

Research Article

Real World Outcomes of First Line Pertuzumab Based Therapy in HER2 Positive Metastatic Breast Cancer: Performance Status, Metastatic Burden and Nutritional Status as Prognostic Factors

 Savaş Gökçek,¹  Emine Bihter Eniseler,²  Özge Yetginoğlu,³  Ferhat Ekinci,²  Atike Pınar Erdoğan,²  Mehmet Uzun,⁴
 Hüseyin Salih Semiz,³  İlkey Tuğba Ünek³

¹Department of Medical Oncology, Necip Fazıl City Hospital, Kahramanmaraş, Türkiye

²Department of Medical Oncology, Manisa Celal Bayar University Faculty of Medicine, Manisa, Türkiye

³Department of Medical Oncology, Dokuz Eylül University Faculty of Medicine, İzmir, Türkiye

⁴Department of Medical Oncology, University of Health Sciences Tepecik Training and Research Hospital, İzmir, Türkiye

Abstract

Objectives: To describe real-world outcomes of first-line pertuzumab, trastuzumab, and taxane therapy in HER2-positive metastatic breast cancer and identify factors associated with survival

Methods: We retrospectively reviewed 110 consecutive patients treated at two centres between August 2016 and December 2025. Progression-free survival (PFS) and overall survival (OS) were measured from the first pertuzumab infusion. Survival factors were evaluated using Cox regression. Seven inflammatory and nutritional indices were dichotomised at their medians, with Benjamini–Hochberg correction.

Results: The median age was 56 years; 82 patients (74.5%) had de novo metastatic disease. During a median follow-up of 33.4 months, 61 progression events and 37 deaths occurred. Median PFS was 21.6 months, and median OS was 47.1 months. ECOG performance status 1 (HR=2.74; p=0.003) and at least three metastatic sites (HR=2.29; p=0.013) were independently associated with shorter OS. At least three metastatic sites (HR=2.14; p=0.005) and a low prognostic nutritional index (HR=1.87; p=0.023) were associated with shorter PFS. No index remained significant after multiple-testing correction. No grade 3–4 event was documented.

Conclusion: Performance status and metastatic burden were the strongest prognostic factors. De novo versus recurrent presentation was not prognostic when measured from a common starting point.

Keywords: Dual HER2 blockade, HER2 positive breast cancer, metastatic breast cancer, pertuzumab, prognostic nutritional index, real world outcomes

Cite This Article: Gökçek S, Eniseler EB, Yetginoğlu Ö, Ekinci F, Erdoğan AP, Uzun M, et al. Real World Outcomes of First Line Pertuzumab Based Therapy in HER2 Positive Metastatic Breast Cancer: Performance Status, Metastatic Burden and Nutritional Status as Prognostic Factors. EJMI 2026;10(4):459–472.

Address for correspondence: Savas Gokcek, MD, Department of Medical Oncology, Necip Fazıl City Hospital, Kahramanmaraş, Türkiye

E-mail: gokceksavas35@gmail.com

Submitted Date: June 4, 2026 **Revised Date:** August 31, 2026 **Accepted Date:** September 2, 2026

©Copyright 2026 by Eurasian Journal of Medical Investigation - Available online at www.ejmi.org

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



Human epidermal growth factor receptor 2 (HER2) is overexpressed or amplified in approximately 15 to 20 percent of breast cancers and was historically associated with an aggressive course and short survival.^[1,2] The sequential introduction of trastuzumab, and subsequently of dual HER2 blockade, has changed that trajectory,^[3,4] to the point where metastatic HER2 positive disease is now among the more treatable metastatic subtypes.

The CLEOPATRA trial established the combination of pertuzumab, trastuzumab, and docetaxel as the first-line standard of care,^[4] reporting a median progression-free survival of 18.7 months and a median overall survival of 57.1 months in its final analysis, compared with 40.8 months with trastuzumab and docetaxel alone.^[5,6] Those figures were obtained in a population selected by trial eligibility criteria, with a performance status of 0 or 1, adequate cardiac function, and no untreated central nervous system disease. Whether they are reproduced in routine practice, where older patients, comorbidity, and poorer performance status are all common, is a separate question and one that matters for the counselling of individual patients.

Real-world series of first-line dual blockade have generally reported progression-free survival in the range of 18 to 24 months, with overall survival estimates that vary more widely and are frequently immature.^[7-10] Alongside the established clinical prognostic factors of performance status, disease burden, and visceral involvement, there has been considerable interest in whether inexpensive markers derived from routine blood counts add prognostic information. Indices such as the neutrophil-to-lymphocyte ratio, the systemic immune-inflammation index, and the prognostic nutritional index have been associated with outcomes in several tumour types,^[11-13] although the evidence in HER2 positive metastatic breast cancer treated with dual blockade remains limited, and the cut-off values used are inconsistent between studies.

We therefore reviewed our own consecutive experience of first-line pertuzumab-based therapy with two aims: to report progression-free and overall survival with the maturity of follow-up made explicit and to test whether clinical, pathological, and blood-based inflammatory factors are associated with those outcomes. Because the cohort contains both de novo metastatic and recurrent patients, we measured survival from the start of pertuzumab therapy for all patients, which is the only index date that is defined identically in both groups.

