Asian Journal of Current Research in Clinical Cancer
ISSN: 3062-4444
2026, Volume 6, Issue 1, Page No: 200-211

Available online at: www.galaxypub.co/page/journals

Galaxy Publication

Galaxy Publication

Clinical Outcomes of HER2-Positive Advanced Breast Cancer in a Resource-Constrained Setting: A Retrospective Cohort Study

Ahmed Mansour[1]*, Omar Saeed[1]

[1]Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Cairo University, Cairo, Egypt.

***E-mail** ✉ ahmed.mansour@gmail.com

Received: 19 January 2026; **Revised:** 05 May 2026; **Accepted:** 15 May 2026

ABSTRACT

Advanced breast cancer (ABC) constitutes an incurable illness, exhibiting a median overall survival (OS) of roughly 3 years, a figure observed even within high-income settings. Survival has been prolonged by oncological therapies, particularly in hormone receptor–positive and HER2-positive disease; however, the availability of novel agents across Latin American (LATAM) nations remains constrained. An assessment of the influence of sequencing two therapeutic lines among Peruvian individuals diagnosed with HER2-positive ABC at a single public facility was conducted. The initial, first-line (1L) regimen combined trastuzumab with chemotherapy (CT, including taxanes), followed by a second-line (2L) regimen of lapatinib plus capecitabine. This study is a retrospective analysis that investigates clinico-pathological attributes (including blood biomarkers) derived from medical documentation of HER2-positive ABC patients managed at a public oncological center in Peru, along with their relationship to survival recorded from 2020 through 2022. Effectiveness was gauged by OS and progression-free survival (PFS). A commentary was incorporated on the impact of clinicopathological parameters on OS, including results from 2L "long-term responder" subjects (who attained a response to 2L treatment lasting $\geqslant$ 6 months), as well as an appraisal of blood biomarkers. Treatment sequencing extends OS in HER2-positive ABC patients, with a median OS of 34 months. The effect is amplified within the long-term responder group (37 months), particularly for those free from central nervous system (CNS) disease, relative to individuals harboring CNS metastases (51 vs 34 months). Blood biomarkers failed to emerge as prognostic factors for either PFS or OS. Treatment sequencing has been shown to extend OS among LATAM patients with HER2-positive ABC. The present investigation uncovered no prognostic blood biomarkers. Such findings may shape the criteria for selecting patients for treatment sequencing in settings where innovative oncological drugs are not fully available.

Keywords: Advanced breast cancer, HER2-positive, Sequencing treatment, Overall survival, Long-term responder patients, Blood biomarkers

How to Cite This Article: Mansour A, Saeed O. Clinical Outcomes of HER2-Positive Advanced Breast Cancer in a Resource-Constrained Setting: A Retrospective Cohort Study. Asian J Curr Res Clin Cancer. 2026;6(1):200-11. https://doi.org/10.51847/DlOnxGeH3D

Introduction

Among women across the globe, breast carcinoma stands as the most commonly identified malignancy and a principal contributor to cancer-related death [1]. It similarly represents the most frequent tumor diagnosis among women in Latin America (LATAM) and the Caribbean, where both new case numbers and death rates are climbing [2]. Data from GLOBOCAN 2022 placed breast carcinoma at the top for incidence (7797 newly diagnosed cases) and at seventh for mortality (1951 fatalities) within Peru [3]. Figures released by the Instituto Nacional de Enfermedades Neoplásicas (INEN, the national cancer referral institution in Lima, Peru) revealed that breast carcinoma ranked second in incidence (25,344 new cases) and that between 2000 and 2020, 10.41% of individuals initially presented with stage IV disease [4]. In parallel, the most recent Cancer Registry of Metropolitan Lima (2013-2015) positions breast carcinoma as the foremost cause of both new cases and deaths among the female population of Lima [5]. A further release from the Peruvian Ministry of Health (MINSA) covering the initial quarter of 2024 identified a de novo stage IV advanced breast cancer (ABC) rate of 31% [6]. This figure diverges from the information supplied by INEN, Lima, and other national data sources. At the current time, breast

carcinoma is viewed as a critical threat to public health, a judgment underscored by recent ministerial decrees in Peru that designate the management of this neoplasm, alongside cervical cancer, as a national health priority for women [7].

Advanced breast cancer is a condition that cannot be cured, carrying a median overall survival (OS) of nearly 3 years and a 5-year survival proportion of 25%, outcomes seen even in nations where novel oncological agents are unavailable [8]. Roughly 15% to 20% of breast malignancies overexpress human epidermal growth factor receptor 2 (HER2), a biologically aggressive variant tied to unfavorable prognoses [9]. The addition of trastuzumab to chemotherapy (CT) has been proven to lengthen OS, progression-free survival (PFS), and the objective response rate (ORR) relative to CT given alone to women bearing HER2-positive tumors [10]. Still, resistance to trastuzumab commonly emerges, precipitating disease advancement [11], and as many as half of those living with HER2-positive ABC will experience spread to the brain, manifesting as brain metastases (BMs). Recently introduced HER2-targeted agents have reshaped the therapeutic landscape and improved OS. The 1L standard is comprised of pertuzumab + trastuzumab + taxane, [12] whereas trastuzumab deruxtecan (T-DXd) serves as the 2L cornerstone [13]. For patients with active BMs, tucatinib + trastuzumab + capecitabine is a favored third-line (3L) option [14]. Trastuzumab emtansine (T-DM1) provides an alternative 3L strategy. Fourth-line (4L) approaches and regimens used beyond that point encompass trastuzumab + other CT drugs, trastuzumab + lapatinib, lapatinib + capecitabine, neratinib + capecitabine, and margetuximab + CT. Clinical practice guidelines (CPGs) endorse these regimens [15, 16], and they are obtainable in high-income economies. Conversely, low- and middle-income countries (LMICs) face substantial barriers to procuring most of these treatments.

