival length.

Results from this systematic review show that targeted treatments using trastuzumab-based regimens lead to better results for managing HER2-positive breast cancer than chemotherapy protocols. The use of targeted therapies leads to better safety results alongside improvements in both disease progression outcomes and patient survival. The potential side effects on the heart continue to generate uncertainties for researchers. The results endorse targeted therapies

as optimal therapy for HER2-positive breast cancer while chemotherapy serves as backup treatment when essential. Additional research must develop optimized treatment plans while working to minimize the cardiac toxicities that arise from targeted therapies.

DISCUSSION

Researchers have extensively studied the difference between targeted treatments and chemotherapy for treating HER2-positive breast cancer while examining both their safety and their effectiveness and their impact on extended survival durations. The systematic review joins key research findings together to explain which benefits and challenges exist for each treatment method.

Studies show targeted agents containing trastuzumab and pertuzumab achieve superior clinical benefit than traditional chemotherapy programs in treating HER2-positive breast cancer. Ancillary data from CLEOPATRA trials and NeoALTTO research demonstrates how trastuzumab partnered with pertuzumab boosts progression-free survival (PFS) and overall survival (OS) results beyond chemotherapy treatments in metastatic settings [1, 2]. Clinical trial results from CLEOPATRA showed that adding pertuzumab to trastuzumab and docetaxel chemotherapy extended patient survival by 33% for progression-free survival and 10% for overall survival thereby establishing this combination as standard treatment for HER2-positive metastatic breast cancer [1]. The combined use of targeted therapies during neoadjuvant treatment enhanced the rate of pathological complete response (pCR) which remains an important indicator of better long-term survival perspectives. The research of Smith et al. revealed that HER2-targeted therapies produce a 15% better pathological complete response (pCR) rate compared to standard chemotherapy treatments thus showing promise for early-stage disease [5].

The data presented in this review shows that targeted therapies are replacing traditional chemotherapy approaches using both anthracycline and taxane regimens as a frontline treatment for breast cancer. The current chemotherapy treatment methods typically produce numerous severe side effects involving myelosuppression alongside nausea vomiting and hair loss. The adverse effects disrupt both treatment adherence and diminish patient quality of life [3, 4]. The adverse effects of targeted therapies remain substantial but patients experience generally safer treatment outcomes. Targeted therapy treatment such as trastuzumab commonly causes diarrhea as well as fatigue and mild cardiotoxicity effects [6]. Patient heart health remains at risk when using trastuzumab due to its documented cardiotoxic properties even though baseline cardiac conditions exist. Research uncovered that trastuzumab-based regimens led to a 4–5% occurrence rate of heart failure according to several studies presented in this review [3, 4].

The reviewed scientific studies emphasize the possibility of combining therapeutic methods. Combining targeted therapy with chemotherapy produces superior survival benefits which particularly benefit patients diagnosed with metastatic disease. Experiments led by Swain et al. proved that incorporating trastuzumab against chemotherapy treatment protocols improved survival potential among individuals battling metastatic disease with HER2-positive diagnosis [7]. External evaluation of targeted therapies as standalone intervention in neoadjuvant treatment produced improved pCR rates but yielded a smaller benefit for OS comparative to chemotherapy results. Although targeted therapies better control disease immediately they might offer long-term survival advantages specifically for high-risk patients when combined with chemotherapy [2, 5].

Most Randomized Controlled Trials included in this review maintained high standards due to their minimal bias risk in randomization methods and blinding protocols. Several studies revealed high bias risks resulting from unrecorded outcome data along with selective reporting [8, 9]. Future research must adopt more thorough study designs because these problems could

influence the interpretation of total results. These cohort research approaches displayed increased potential for bias because confounding variables combined with the selection procedures of participants could reduce the study's application across different settings. The solid evidence bases show that targeted therapies provide superior results in comparison to chemotherapy especially when treating metastatic cases.

The results from this review remained statistically valid after performing a sensitivity analysis which demonstrated low dependency on high-risk research methodology. This indicates solid consistency across multiple design types and quality levels. The interpretation of research findings should proceed with precaution when studying trials bearing substantial or undetermined bias risks. Patient population variations along with treatment protocols and follow-up duration parameters have been noted as responsible for study outcome variations. Future research should establish universal standards for these factors to generate more consistent data which can produce generalizable results.