Methods

Study design and patients

This was a retrospective observational cohort study conducted at two centres. We identified all consecutive pa-

tients with HER2-positive metastatic breast cancer who began first-line pertuzumab, trastuzumab, and a taxane between 3 August 2016 and 19 December 2025. The date of the last recorded follow-up or death in the database, 20 February 2026, was used as the data cut-off.

Patients were included if HER2 positivity had been confirmed by immunohistochemistry with a score of 3 plus or by in situ hybridisation where the immunohistochemical score was 2 plus,^[2] and if the pertuzumab-containing regimen was given as the first systemic treatment for metastatic disease. Patients who had received a HER2-directed agent for metastatic disease before pertuzumab were excluded. Prior neoadjuvant or adjuvant trastuzumab was permitted. Ethical approval was obtained from the institutional clinical research ethics committee, and because the study used data collected in the course of routine care with no additional intervention, the requirement for individual informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki and is reported in accordance with the STROBE statement.^[14]

Data collection and definitions

Demographic, clinicopathological, treatment, and outcome data were extracted from electronic records and recorded in a single database. Presentation was classified as de novo metastatic when metastatic disease was present at first diagnosis and as systemic recurrence when metastatic disease developed after treatment for non-metastatic disease. Metastatic burden was recorded as the number of involved anatomical sites among the liver, lung, brain, bone, and lymph nodes and was analysed as one or two sites versus three or more; this is a count of sites and not of individual lesions. Because regional and distant lymph nodes were involved in almost all patients, we also report the distribution excluding nodal sites. Comorbidity, height, and weight were recorded where available; height and weight were documented in fewer than half of the patients and were not used in any analysis.

Treatment and assessment

Pertuzumab was given at a loading dose of 840 mg followed by 420 mg every three weeks, with trastuzumab at standard intravenous or subcutaneous dosing and docetaxel or paclitaxel as the taxane partner. The taxane was given for a planned six cycles and continued or stopped at the discretion of the treating physician; the number of taxane cycles actually delivered is reported in full. Antibody therapy was continued until progression or unacceptable toxicity. Concurrent endocrine therapy was permitted in hormone receptor-positive disease at physician discretion. Disease was assessed by computed tomography and, where clinically

indicated, by positron emission tomography or magnetic resonance imaging at intervals of approximately three months, and responses were classified according to RECIST version 1.1.^[15] Adverse events were graded according to the Common Terminology Criteria for Adverse Events version 5.0 and were recorded as absent, grade 1 or 2, or grade 3 or 4. Because toxicity was documented for a variable subset of patients depending on the completeness of the treatment records, the denominator is reported separately for each event, and no event is assumed to be absent where it was not recorded. Left ventricular ejection fraction was measured by echocardiography before treatment and at the last available assessment on treatment.

Inflammatory and nutritional indices

Complete blood counts and biochemistry obtained before the first cycle were used to calculate the following, with absolute counts expressed as 10 to the power of 3 per microlitre and albumin in grams per decilitre: the neutrophil-to-lymphocyte ratio as neutrophils divided by lymphocytes; the platelet-to-lymphocyte ratio as platelets divided by lymphocytes; the systemic immune-inflammation index as platelets multiplied by neutrophils divided by lymphocytes; the pan-immune-inflammation value as neutrophils multiplied by platelets multiplied by monocytes divided by lymphocytes; the lymphocyte-to-monocyte ratio as lymphocytes divided by monocytes; the prognostic nutritional index as ten times albumin in grams per decilitre plus 0.005 multiplied by the absolute lymphocyte count per microlitre; and the C-reactive protein-to-albumin ratio as C-reactive protein in milligrams per litre divided by albumin in grams per decilitre. Each index was dichotomised at its own median within this cohort, since no externally validated cut-off exists for this population, and the median value used is reported for each index.

Statistical Analysis

Progression-free survival was defined as the interval from the first pertuzumab infusion to radiological or clinical progression or death from any cause, whichever came first, and overall survival as the interval from the first pertuzumab infusion to death from any cause. Patients without an event were censored at the date of last contact. The first pertuzumab infusion was chosen as the index date for both endpoints because it is defined identically for patients presenting with de novo metastatic disease and for those with systemic recurrence; survival measured from the date of primary diagnosis is reported once for comparison with series that use that convention and is not used for any group comparison.

Median follow-up was estimated by the reverse Kaplan-Meier method.^[16] Survival curves were estimated by

the Kaplan-Meier method with 95 percent confidence intervals and compared using the log-rank test; medians not reached within the observed follow-up are reported as not reached. Variables associated with survival at p below 0.10 on univariate analysis were entered into a Cox proportional hazards model, with the number of covariates limited so that at least ten events were available per variable. The proportional hazards assumption was assessed using scaled Schoenfeld residuals. Because the number of taxane cycles accrues during follow-up and cannot be treated as a baseline covariate, its association with survival was examined in a landmark analysis restricted to patients alive and under observation at six months.^[17,18] The log-rank comparisons across subgroups and indices were not adjusted for multiple testing and are reported as exploratory.

Analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA), and a p -value of <0.05 was considered statistically significant. Because seven indices were each tested against two endpoints, we additionally report Benjamini-Hochberg false discovery rates across those 14 tests in Table 1; these are descriptive, and the study was not powered for them. For context on power, 37 deaths and 61 progression events give 80 percent power at a two-sided alpha of 0.05 to detect hazard ratios of about 2.51 and 2.05, respectively, so effects of the magnitude reported for these indices in the literature would require roughly 70 to 80 deaths to detect reliably.

Results

Patients

One hundred and ten patients were included. Accrual was 3 patients in 2016, 1 in 2017, 2 in 2018, 6 in 2019, 3 in 2020, 13 in 2021, 21 in 2022, 15 in 2023, 28 in 2024, and 18 in 2025. Baseline characteristics are shown in Table 2. The median age was 56 years (range, 25 to 91), and 21 patients (19.1 percent) were under 40. Performance status was 0 in 83 patients (75.5 percent) and 1 in 27 (24.5 percent). Eighty-two patients (74.5 percent) presented with de novo metastatic disease and 28 (25.5 percent) with systemic recurrence. Histology was invasive ductal carcinoma in 104 patients (94.5 percent). Estrogen receptor was positive in 66 patients (60.0 percent) and negative in 25, and progesterone receptor was positive in 50 (45.5 percent) and negative in 37; receptor status was not recorded in 19 and 23 patients, respectively. Sixty-nine patients (62.7 percent) had hormone receptor-positive disease, defined as a positive result for either receptor, so patients with no recorded result are counted as not positive. Ki-67 was 14 percent or above in 100 patients (90.9 percent). Histological grade was 1 in 1 patient, 2 in 52, and 3 in 47, and was not recorded in 10

Table 1. Inflammatory and nutritional indices, dichotomised at the cohort median

Index	Median cut off	n	Median OS (95% CI)	p (q)	Median PFS (95% CI)	p (q)
Neutrophil to lymphocyte ratio	2.52					
At or below median		55	82.4 (43.1 to NR)	0.048 (0.17)	23.9 (15.8 to NR)	0.103 (0.18)
Above median		55	38.4 (19.7 to NR)		19.7 (11.3 to 29.4)	
Platelet to lymphocyte ratio	148.26					
At or below median		55	47.1 (43.1 to 82.4)	0.503 (0.59)	20.6 (16.9 to NR)	0.169 (0.24)
Above median		55	46.3 (31.0 to NR)		21.6 (11.6 to 30.8)	
Systemic immune inflammation index	680.56					
At or below median		55	82.4 (43.1 to NR)	0.050 (0.17)	23.5 (15.8 to NR)	0.136 (0.21)
Above median		55	38.4 (19.7 to NR)		19.7 (11.6 to 30.8)	
Pan immune inflammation value	217.12					
At or below median		55	45.8 (38.4 to NR)	0.660 (0.71)	18.1 (13.1 to 23.5)	0.087 (0.18)
Above median		55	82.4 (31.0 to NR)		31.0 (18.7 to 55.2)	
Lymphocyte to monocyte ratio	4.65					
Above median		55	46.3 (38.4 to NR)	0.968 (0.97)	18.6 (13.1 to 29.4)	0.098 (0.18)
At or below median		55	82.4 (31.0 to NR)		26.3 (16.9 to 55.2)	
Prognostic nutritional index	51.45					
Above median		55	82.4 (45.8 to NR)	0.020 (0.14)	30.8 (18.1 to NR)	0.009 (0.13)
At or below median		55	38.4 (28.1 to NR)		20.6 (11.6 to 23.9)	
C reactive protein to albumin ratio	0.96					
At or below median		55	43.1 (18.7 to NR)	0.088 (0.18)	19.1 (11.8 to 55.2)	0.439 (0.56)
Above median		55	82.4 (35.4 to NR)		23.9 (16.9 to 32.4)	

OS: Overall survival; PFS: Progression free survival; NR: Not reached. Cut off values are the medians of this cohort; no externally validated cut off exists for this population. For the prognostic nutritional index and the lymphocyte to monocyte ratio the favourable stratum is the one above the median, and for the remaining indices it is the one at or below the median. Units: absolute counts as 10^3 per microlitre, albumin in g/dL, C reactive protein in mg/L. Seven indices were tested against two endpoints without adjustment for multiple comparisons, so these results are exploratory. The value in parentheses after each p value is the Benjamini Hochberg false discovery rate across all 14 tests in this table; no index reaches a q value below 0.05, and the smallest is 0.126 for the prognostic nutritional index against progression free survival.

(9.1 percent). Diabetes mellitus and coronary artery disease were each present in 21 patients (19.1 percent).

Disease extent

Bone was the most frequently involved distant site (70 patients, 63.6 percent), followed by liver (37, 33.6 percent), lung (32, 29.1 percent), and brain (7, 6.4 percent). Lymph nodes were involved in 105 patients (95.5 percent). Counting all five sites, 74 patients (67.3 percent) had one or two involved sites and 36 (32.7 percent) had three or more. Excluding nodal disease, 7 patients had no distant site recorded, 66 had one, and 37 had two or more, which shows that the site count is driven largely by the near-universal nodal involvement and should be interpreted with that in mind.