In Peru (a middle-income nation), the majority of public-sector institutions have limited access to anti-HER2-directed regimens for HER2-positive ABC [17]. The present report delineates the treatment outcomes of Peruvian patients who received 1L trastuzumab + CT and subsequent 2L lapatinib + capecitabine at a sole public institution.

Materials and Methods

Patient eligibility

The present work consisted of a retrospective review encompassing Peruvian subjects no younger than 18 years who carried a histologically proven diagnosis of stage IV, locally advanced, unresectable, or recurrent HER2-positive breast carcinoma and who obtained care at the INEN (n = 102) over the 2020–2022 timeframe. Entry into the study required that participants had undergone 1L treatment combining trastuzumab with CT (taxanes), after which a switch to 2L lapatinib plus capecitabine was made, with therapy persisting until either progressive disease supervened or toxicity became prohibitive. Data captured for analysis comprised the clinical-pathological picture as well as a panel of immune-inflammatory blood-based measures: the neutrophil-to-lymphocyte ratio [NLR], the platelet-to-lymphocyte ratio [PLR], and the prognostic nutritional index [PNI].

The sample size was derived based on the anticipated overall response rate—defined as the proportion of patients achieving either a complete or a partial response—for those exposed to 2L lapatinib + capecitabine. This figure, reported as 22% in the seminal publication by Geyer *et al*. [18], served as the benchmark. Setting a 95% confidence level and a precision of 10%, the minimum cohort size was computed to stand at 66 patients.

Endpoints and statistical analysis

Curves depicting OS and PFS were derived using the Kaplan-Meier method. The log-rank test was subsequently applied to assess disparities in survival associated with the characteristics under investigation. Associations between clinicopathological variables and both OS and PFS were explored using a Cox proportional hazards regression framework.

Potential associations between the traits under study and ORR (evaluated using RECIST criteria) were examined using the $\chi 2$ test. No correction for multiple comparisons was applied, and findings with P-values $< .05$ (SPSS) were interpreted as statistically significant. The R Software platform (version 4.3.2) was tasked with performing all calculations and producing all figures. Classification of adverse event (AE) intensity was aligned with the Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The following laboratory parameters, sampled before commencement of 1L trastuzumab + CT, served as the basis for calculating the blood biomarkers: absolute neutrophil and lymphocyte counts (NLR), platelet and lymphocyte counts (PLR), and albumin concentration (PNI). Individuals designated as “long-term responders” were those who realized a

sustained clinical benefit—manifesting as a complete response, a partial response, or stable disease constituting the best overall response—that was maintained across a period not shorter than 24 weeks [19].

Ethical statements

Before starting 1L treatment, informed consent was obtained from each patient, with documentation placed in the patient's medical record. The authors attest to their recognition of the imperative to uphold patient data security, ensure confidentiality, and conduct investigations involving human participants in strict adherence to the ethical principles articulated in the Declaration of Helsinki. Retrospective personal details, extracted from clinical charts, were anonymized through the use of a coded Excel spreadsheet to protect confidentiality. Beyond this, the manuscript was approved on January 2, 2025, by the Institutional Review Board (IRB) operating under the name "Review Committee of the Instituto Nacional de Enfermedades Neoplásicas (CRPI-INEN)" and assigned the reference code "INEN 25-01."

Results and Discussion

Patient demographics and clinicopathological characteristics

A summary of the clinicopathological attributes characterizing the patient cohort is furnished in **Table 1.** The series comprised 102 female patients harboring a diagnosis of HER2-positive ABC, with the median age standing at 55 years (the age distribution extended from 31 to 82). ECOG performance status of 0-1 was recorded for the majority of participants (84%); postmenopausal status was observed in 70%, and co-expression of hormonal receptors was identified in 51%. De novo presentation was noted in one-third of cases, an equal fraction had central nervous system (CNS) disease, and visceral metastases were present in 48% of the women studied.

Table 1. Clinic pathological features of HER2 (+) ABC Peruvian patients (pts).

Clinicopathological characteristics of HER2-positive ABC patients (Peru)	Total (n = 102)
Age at diagnosis (years)	
Median [range]	55 [31–82]
ECOG performance status	
1	86 (84.3%)
2	16 (15.7%)
Disease presentation	
De novo disease	33 (32.7%)
Progressive disease	49 (48.5%)
Locally advanced unresectable	13 (12.9%)
Recurrent disease	6 (5.9%)
Luminal subtype co-expression	
Present	52 (51.0%)
Absent	50 (49.0%)
Menopausal status	
< 50 years	31 (30.4%)
≥ 50 years	71 (69.6%)
Central nervous system (CNS) metastases	
Present	31 (33.0%)
Absent	63 (67.0%)

Efficacy

Assessment of 1L PFS among the treated population revealed a median interval of 11 months (the observed range stretched from 1 to 41 months) **(Figure 1).** At the landmark time points of 12, 24, and 36 months, the proportion of patients remaining free of progression under 1L therapy reached 41%, 14%, and 2%, respectively. The CNS (33%) and the pulmonary parenchyma (9.8%) were the predominant sites of metastatic dissemination following 1L. Moreover, 44% of participants underwent radiotherapy, with whole-brain irradiation being the most

commonly delivered. Longer PFS was observed in postmenopausal compared with premenopausal women (12 vs 9 months, P = .014).