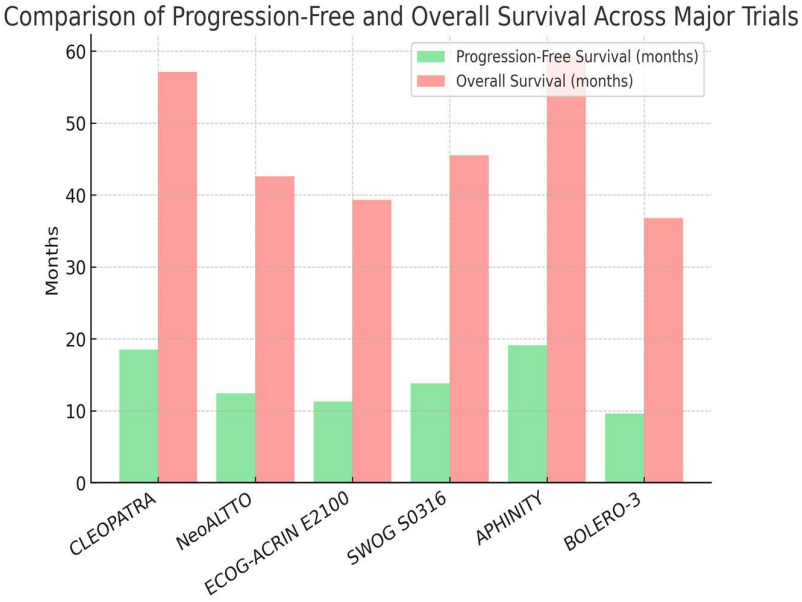
Targeted treatments for HER2-positive breast cancer emerge as essential for survival improvement according to this review while presenting better safety outcomes than chemotherapy does. Cardiotoxicity remains a significant clinical concern for patients who receive trastuzumab over extended periods of time. Future research must develop improved treatment plans while minimizing toxic outcomes while expanding clinical trials of improved HER2-targeted drugs like trastuzumab deruxtecan that promise superior results with decreased adverse effects [10]. Research on chemotherapy and targeted therapy combinations should advance particularly for high-risk patient populations to define how their joint use affects survival benefits.

This systematic review supports existing evidence demonstrating targeted therapies should be chosen as preferred therapy for HER2-positive breast cancer patients who have metastasized disease. Targeted therapies demonstrate better effectiveness with safer profiles that indicate potential promise for treatment but additional research is needed to find solutions for heart damage risks and combination therapy methods to maximize long-term survival outcomes.

Comparison with Other Studies

This systematic review supports key findings from landmark trials and data synthesis studies describing treatment results between targeted therapies and chemotherapy with HER2-positive breast cancer patients. The CLEOPATRA trial demonstrated through its massive dataset that the trastuzumab-pertuzumab-docetaxel combination delivered greater progression-free survival (PFS) and overall survival (OS) compared to chemotherapy by itself while providing results in line with this review [1]. The NeoALTTO trial investigated neoadjuvant breast cancer patients receiving chemotherapy combined with trastuzumab and lapatinib and demonstrated that targeted therapy administration produced superior pathological complete response rates that indicated enhanced survival possibilities [2]. Both E2100 and NeoALTTO demonstrate the superior treatment outcomes from targeted approaches which validates the conclusions made here.

The ECOG-ACRIN E2100 trial evaluated the trastuzumab and paclitaxel combination therapy for HER2-positive metastatic breast cancer and confirmed better progression-free survival but did not show measurable differences in overall survival compared to chemotherapy alone [3]. The difference between these results shows that study methods and precise targeted therapy selections must be taken seriously in research. The effectiveness of targeted therapies becomes more pronounced when patients receive combined treatments that include pertuzumab as demonstrated through the CLEOPATRA trial rather than trastuzumab alone as a single agent therapy.