Treatment delivered

Docetaxel was the taxane partner in 105 patients (95.5 percent) and paclitaxel in 5 (4.5 percent). The median number of taxane cycles delivered was 6 (range, 1 to 19): 75 patients

(68.2 percent) received exactly the planned six cycles, 17 (15.5 percent) received fewer, and 18 (16.4 percent) received more. The median number of pertuzumab cycles was 18 (range, 1 to 97). Concurrent endocrine therapy was given to 63 of the 69 hormone receptor-positive patients.

Follow-up and survival

Median follow-up by the reverse Kaplan-Meier method was 33.4 months. At the data cut-off, 61 progression-free survival events and 37 deaths (33.6 percent) had occurred. Median progression-free survival was 21.6 months (95 percent CI, 15.8 to 30.8), and median overall survival was 47.1 months (95 percent CI, 38.4 to not reached) (Fig. 1). Progression-free survival was 68.0 percent at one year, 43.9 percent at two years, and 33.7 percent at three years; overall survival was 84.8 percent at one year, 72.6 percent at two years, 63.2 percent at three years, and 48.0 percent at five years. Because only a third of the cohort had died and median follow-up was 33.4 months, the overall survival estimate beyond three

Table 2. Baseline patient and disease characteristics (n=110)

Characteristic	n or value	Percent
Age, years, median (range)	56 (25 to 91)	
Age group		
Under 40	21	19.1
40 or over	89	80.9
ECOG performance status		
0	83	75.5
1	27	24.5
Menopausal status at diagnosis		
Premenopausal	43	39.1
Postmenopausal	66	60.0
Not recorded	1	0.9
Stage at initial diagnosis		
II	5	4.5
III	23	20.9
IV	82	74.5
Presentation		
De novo metastatic	82	74.5
Systemic recurrence	28	25.5
Tumour laterality		
Right	51	46.4
Left	58	52.7
Bilateral	1	0.9
Multifocality		
Absent	86	78.2
Present	23	20.9
Not recorded	1	0.9
Histology		
Invasive ductal	104	94.5
Invasive lobular	3	2.7
Other	3	2.7
Histological grade		
1	1	0.9
2	52	47.3
3	47	42.7
Not recorded	10	9.1
Estrogen receptor		
Not recorded	19	17.3
Positive	66	60.0
Negative	25	22.7
Progesterone receptor		
Not recorded	23	20.9
Positive	50	45.5
Negative	37	33.6
Ki-67 category		
Under 14 percent	10	9.1
14 percent or over	100	90.9

Table 2. Continued

Characteristic	n or value	Percent
Diabetes mellitus		
Absent	89	80.9
Present	21	19.1
Coronary artery disease		
Absent	89	80.9
Present	21	19.1
Chronic lung disease		
Absent	107	97.3
Present	3	2.7
Taxane partner		
Docetaxel	105	95.5
Paclitaxel	5	4.5
Concurrent endocrine therapy		
No	44	40.0
Yes	65	59.1
Not recorded	1	0.9
Metastatic sites		
Liver	37	33.6
Lung	32	29.1
Brain	7	6.4
Bone	70	63.6
Lymph node	105	95.5
Number of metastatic sites		
0	1	0.9
1	9	8.2
2	64	58.2
3	31	28.2
4	4	3.6
5	1	0.9
Taxane cycles, median (range)	6 (1 to 19)	
Pertuzumab cycles, median (range)	18 (1 to 97)	
LVEF before treatment, percent, median (range)	60 (50 to 65)	
LVEF after treatment, percent, median (range)	60 (25 to 65)	

ECOG: Eastern Cooperative Oncology Group; LVEF: Left ventricular ejection fraction. Percentages are calculated on the full cohort of 110 patients. Rows labelled not recorded show missing data. Metastatic sites are not mutually exclusive and therefore do not sum to 110. Where a characteristic was not documented in the source records the count is shown as not recorded rather than being assigned to a category. The column headings repeat on each page where the table continues.

years rests on a small number of patients still at risk, and the numbers at risk are given beneath each curve. For comparison with series that measure survival from the date of prima-

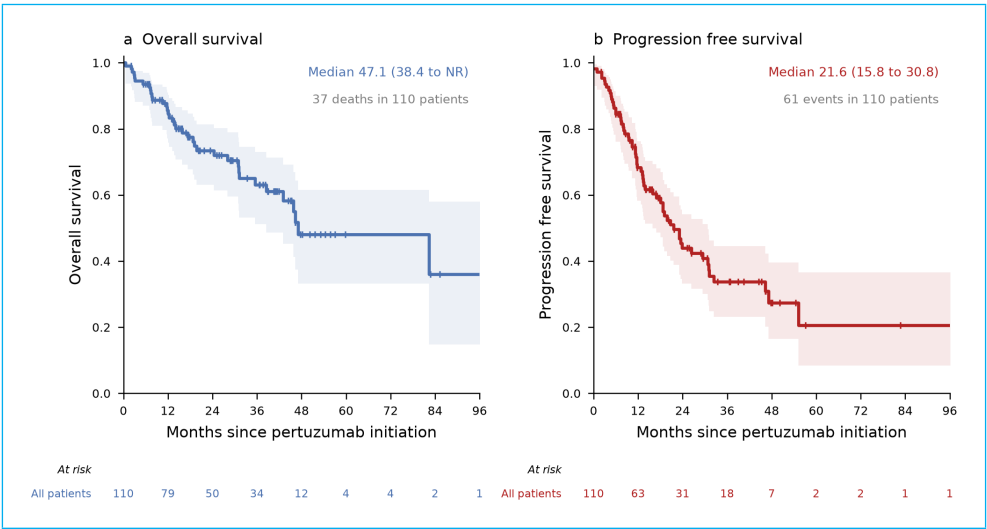


Figure 1. Kaplan Meier estimates of overall survival (a) and progression free survival (b) in the whole cohort, measured from the date of the first pertuzumab infusion. Shaded bands are 95 percent confidence intervals and vertical ticks are censored observations. The number of patients at risk is given beneath each panel. Median overall survival was 47.1 months (95 percent CI 38.4 to not reached) with 37 deaths, and median progression free survival was 21.6 months (95 percent CI 15.8 to 30.8) with 61 events.