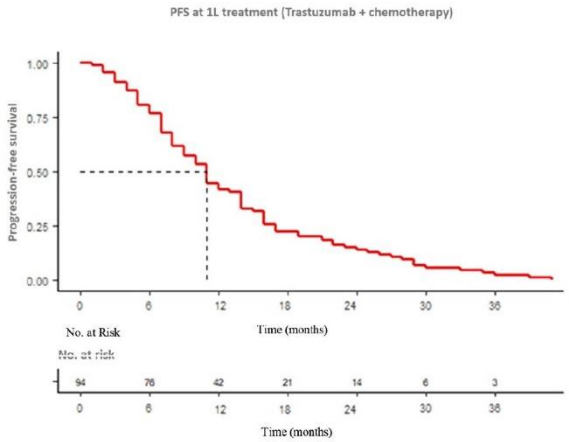

Figure 1. Estimated progression-free survival (PFS) in patients with HER2 (+) advanced breast cancer (ABC) at first-line (1L) treatment.

A sequential treatment approach was applied universally across the cohort. The median PFS for the 2L phase was found to be 8 months (spanning 1 to 30 months) **(Figure 2).** For patients receiving 2L therapy, the probability of remaining progression-free at 12, 24, and 36 months was 34%, 7%, and 0%, respectively. An ECOG performance status of 1, compared with 2, was associated with superior PFS (8 vs 4 months; P = .008). The 2L ORR amounted to 18%.

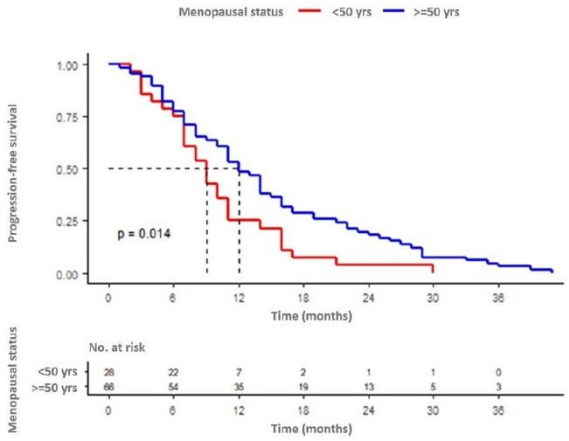

Figure 2. Estimated PFS at 1L according to menopausal status.

At a median follow-up of 24 months (range, 9 to 58 months), the median OS was 34 months **(Figure 3).** The projected survival rates at 12, 36, and 48 months were 93%, 47%, and 34%, respectively. Women in whom CNS metastases had developed fared considerably worse from a survival standpoint **(Figure 4),** with the median OS coming to 38 months for those without such involvement versus 24 months for those with it (P = .0057).

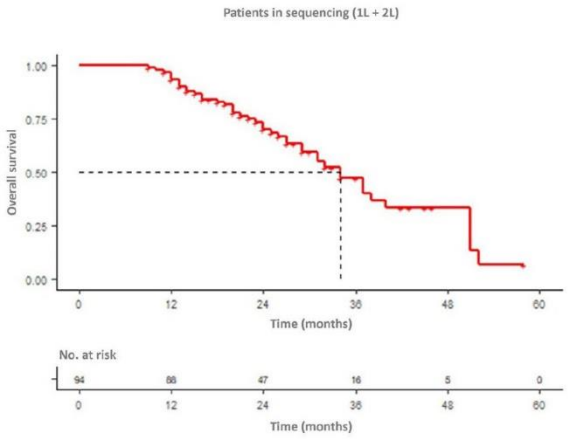

Figure 3. Estimated overall survival (OS) in Peruvian patients with HER2 (+) ABC treated in sequencing (1L + 2L).

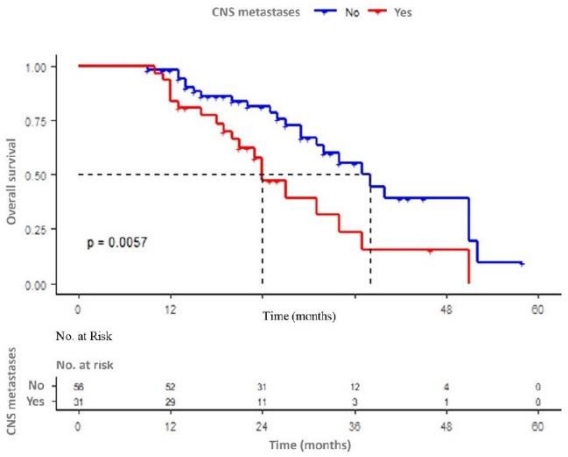

Figure 4. Estimated OS by central nervous system (CNS) metastases.