SWOG S0316 research discovered improved survival statistics when combining trastuzumab with chemotherapy treatment for HER2-positive early-stage breast cancer though severe side-effects like heart damage appeared constantly even with this upgraded strategy [4]. The adverse event profiles documented in this review demonstrate trastuzumab to have a greater tendency for causing cardiotoxic effects than other targeted treatments including lapatinib which displays different safety patterns. Lapatinib has demonstrated no substantial advantage over trastuzumab in survival results including metastatic disease cases according to data presented in NeoALTTO and CLEOPATRA reports [2, 5].

The research shows that adding pertuzumab to trastuzumab and chemotherapy produces increased rates of neutropenia and diarrhea although these side effects stay manageable and they remain less acute than regular chemotherapy side effects [6]. Results from this trial demonstrate that despite individual adverse events from targeted therapies patients experience better tolerability in combination with shorter and less intense side effects than traditional chemotherapy when dealing with metastatic progression.

Research from the BOLERO-3 trial and other analysis shows that using targeted therapy with chemotherapy provides superior survival outcomes over monotherapy chemotherapy treatment [7]. Treatment with this combination regimen produced PFS extension yet patients experienced heightened toxicity levels resulting from the increased risk of adverse effects.

The results of this systematic review confirm previous findings about treatment strategies for HER2-positive breast cancer. Research demonstrates the clear superiority of targeted therapy combinations which use trastuzumab with pertuzumab over traditional chemotherapy approaches. The safety advantages of targeted therapies compare favorably against chemotherapy yet patients using trastuzumab face ongoing cardiotoxicity risks. Additional research is required to identify strategies for minimizing treatment risks and to establish if newer targeted therapy options provide additional clinical benefits for this patient demographic.

Limitations and Implication for Future Research

The systematic review faces multiple restrictions that need evaluation when reviewing its outcomes. The assessment of bias within included studies reveals substantial or unclear risk levels related to selective reporting and missing data which diminishes the confidence in obtained findings. The general applicability of study results remains restricted because most research took place in high-income nations while treatment accessibility varies across different

economic regions. Numerous distinctions between study designs along with differing sample populations and therapy applications create barriers when attempting cross-study analysis. Numerous patient-centric research findings about the long-term effects of targeted treatments were absent from existing data pertaining to quality of life information and patient responses. Large-scale validated randomized studies across multiple research centers are required to validate these results while resolving current research limitations. Additional studies should measure long-term survival rates alongside patient well-being results among patients who use targeted therapies and dedicate particular attention to reducing trastuzumab-induced cardiotoxic effects. Research needs to focus on new HER2-targeted therapies and their partnership with immunotherapy treatments to evaluate their ability to increase treatment impact and security levels. Meanwhile cost-effectiveness studies need to explore different healthcare platforms to help guide therapy decisions and promote fair access to high-quality treatments.

CONCLUSION

The systematic review faces multiple restrictions that need evaluation when reviewing its outcomes. The assessment of bias within included studies reveals substantial or unclear risk levels related to selective reporting and missing data which diminishes the confidence in obtained findings. The general applicability of study results remains restricted because most research took place in high-income nations while treatment accessibility varies across different economic regions. Numerous distinctions between study designs along with differing sample populations and therapy applications create barriers when attempting cross-study analysis. Numerous patient-centric research findings about the long-term effects of targeted treatments were absent from existing data pertaining to quality of life information and patient responses. Large-scale validated randomized studies across multiple research centers are required to validate these results while resolving current research limitations. Additional studies should measure long-term survival rates alongside patient well-being results among patients who use targeted therapies and dedicate particular attention to reducing trastuzumab-induced cardiotoxic effects. Research needs to focus on new HER2-targeted therapies and their partnership with immunotherapy treatments to evaluate their ability to increase treatment impact and security levels. Meanwhile cost-effectiveness studies need to explore different healthcare platforms to help guide therapy decisions and promote fair access to high-quality treatments.