ry diagnosis, the median by that convention in this cohort is 105.4 months (95 percent CI, 60.0 to 148.4); this figure is not comparable with survival measured from the start of treatment and is reported here for that reason alone.

Univariate analysis

Results of the univariate analysis are shown in Table 3. An ECOG performance status of 1 was associated with shorter overall survival (28.1 versus 82.4 months, $p=0.002$), and three or more metastatic sites were associated with shorter overall survival (38.4 months versus not reached, $p=0.020$) and shorter progression-free survival (13.1 versus 29.4

months, $p=0.005$) (Fig. 2). Receiving fewer than six taxane cycles was associated with markedly shorter survival for both endpoints (overall survival, 7.3 versus 82.4 months, $p<0.001$), a finding examined further below. Coronary artery disease showed a borderline association with shorter overall survival (38.4 versus 82.4 months, $p=0.062$), and liver metastasis showed a trend toward shorter progression-free survival (15.8 versus 23.5 months, $p=0.064$). Age, menopausal status, hormone receptor status, Ki-67, histological grade, taxane partner, diabetes mellitus, bone, lung, and brain metastasis, and concurrent endocrine therapy in

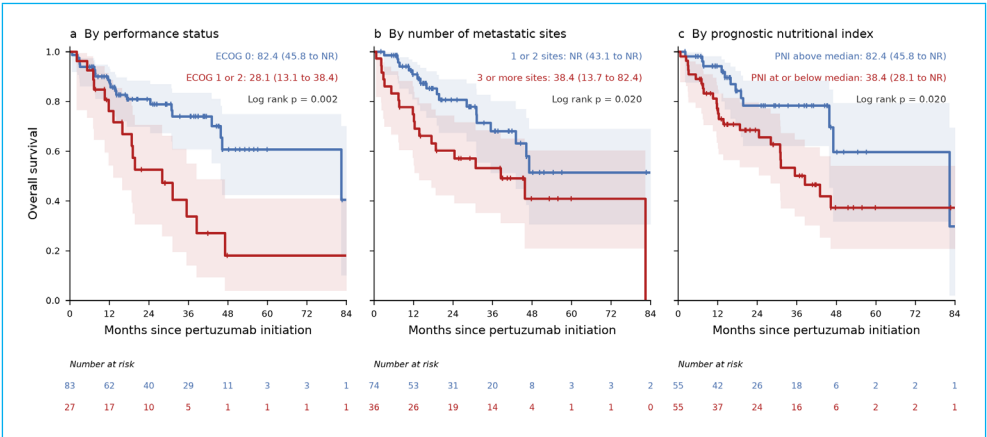


Figure 2. Overall survival by ECOG performance status (a), by the number of involved metastatic sites (b) and by the prognostic nutritional index dichotomised at the cohort median of 51.45 (c). Shaded bands are 95 percent confidence intervals, vertical ticks are censored observations and p values are from the log rank test. The number of patients at risk is given beneath each panel.