Long-term responder patients

When the analysis was confined to long-term responders, OS rates at 12, 36, and 48 months were 92%, 54%, and 47%, respectively **(Table 2).** A median OS of 37 months was estimated within this subgroup **(Figure 5).** For these individuals, freedom from CNS metastases translated into a sizable survival advantage relative to those harboring CNS deposits, with median OS values of 51 and 24 months, respectively (P = .0034) **(Figure 6).**

Table 2. Estimates of overall survival (OS) according to study features.

Variables	P-value	48 months	36 months	12 months
Overall cohort	—	34%	47%	93%
Age category (years)				
< 60	.15	27%	44%	92%
≥ 60		45%	54%	97%
ECOG performance status				
1	.72	35%	51%	95%
2		—	19%	87%
Disease presentation				
De novo	.94	30%	40%	100%
Other categories		36%	52%	90%
Luminal co-expression				
Present	.14	40%	50%	98%
Absent		23%	46%	89%

Menopausal status (years)				
<50	.31	37%	37%	86%
≥50		32%	51%	97%
Central nervous system metastases				
Present	.0057	16%	24%	84%
Absent		39%	56%	98%
Response to second-line (2L) therapy				
Complete response	.22	100%	100%	100%
Partial response		76%	76%	100%
Stable disease		37%	47%	90%
Progressive disease		28%	42%	100%

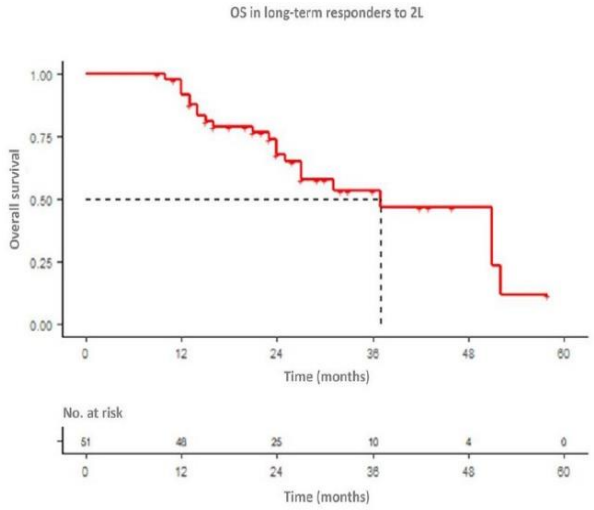

Figure 5. Estimated OS in long-term responder patients to 2L therapy.

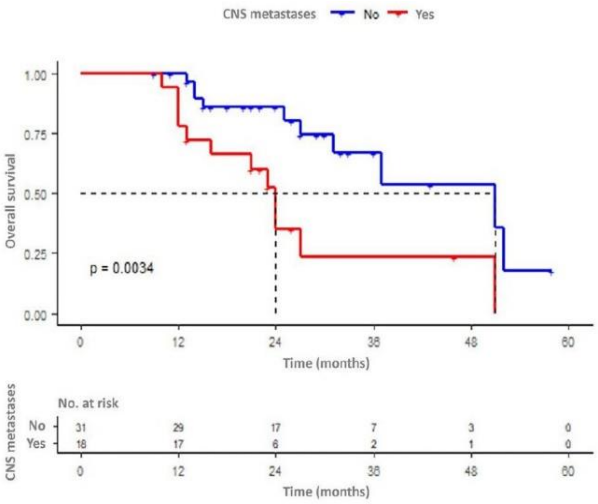

Figure 6. Estimated OS curves by CNS metastasis in long-term responders.

Of patients who progressed through 2L treatment, 43% received additional lines of therapy; CT (with gemcitabine most frequently selected) was administered in 22% of cases, and palliative radiotherapy in 9%.

Safety

Table 3 catalogs the treatment-emergent AEs attributed to 2L therapy, which were encountered by 46% of the cohort. The overwhelming majority of these events were of mild intensity, with grade 3 toxicity representing

merely 4% of the total and no occurrences of grade 4 AEs whatsoever. The most prominent AE was hand-foot syndrome, affecting 51% of patients, followed by rash (11%) and diarrhea (9%). Permanent discontinuation of 2L therapy as a consequence of AEs took place in 22% of cases. Crucially, no treatment-related deaths were recorded.

Table 3. Treatment-related adverse events of Peruvian patients with HER2 (+) ABC with 2L lapatinib + capecitabine.