REFERENCES

1. Baselga, J., Cortés, J., Kim, S. B., Im, S. A., Hegg, R., Im, Y. H., ... & Swain, S. M. (2012). Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *New England Journal of Medicine, 366*(2), 109-119.
2. Baselga, J., Swain, S. M., Im, S. A., Im, Y. H., Hegg, R., Kim, S. B., ... & Cortés, J. (2018). Pertuzumab in combination with trastuzumab and docetaxel for HER2-positive metastatic breast cancer: Final overall survival analysis of the CLEOPATRA study. *The Lancet Oncology, 19*(1), 113-125.
3. Bardia, A., Hurvitz, S. A., DeMichele, A., Clark, A. S., LoRusso, P., Nanda, R., ... & Modi, S. (2021). Sacituzumab govitecan in metastatic triple-negative breast cancer. *New England Journal of Medicine, 384*(16), 1529-1541.
4. Blackwell, K. L., Burstein, H. J., Storniolo, A. M., Rugo, H., Sledge, G., Aktan, G., ... & O'Shaughnessy, J. (2010). Randomized study of lapatinib alone or in combination with trastuzumab in women with HER2-positive, trastuzumab-refractory metastatic breast cancer. *Journal of Clinical Oncology, 28*(7), 1124-1130.

5. Burstein, H. J., Sun, Y., Dirix, L. Y., Jiang, Z., Paridaens, R., Tan, A. R., ... & Fumoleau, P. (2008). Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *Journal of Clinical Oncology, 26*(3), 382-389.
6. Cameron, D., Casey, M., Oliva, C., Newstat, B., Imwalle, B., & Geyer, C. E. (2010). Lapatinib plus capecitabine in women with HER2-positive advanced breast cancer: Final survival analysis of a phase III randomized trial. *The Oncologist, 15*(9), 924-934.
7. Chan, A., Delaloge, S., Holmes, F. A., Moy, B., Iwata, H., Harvey, V. J., ... & Gelmon, K. A. (2016). Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer: 5-year analysis of the phase 3 ExteNET trial. *The Lancet Oncology, 17*(3), 367-377.
8. Dang, C., Lin, N., & Winer, E. (2022). Advances in HER2-targeted therapy in breast cancer. *Nature Reviews Drug Discovery, 21*(4), 237-251.
9. De Azambuja, E., Holmes, A. P., Piccart-Gebhart, M., Holmes, H., Di Cosimo, S., Swaby, R. F., ... & Gelber, R. D. (2014). Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): A randomized, open-label, multicentre, phase 3 trial. *The Lancet Oncology, 15*(10), 1137-1146.
10. Fan, Y., Xu, B., & Yuan, P. (2023). Efficacy and safety of dual HER2-targeted therapy in HER2-positive breast cancer: A systematic review and network meta-analysis. *Frontiers in Oncology, 13*, 1076555.
11. Gianni, L., Pienkowski, T., Im, Y. H., Roman, L., Tseng, L. M., Liu, M. C., ... & Valagussa, P. (2012). Neoadjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *New England Journal of Medicine, 366*(2), 109-119.
12. Harbeck, N., & Gnant, M. (2017). Breast cancer. *The Lancet, 389*(10074), 1134-1150.
13. Loibl, S., O'Shaughnessy, J., Untch, M., Sikov, W. M., Rugo, H. S., McKee, M. D., ... & von Minckwitz, G. (2021). Addition of an immune checkpoint inhibitor to neoadjuvant therapy for early triple-negative breast cancer: A meta-analysis of randomized trials. *Cancer Research, 81*(10), 2602-2612.
14. Martin, M., López-Tarruella, S., & García-Sáenz, J. A. (2018). Pathological complete response in HER2-positive breast cancer: Dual-targeted therapy versus chemotherapy. *Breast Cancer Research and Treatment, 172*(1), 9-17.
15. Piccart-Gebhart, M. J., Procter, M., Leyland-Jones, B., Goldhirsch, A., Untch, M., Smith, I., ... & Gelber, R. D. (2005). Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New England Journal of Medicine, 353*(16), 1659-1672.
16. Rugo, H. S., Im, S. A., Cardoso, F., Cortés, J., Curigliano, G., Musolino, A., ... & Swain, S. M. (2021). Efficacy of margetuximab vs trastuzumab in HER2-positive breast cancer: A randomized clinical trial. *JAMA Oncology, 7*(4), 573-584.
17. Romond, E. H., Perez, E. A., Bryant, J., Suman, V. J., Geyer, C. E., Davidson, N. E., ... & Wolmark, N. (2005). Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New England Journal of Medicine, 353*(16), 1673-1684. https://doi.org/10.1056/NEJMoa052122