Table 3. Univariate analysis of clinical and pathological factors

Factor	n	Median OS, months (95% CI)	p	Median PFS, months (95% CI)	p
Age					
Under 40	21	NR (17.4 to NR)	0.245	29.4 (9.4 to NR)	0.642
40 or over	89	46.3 (31.1 to NR)		19.7 (13.4 to 31.0)	
ECOG performance status					
0	83	82.4 (45.8 to NR)	0.002	23.5 (15.8 to 46.3)	0.112
1 or 2	27	28.1 (13.1 to 38.4)		19.1 (8.0 to 23.9)	
Menopausal status					
Premenopausal	43	82.4 (43.1 to NR)	0.369	23.1 (13.4 to 32.4)	0.749
Postmenopausal	66	45.8 (31.0 to NR)		20.6 (13.4 to 46.3)	
Presentation					
De novo metastatic	82	47.1 (35.4 to NR)	0.583	23.5 (16.9 to 46.3)	0.428
Systemic recurrence	28	45.8 (19.1 to NR)		19.1 (11.3 to 31.1)	
Estrogen receptor					
Positive	66	47.1 (35.4 to NR)	0.615	21.6 (13.8 to 29.4)	0.829
Negative	44	82.4 (30.9 to NR)		23.9 (11.6 to 47.2)	
Progesterone receptor					
Positive	50	45.8 (35.4 to NR)	0.960	18.7 (13.1 to 26.3)	0.250
Negative	60	82.4 (30.9 to NR)		23.9 (13.4 to 55.2)	
Ki-67					
Under 14 percent	10	NR (15.9 to NR)	0.128	55.2 (5.1 to 55.2)	0.305
14 percent or over	100	46.3 (35.4 to NR)		20.6 (13.4 to 30.8)	
Histological grade					
1	1	NR (NR to NR)	0.874	NR (NR to NR)	0.935
2	52	82.4 (31.0 to NR)		23.1 (13.8 to 31.0)	
3	47	47.1 (31.1 to NR)		23.1 (15.8 to 46.3)	
Taxane					
Docetaxel	105	47.1 (38.4 to NR)	0.602	21.6 (16.9 to 30.8)	0.489
Paclitaxel	5	82.4 (2.1 to 82.4)		7.4 (0.0 to NR)	
Number of metastatic sites					
1 or 2	74	NR (43.1 to NR)	0.020	29.4 (19.7 to 46.3)	0.005
3 or more	36	38.4 (13.7 to 82.4)		13.1 (9.4 to 18.7)	
Liver metastasis					
Absent	73	NR (43.1 to NR)	0.154	23.5 (18.1 to 46.3)	0.064
Present	37	45.8 (19.7 to NR)		15.8 (9.4 to 30.8)	
Lung metastasis					
Absent	78	47.1 (38.4 to NR)	0.432	23.1 (15.8 to 31.0)	0.736
Present	32	NR (13.7 to NR)		20.6 (10.3 to NR)	
Brain metastasis					
Absent	103	47.1 (38.4 to NR)	0.678	21.6 (15.8 to 31.0)	0.801
Present	7	30.9 (2.1 to NR)		20.6 (0.0 to NR)	

Table 3. Continued

Factor	n	Median OS, months (95% CI)	p	Median PFS, months (95% CI)	p
Bone metastasis					
Absent	40	NR (31.0 to NR)	0.268	23.9 (13.4 to NR)	0.336
Present	70	46.3 (35.4 to NR)		18.7 (13.2 to 29.4)	
Diabetes mellitus					
Absent	89	47.1 (43.1 to NR)	0.404	20.6 (15.8 to 29.4)	0.917
Present	21	31.1 (12.3 to NR)		31.0 (9.4 to NR)	
Coronary artery disease					
Absent	89	82.4 (43.1 to NR)	0.062	23.1 (18.6 to 32.4)	0.087
Present	21	38.4 (11.7 to NR)		13.1 (7.4 to 23.9)	
Concurrent endocrine therapy (hormone receptor positive only)					
No	5	NR (2.3 to NR)	0.666	NR (2.1 to NR)	0.575
Yes	63	47.1 (35.4 to NR)		21.6 (13.4 to 30.8)	
Taxane cycles					
6 or more	93	82.4 (43.1 to NR)	0.000	23.1 (18.6 to 31.1)	0.002
Fewer than 6	17	7.3 (2.9 to 45.8)		5.3 (2.1 to NR)	

ECOG: Eastern Cooperative Oncology Group; OS: Overall survival; PFS: Progression free survival; NR: Not reached. Both endpoints are measured from the first pertuzumab infusion. p values are from the log rank test and are not adjusted for multiple comparisons.

hormone receptor-positive patients were not associated with either endpoint.^[19] Presentation as de novo metastatic disease versus systemic recurrence was not associated with overall survival (47.1 versus 45.8 months, $p=0.583$) or progression-free survival (23.5 versus 19.1 months, $p=0.428$).

Inflammatory and nutritional indices

The seven inflammatory and nutritional indices are shown in Table 1 with the cohort median as the cut-off, and their estimates after adjustment for performance status and the number of metastatic sites are shown in Table 4. On univariate analysis, the prognostic nutritional index separated

both endpoints (overall survival, 82.4 versus 38.4 months, $p=0.020$; progression-free survival, 30.8 versus 20.6 months, $p=0.009$), the neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index separated overall survival ($p=0.048$ and $p=0.050$), and the pan-immune-inflammation value, the lymphocyte-to-monocyte ratio, and the C-reactive protein-to-albumin ratio reached $p<0.10$ for one endpoint each, but in the direction opposite to that expected, with the apparently adverse stratum showing the longer median. The platelet-to-lymphocyte ratio was not associated with either endpoint. After adjustment, only the prog-

Table 4. Each index entered separately into a model containing performance status and the number of metastatic sites

Index	Adverse stratum	OS hazard ratio (95% CI)	p	PFS hazard ratio (95% CI)	p
Neutrophil to lymphocyte ratio	above median	1.57 (0.77 to 3.17)	0.212	1.4 (0.82 to 2.38)	0.213
Platelet to lymphocyte ratio	above median	1.07 (0.55 to 2.1)	0.835	1.37 (0.81 to 2.34)	0.241
Systemic immune inflammation index	above median	1.49 (0.74 to 3.0)	0.260	1.31 (0.77 to 2.21)	0.319
Pan immune inflammation value	above median	0.95 (0.49 to 1.83)	0.873	0.65 (0.38 to 1.08)	0.098
Lymphocyte to monocyte ratio	at or below median	1.14 (0.58 to 2.23)	0.709	0.69 (0.4 to 1.19)	0.184
Prognostic nutritional index	at or below median	1.86 (0.92 to 3.78)	0.085	1.88 (1.1 to 3.2)	0.020
C reactive protein to albumin ratio	above median	0.64 (0.33 to 1.25)	0.192	0.84 (0.51 to 1.4)	0.511