Category	Event	Grade 4 n (%)	Grade 3 n (%)	Grade 2 n (%)	Grade 1 n (%)
Overall incidence	—	0 (0)	2 (4.3)	12 (25.5)	33 (70.2)
General and administration site conditions	Asthenia[a]	0 (0)	0 (0)	1 (2.1)	0 (0)
Hematologic disorders	Anemia	0 (0)	0 (0)	0 (0)	3 (6.4)
	Neutropenia	0 (0)	0 (0)	1 (2.1)	0 (0)
Gastrointestinal disorders	Diarrhea	0 (0)	0 (0)	3 (6.4)	1 (2.1)
	Transaminitis[b]	0 (0)	0 (0)	2 (4.3)	0 (0)
	Vomiting (Emesis)	0 (0)	1 (2.1)	1 (2.1)	1 (2.1)
	Nausea	0 (0)	0 (0)	0 (0)	1 (2.1)
	Abdominal pain	0 (0)	0 (0)	1 (2.1)	1 (2.1)
	Hyperbilirubinemia	0 (0)	1 (2.1)	2 (4.3)	1 (2.1)
Skin and subcutaneous tissue disorders	Hand–foot syndrome	0 (0)	3 (6.4)	12 (25.2)	9 (18.9)
	Rash[c]	0 (0)	1 (2.1)	3 (6.4)	2 (4.3)
Infections	Infection	0 (0)	0 (0)	1 (2.1)	0 (0)
Musculoskeletal and neurologic disorders	Peripheral neuropathy	0 (0)	0 (0)	0 (0)	1 (2.1)
Thoracic and mediastinal disorders	Dyspnea	0 (0)	0 (0)	0 (0)	1 (2.1)

Severity of adverse events was graded according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

[a] Includes asthenia, decreased activity, fatigue, and malaise.

[b] Includes AST and/or ALT elevated.

[c] Includes dermatitis, dermatitis acneiform, erythematous rash, macular rash, papular rash, pruritic rash, erythema, and erythema multiform.

Blood biomarkers

When PFS and OS were examined in relation to the array of inflammatory blood biomarkers—namely NLR, PLR, and PNI—no statistically significant divergences were observed, regardless of whether patients were undergoing 1L or 2L therapy.

A sequential therapeutic strategy is the preferred approach for those diagnosed with HER2-positive ABC, particularly for individuals with a favorable performance status (ECOG 0-1) and minimal or no CNS burden. It bears mentioning that even the CLEOPATRA investigation specifically barred entry to patients presenting with active CNS metastases [20]. In comparison with those landmark studies, the present research recruited a larger contingent of subjects with de novo advanced illness, an ECOG score of 2, and CNS disease. The rate of de novo cases we observed (33%) is roughly in line with those reported by the CLEOPATRA study (38%) and various LATAM registries (30%–50%). Prior analyses centered on Peruvian women with HR (+)/HER2-negative ABC brought to light a propensity toward an "aggressive disease" phenotype in this demographic, characterized by rapid clinical deterioration and a heavy tumor load, a constellation of features that contributes to the heightened rate of de novo presentation [21]. An investigation rooted in real-world practice found a median OS of 40 months among treatment-naïve HER2-positive ABC patients receiving 1L pertuzumab + trastuzumab + CT (taxanes) and selected for visceral metastases alone, further attesting to the aggressive disease trajectory observed in specific subgroups [22].

Findings from the study at hand point to a 34-month OS gain achieved via the use of sequential treatment, a figure that aligns with the range of median OS values—spanning from 25.1 to 38.1 months—reported in the preceding era of 1L trastuzumab + CT trials, which employed an approach analogous to our sequence [23-25]. In a separate real-world series, the 2L median OS with T-DM1 was 41 months, though it is worth noting that this evidence did not arise from a LATAM population [26].

Participants whose disease did not involve the CNS had longer OS (38 vs 24 months; P = 0.0057). Such data reinforce the dire prognostic implications of CNS metastases, which continue to compromise survival in HER2-positive ABC—an effect evident even with lapatinib, an agent long distinguished for its purported ability to cross the blood-brain barrier. The therapeutic impact of this mechanistic property is both amplified and corroborated by the advent of next-generation tyrosine kinase inhibitors, namely tucatinib [27] and T-DXd [28], both of which are recognized to have CNS activity. The contemporary therapeutic armamentarium for HER2-positive ABC patients who develop BMs now comprises more effective choices. These include the subgroup of individuals with untreated or active brain lesions, a population that prior randomized studies have systematically excluded from participation.

For 1L PFS in our cohort, the median was 11 months, a longer interval in postmenopausal patients. Turning to the 2L phase, a median PFS of 8 months was secured—closely mirroring the pivotal trial's result (8.4 months) [18]—and a notable divergence in 2L PFS emerged in relation to ECOG status. This finding underscores the importance of maintaining adequate functional status after progressing to 1L. An analysis of European patients in a real-world setting, who were treated with 1L pertuzumab + trastuzumab + CT followed by 2L T-DM1, described a median OS of 42 months; their 1L and 2L PFS times were 13.4 and 6.6 months, respectively, values that are broadly congruent with the sequential approach evaluated in the present study [29].

When the focus was narrowed to long-term responders, the median OS exceeded that of the overall population. The advantage was amplified further among those without CNS metastases, whose OS reached 51 months compared with 24 months (P = .0034). Isolated reports of protracted responses to trastuzumab + CT in HER2-positive ABC exist, yet the precise prevalence of such durable regressions remains unclear [30-32]. According to the end-of-study analysis of the CLEOPATRA trial, approximately one-third of patients with HER2 (+) ABC survive to 8 years of follow-up [33]. An exploratory analysis, meanwhile, probed the significance of an early radiologic response—gauged at the initial tumor assessment 9 weeks into treatment—revealing that individuals who attained either a CR (12.7%), a PR (67.1%), or SD (20.2%) differed in outcome; specifically, subjects achieving CR combined with an early radiologic response surpassed those with PR or SD in terms of both PFS (P < .001) and OS (P = .002) [34]. Deeper investigation remains necessary to isolate additional factors that may either enable or clarify instances of long-term response.

Regarding the safety of patients receiving our 2L regimen, the toxicity profile was both consistent with and no less manageable than that observed with lapatinib + capecitabine in clinical trials. Most AEs fell into the mild category, with grade 3 hand-foot syndrome emerging in just 6.4% of cases—mirroring the pivotal trial's rate of 7%. The complete absence of grade 4 AEs or any treatment-attributable fatalities in the current report further supports the acceptable safety record of this combination. Although earlier data have identified diarrhea as the most prominent grade 3 AE (at a rate of 12%), no such events were documented in this cohort.

A recently updated consensus has underscored the imperative of sequencing treatments for ABC and has put forth subtype-specific recommendations [35]. In the domain of HER2-positive disease, multiple therapeutic avenues beyond the 3L line—or even later—were formerly judged to be suboptimal before the introduction of novel anti-HER2 therapies like T-DXd and tucatinib [36]. As potent new treatments are introduced and evidence-based CPGs are revised, the landscape of treatment sequencing continues to evolve [37].

Lapatinib combined with capecitabine is currently considered a 4L or later option for managing HER2-positive ABC. Notwithstanding this positioning, resource-stratified guidelines [38] and local consensus statements [39] continue to validate its application in environments characterized by resource limitations, thereby supporting the 2L strategy we employed. Such recommendations stem from the imperative to craft feasible sequential therapy pathways, given that most LATAM nations still lack access to new oncological agents for HER2-positive ABC. Public health systems in LMICs, underpinned by ethical obligations, must ensure the provision of effective cancer drugs at affordable prices by implementing sound health policies. Peru, for its part, has directed notable efforts toward expanding access to anti-HER2 agents for individuals confronting HER2-positive ABC. The Ministry of Health (MINSA) initially endorsed trastuzumab + CT as a 1L intervention for metastatic disease in 2019. Thereafter, our own institution (INEN) greenlit the use of lapatinib + capecitabine as a 2L option in 2020 for HER2-positive ABC patients who demonstrated progression on trastuzumab-containing therapy. Building on this progress, in March 2023, pertuzumab + trastuzumab + docetaxel was approved as a 1L regimen for HER2-positive ABC by the National Network for the Evaluation of Health Technologies ("Red Nacional de Tecnologias Sanitarias," RENETSA) for national deployment across Peru [40]. In a complementary move, INEN has endorsed

a local technical document (CPG) on the multidisciplinary management of ABC, intended to serve as a nationwide reference and be implemented within MINSA-affiliated oncological institutions [41].

Turning to biomarkers, the present trial failed to identify any prognostic factors. Across a wide range of tumor types, both NLR and PLR have emerged as prognostic biomarkers. Yet, when scrutinized for their predictive capacity, the data prove inconsistent, with the notable exception of the HER2-positive subtype. One phase II study, which recruited HER2-positive ABC patients assigned to pertuzumab plus trastuzumab with either eribulin (n = 30) or nab-paclitaxel (n = 21), analyzed ALC, NLR, and PLR. Thresholds were predefined as follows: ALC at 1000 or 1500 cells/μL, NLR at 2, and PLR at 250. When gauged against those whose ALC fell between 1000 and ⩽ 1500/μL or dipped below 1000/μL, subjects whose ALC reached ⩾ 1500/μL derived a significant PFS advantage (P = .0106). An elevated ALC at baseline (⩾ 1500/μL) bore a strong independent association with prolonged PFS (HR: 0.37, 95% CI: 0.17-0.79; P = .0108); meanwhile, no comparable PFS improvement was linked to either NLR or PLR. The PFS enhancement associated with ALC ⩾ 1500/μL was held regardless of whether visceral metastases were present or which CT backbone was used. Within this modestly sized cohort of HER2-positive ABC patients receiving pertuzumab + trastuzumab + CT, pretreatment ALC was predictive of PFS [42].

An additional investigation examined the relationship between baseline NLR or PLR and PFS across two ABC subgroups (HR-positive/HER2-negative and triple-negative). Among the triple-negative subset treated with platinum-based CT (n = 57), both high NLR and high PLR correlated with substantially shorter PFS in univariate as well as multivariate models. No such association, however, materialized within the HR (+)/HER2 (−) arm (n = 148). It therefore appears that the predictive value of NLR and PLR is limited to patients with triple-negative ABC [43].

One further study focused on NLR assessment in HER2-positive ABC patients receiving T-DM1 therapy (n = 53). The neutrophil-to-lymphocyte ratio was derived from peripheral blood samples obtained before treatment initiation and after the first cycle of therapy, with a cutoff of 2.56. When compared against those classified as NLR-high (n = 27), patients who fell into the NLR-low category at baseline (n = 26) experienced a markedly superior PFS (HR: 0.22; 95% CI: 0.11-0.49, P = .0001). An extended OS was significantly correlated with NLR-low status (HR: 0.38, 95% CI: 0.17-0.91, P = .0296). Subgroup analysis within this trial showed that the PFS advantage for NLR-low individuals persisted across strata defined by the number of prior CT lines, earlier trastuzumab exposure, visceral metastatic burden, HR status, and HER2 immunohistochemical score. The mode of action underlying T-DM1 efficacy involves stimulating the immune system. For those carrying a HER2-positive ABC diagnosis, a low baseline NLR reading would appear to create a milieu more conducive to deriving benefit from T-DM1 [44].