Each row is a separate Cox model containing ECOG performance status, three or more involved metastatic sites and the index shown, dichotomised at the cohort median. The adverse stratum column states which side of the median was hypothesised to carry the worse prognosis. A hazard ratio below 1 therefore indicates an association in the direction opposite to that expected.

nostic nutritional index retained an association, with progression-free survival at a hazard ratio of 1.88 (95 percent CI, 1.10 to 3.20; $p=0.020$) and overall survival at 1.86 (95 percent CI, 0.92 to 3.78; $p=0.085$); the remaining six indices were null for both endpoints, including the three whose univariate direction was reversed. The strata driving those reversals were imbalanced at baseline: patients above the median pan-immune-inflammation value included 18.2 percent with ECOG 1 or 2, compared with 30.9 percent below it, and patients at or below the median lymphocyte-to-monocyte ratio included 23.6 percent with three or more involved sites, compared with 41.8 percent above it. Seven indices were tested against two endpoints without correction for multiple comparisons, and all cut-offs were derived within this cohort, so these results are exploratory.

Multivariable analysis

Variables associated with either endpoint at $p<0.10$ were entered into Cox models, restricted in number so that at least ten events were available per covariate (Table 5). For overall survival, with 37 events and three covariates, an ECOG performance status of 1 (hazard ratio, 2.74; 95 percent CI, 1.40 to 5.35; $p=0.003$) and three or more metastatic sites (hazard ratio, 2.29; 95 percent CI, 1.19 to 4.42; $p=0.013$) remained independently associated with shorter survival, while a low prognostic nutritional index did not reach significance (hazard ratio, 1.86; 95 percent CI, 0.92 to 3.78; $p=0.085$).

For progression-free survival, with 61 events, three or more metastatic sites (hazard ratio, 2.14; 95 percent CI, 1.26 to

3.66; $p=0.005$) and a low prognostic nutritional index (hazard ratio, 1.87; 95 percent CI, 1.09 to 3.20; $p=0.023$) were independently associated with shorter progression-free survival, whereas performance status and coronary artery disease were not. Because the study is retrospective and the index analyses do not survive correction for multiple comparisons, we describe these as independent associations rather than as independent predictors. Scaled Schoenfeld residuals gave no evidence against the proportional hazards assumption in either model.

The number of taxane cycles

The number of taxane cycles delivered was strongly associated with survival on univariate analysis, but it accrues during follow-up: a patient must remain alive and on treatment to receive more cycles, and cycle number correlated with time under observation (Spearman $\rho=0.379$, $p<0.001$). Treating it as a baseline covariate would therefore attribute survival time to the variable that measures it. In a landmark analysis restricted to the 100 patients alive and under observation at six months, with 30 subsequent deaths, receiving fewer than six cycles was no longer significantly associated with overall survival (hazard ratio, 2.57; 95 percent CI, 0.86 to 7.68; $p=0.090$) once performance status and metastatic burden were included, while performance status remained significant (hazard ratio, 3.86; 95 percent CI, 1.83 to 8.15; $p<0.001$). We therefore interpret early discontinuation of the taxane as a marker of clinical deterioration or toxicity rather than as an independent determinant of outcome.

Table 5. Multivariable Cox proportional hazards models

Covariate	Hazard ratio	95% CI	p
Overall survival (37 events, 3 covariates)			
ECOG performance status 1 versus 0	2.740	1.404 to 5.349	0.003
Three or more metastatic sites versus one or two	2.292	1.190 to 4.417	0.013
Prognostic nutritional index at or below median	1.862	0.917 to 3.779	0.085
Progression free survival (61 events, 4 covariates)			
ECOG performance status 1 versus 0	1.506	0.784 to 2.891	0.219
Three or more metastatic sites versus one or two	2.142	1.255 to 3.655	0.005
Prognostic nutritional index at or below median	1.868	1.091 to 3.199	0.023
Coronary artery disease	1.055	0.499 to 2.228	0.889
Landmark analysis at six months, overall survival (30 events)			
ECOG performance status 1 versus 0	3.857	1.826 to 8.147	<0.001
Three or more metastatic sites versus one or two	1.688	0.795 to 3.584	0.173
Fewer than six taxane cycles	2.574	0.863 to 7.680	0.090

ECOG: Eastern Cooperative Oncology Group. Variables associated with the endpoint at p below 0.10 on univariate analysis were entered, limited so that at least ten events were available per covariate. Scaled Schoenfeld residuals gave no evidence against the proportional hazards assumption. The landmark model is restricted to the 100 patients alive and under observation at six months.

Table 6. Adverse events, with the denominator for each event

Adverse event	Patients with the event documented	Grade 1 or 2, n	Grade 3 or 4, n	Percent grade 1 or 2
Nausea or vomiting	57	29	0	50.9
Headache	55	9	0	16.4
Myalgia	60	12	0	20.0
Hypertension	55	0	0	0.0
Thrombocytopenia	55	16	0	29.1
Anaemia	55	23	0	41.8
Leucopenia	55	18	0	32.7
Raised liver enzymes	65	24	0	36.9
Any of the above	73	51	0	

Denominators differ between events because toxicity documentation was incomplete in a variable proportion of records; the absence of an entry is not evidence that the event did not occur. Diarrhoea and neutropenia were not recorded as separate fields and cannot be reported. Grading follows CTCAE version 5.0.