The work presented here is not without its limitations. It first draws on retrospective data extraction from clinical records. A second concern is the small sample size, which may have influenced the findings. In addition, the data constitute a real-world evidence report; it is worth noting that real-world datasets not infrequently yield results that differ from those of pivotal trials, which are rooted in carefully curated, highly selective patient populations.

Conclusion

The practice of sequencing therapies—specifically, delivering 1L trastuzumab + CT and subsequently transitioning to 2L lapatinib + capecitabine—was demonstrated to prolong OS among Peruvian women diagnosed with HER2-positive ABC, while maintaining a side-effect burden within acceptable limits. The greatest magnitude of benefit accrued to postmenopausal patients who possessed an ECOG score of 1 and whose disease had not invaded the CNS. In addition, a distinct fraction of long-term responders was identified. Within that group, the absence of CNS metastases was associated with an OS substantially longer than that observed in individuals with CNS compromise. No biomarker measured in peripheral blood was identified as carrying prognostic weight in this analysis. The outcomes achieved with the 2L regimen position this sequential strategy as an effective therapeutic recourse within a middle-income context marked by resource scarcity—a conclusion supported by both local consensus guidance and institutional CPGs.

Acknowledgments: The authors are grateful to the Instituto Nacional de Enfermedades Neoplásicas (INEN) and GECOPERU for offering the facilities and support for our study. We also extend our gratitude to Dr. Ian Tannock for his support in the development of this manuscript.

Conflict of Interest: None

Financial Support: None

Ethics Statement: This study was approved by the Ethics Committee of the Instituto Nacional de Enfermedades Neoplásicas (Ethics Code: INEN 25-01 on January 2, 2025). All participants provided written informed consent before medical treatment. This study was conducted in accordance with the World Medical Association Declaration of Helsinki guidelines.
Written informed consent for treatment was obtained from patients before 1L treatment for HER2-positive ABC.

References

1. Siegel R, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12-49.
2. Piñeros M, Laversanne M, Barrios E, de Camargo Cancela M, de Vries E, Pardo C, et al. An updated profile of the cancer burden, patterns and trends in Latin America and the Caribbean. Lancet Reg Health Am. 2022;13:100294.
3. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74:229–63.
4. Cancer News Cases 2020-2020. Lima, Peru: Cancer Epidemiology Unit, Instituto Nacional de Enfermedades Neoplásicas (INEN).
5. Payet E. Registro de Cáncer de Lima Metropolitana. Incidencia y Mortalidad 2013-2015. Vol. 6. Lima, Peru: Instituto Nacional de Enfermedades Neoplásicas (INEN); 2021.
6. Sala Situacional de Cáncer en el Perú. I Trimestre 2024. Lima, Peru: Vigilancia Epidemiológica del Cáncer, Ministerio de Salud (MINSA); 2024.
7. Ley Nacional del Cáncer. N° 31336. Diario Oficial El Peruano. 2021 Aug 10.
8. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31:1623–49.
9. Marra A, Chandarlapaty S, Modi S. Management of patients with advanced-stage HER2-positive breast cancer: current evidence and future perspectives. Nat Rev Clin Oncol. 2024;21:185-202.
10. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. Nat Rev Drug Discov. 2023;22:101-26.
11. Vivekanandhan S, Knutson K. Resistance to trastuzumab. Cancers (Basel). 2022;14:5115.
12. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, et al. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. N Engl J Med. 2012;366:109–19.
13. Hurvitz SA, Hegg R, Chung WP, Im SA, Jacot W, Ganju V, et al. Trastuzumab deruxtecan versus trastuzumab emtansine in patients with HER2-positive metastatic breast cancer: updated results from DESTINY-Breast03, a randomised, open-label, phase 3 trial. Lancet. 2023;401:105–17.
14. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med. 2020;382:597–609.
15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 2.2025. Plymouth Meeting (PA): NCCN; 2025.
16. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021;32:1475–95.
17. Valencia-Mesías G, Rioja-Viera P, Morante-Cruz Z, Toledo-Morote Y, Neciosup-Delgado S, Gómez-Moreno H. The current situation regarding the availability and accessibility of anticancer drugs for breast cancer in the Peruvian public health systems. Ecancermedicalscience. 2021;15:1224.
18. Geyer CE, Forster J, Lindquist D, Chan S, Romieu CG, Pienkowski T, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med. 2006;355:2733–43.
19. Schmid S, Klingbiel D, Aebi S, Goldhirsch A, Mamot C, Munzone E, et al. Long-term responders to trastuzumab monotherapy in first-line HER2-positive advanced breast cancer: characteristics and survival data. BMC Cancer. 2019;19:902.

20. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372:724–34.
21. Esin E, Oksuzoglu B, Bilici A, Cicin I, Kostek O, Kaplan MA, et al. Pertuzumab, trastuzumab and taxane-based treatment for visceral organ metastatic, trastuzumab-naïve breast cancer: real-life practice outcomes. Cancer Chemother Pharmacol. 2019;83:131-43.
22. Esin E, Oksuzoglu B, Bilici A, Cicin I, Kostek O, Kaplan MA, et al. Pertuzumab, trastuzumab and taxane-based treatment for visceral organ metastatic, trastuzumab-naïve breast cancer: real-life practice outcomes. Cancer Chemother Pharmacol. 2019;83:131–43.
23. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med. 2001;344:783–92.
24. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23:4265–74.
25. Valero V, Forbes J, Pegram MD, Pienkowski T, Eiermann W, von Minckwitz G, et al. Multicenter phase III randomized trial comparing docetaxel and trastuzumab with docetaxel, carboplatin, and trastuzumab as first-line chemotherapy for patients with HER2-gene-amplified metastatic breast cancer (BCIRG 007 study): two highly active therapeutic regimens. J Clin Oncol. 2011;29:149–56.
26. Bahçeci A, Paydaş S, Ak N, Karakurt O, Gürleyik MG, Kızıltan Ç, et al. Efficacy and safety of trastuzumab emtansine in HER2-positive metastatic breast cancer: real-world experience. Cancer Invest. 2021;39:473–81.
27. Lin NU, Murthy RK, Abramson V, Anders C, Bachelot T, Bedard PL, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB randomized clinical trial. JAMA Oncol. 2023;9:197–205.
28. Artzi D, Berg T, Celik A, Kümler I, Kenholm J, Al-Rawi S, et al. Real-world survival of Danish patients with HER2-positive metastatic breast cancer. Acta Oncol. 2023;62:601-7.
29. Maciá Escalante S, Rodríguez Lescure A, Sanz VP, Martinez-Banaclocha N, Ponce CG, Mena AC. A patient with breast cancer with hepatic metastases and a complete response to herceptin as monotherapy. Clin Transl Oncol. 2006;8(10):761-3.
30. Beda M, Basso U, Ghiotto C, Monfardini S. When should trastuzumab be stopped after achieving complete response in HER2-positive metastatic breast cancer patients? Tumori. 2007;93:491-2.
31. Badulescu F, Badulescu A, Paul D, Popescu CF, Florescu C. More than 9 years of continuous trastuzumab treatment in metastatic breast cancer without cardiac toxicity: a case report and literature review. Onco Targets Ther. 2014;7:1911-7.
32. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:519–30.
33. Debien V, Agostinetto E, Bruzzone M, de Azambuja E, Piccart M, Barroso R, et al. The impact of initial tumor response to docetaxel, trastuzumab, and pertuzumab on survival outcomes of patients with HER2-positive metastatic breast cancer: an exploratory analysis of the CLEOPATRA trial. ESMO Open. 2023;8:101417.
34. Cardoso F, Paluch-Shimon S, Schumacher-Wulf E, Bergh J, Biganzoli L, Cardoso MJ, et al. 6th and 7th ESO-ESMO international consensus guidelines for the management of advanced breast cancer (ABC guidelines 6 and 7). Breast. 2024;76:103756.
35. Cesca MG, Vian L, Cristóvão-Ferreira S, Pondé N, de Azambuja E. HER2-positive advanced breast cancer treatment in 2020. Cancer Treat Rev. 2020;88:102033.
36. ABC Global Charter & Decade Report 2015-2025. ABC Global Alliance; 2025.
37. Al Sukhun S, Temin S, Barrios CH, Martei YM, Muss H, Roitberg F, et al. Systemic treatment of patients with metastatic breast cancer: ASCO resource-stratified guideline. JCO Glob Oncol. 2024;10:e2300285.
38. Valencia F, Gómez HL, Neciosup SP, Juárez O, Corkidi G, Tueros AM, et al. Advanced breast cancer guidelines in Latin America: assessment, adaptation, and implementation of fifth advanced breast cancer consensus guidelines. JCO Glob Oncol. 2024;10:e2200067.

39. Pertuzumab, trastuzumab y quimioterapia como primera línea de tratamiento para el cáncer de mama HER2+ metastásico o localmente avanzado irresecable en adultos con estado funcional ECOG 0-2. Lima, Peru: Red Nacional de Tecnologías Sanitarias (RENETSA), Instituto Nacional de Salud; 2023.
40. Documento técnico: Tratamiento multidisciplinario del cáncer de mama metastásico. Resolución Jefatural N° 166-2021-J-INEN. Lima, Peru: Instituto Nacional de Enfermedades Neoplásicas (INEN); 2021.
41. Araki K, Ito Y, Fukada I, Kobayashi K, Miyagawa Y, Imamura M, et al. Predictive impact of absolute lymphocyte counts for progression-free survival in human epidermal growth factor receptor 2-positive advanced breast cancer treated with pertuzumab and trastuzumab plus eribulin or nab-paclitaxel. BMC Cancer. 2018;18:982.
42. Vernieri C, Mennitto A, Prisciandaro M, Corti C, Milano M, Giacomelli L, et al. The neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios predict efficacy of platinum-based chemotherapy in patients with metastatic triple negative breast cancer. Sci Rep. 2018;8:8703.
43. Imamura M, Morimoto T, Egawa C, Fukui R, Bun A, Ozawa H, et al. Significance of baseline neutrophil-to-lymphocyte ratio for progression-free survival of patients with HER2-positive breast cancer treated with trastuzumab emtansine. Sci Rep. 2019;9:1811.