Toxicity

Adverse events are shown in Table 6, with the denominator given for each event because toxicity documentation was incomplete in a variable proportion of records. Among patients in whom each event was documented, the most frequent were nausea or vomiting in 29 of 57 (50.9 percent), anaemia in 23 of 55 (41.8 percent), raised liver enzymes in 24 of 65 (36.9 percent), leucopenia in 18 of 55 (32.7 percent), thrombocytopenia in 16 of 55 (29.1 percent), myalgia in 12 of 60 (20.0 percent), and headache in 9 of 55 (16.4 percent). All documented events were grade 1 or 2; no grade 3 or 4 event was recorded in the individual toxicity fields. Diarrhoea and neutropenia, which are among the toxicities most characteristic of this regimen, were not recorded as separate fields in the database and therefore cannot be reported; the absence of an entry for any event should be read as an absence of documentation rather than as evidence that the event did not occur. No patient discontinued therapy for toxicity according to the available records.

Cardiac function

Left ventricular ejection fraction was recorded before and during treatment in all 110 patients. The median was 60 percent before treatment (range, 50 to 65) and 60 percent at the last on-treatment assessment (range, 25 to 65). A fall

of 10 percentage points or more occurred in 3 patients (2.7 percent), and 4 patients (3.6 percent) had an on-treatment value below 50 percent, the lowest being 25 percent. Any fall from baseline was seen in 7 patients (6.4 percent).

Progression and subsequent therapy

Fifty-three patients (48.2 percent) were recorded as progressing on pertuzumab-based therapy, and subsequent HER2-directed treatment is summarised in Table 7. Among patients with the relevant field completed, 33 of 73 (45.2 percent) received trastuzumab emtansine,^[20] for a median of 10 cycles (range, 1 to 36), 11 of 72 (15.3 percent) received lapatinib with capecitabine (median, 10 cycles; range, 4 to 22), and 6 of 51 (11.8 percent) received trastuzumab deruxtecan,^[21] (median, 11 cycles; range, 3 to 19). The denominators differ because the field was not completed for every patient, and this incompleteness is a limitation of the subsequent therapy data. Of the 106 patients for whom the total number of treatment lines was recorded, 69 (65.1 percent) had received one line only at the data cut-off, 23 had received two, and 14 had received three or more.

Discussion

In this consecutive series of 110 patients treated with first-line pertuzumab, trastuzumab, and a taxane in rou-

Table 7. Subsequent lines of HER2 directed therapy after progression

Agent	Patients treated, n	Field completed for, n	Percent	Median cycles (range)
Trastuzumab emtansine	33	73	45.2	10 (1 to 36)
Lapatinib with capecitabine	11	72	15.3	10 (4 to 22)
Trastuzumab deruxtecan	6	51	11.8	11 (3 to 19)

Denominators differ because the field was not completed for every patient. Of the 106 patients in whom the total number of treatment lines was recorded, 69 had received one line, 23 two and 14 three or more at the data cut off.

tine practice, median progression-free survival was 21.6 months, and median overall survival was 47.1 months, measured from the first pertuzumab infusion. Performance status and the number of involved metastatic sites were the strongest prognostic factors for both endpoints, and the prognostic nutritional index added independent information for progression-free survival.

Our progression-free survival of 21.6 months is consistent with, and slightly longer than, the 18.7 months reported in CLEOPATRA,^[4] and sits within the 18 to 24-month range described in other real-world series.^[7-9] Overall survival of 47.1 months is shorter than the 57.1 months of the CLEOPATRA final analysis.^[6] Two features of our cohort bear on that comparison. First, our estimate is immature: 37 deaths had occurred among 110 patients, and median follow-up was 33.4 months, so the median overall survival is estimated at a point where a minority of the cohort had been observed for that long, and the confidence interval extends to not reached. Second, our patients were not selected by trial criteria; the cohort includes patients up to 91 years of age, a fifth with diabetes, and a fifth with coronary artery disease. We would therefore present the overall survival figure as a provisional estimate that requires longer follow-up rather than as a mature result to be set against the trial.

The prognostic value of performance status and of the number of metastatic sites is consistent with a large body of evidence in metastatic breast cancer,^[7,10] and requires little comment, although one qualification applies to the site count in our data. Lymph nodes were involved in 95.5 percent of patients, so the count of involved sites is heavily influenced by a category that is present in almost everyone; when nodal disease is excluded, the distribution shifts considerably. The association nevertheless persisted on multivariable analysis and is biologically unsurprising, but the variable should be understood as a measure of disease extent in this specific coding rather than as a count of distant organ systems.

Our finding on presentation type deserves emphasis because it differs from what we initially expected. De novo metastatic disease is frequently reported to carry a better prognosis than metastatic recurrence in HER2-positive disease,^[22,23] and a comparison in which survival is measured from primary diagnosis will reproduce that pattern almost by construction, since a patient whose metastatic disease appears years after an initial diagnosis has already accumulated that interval as survival time. When both groups are measured from the same point, the start of pertuzumab therapy, the difference in our cohort disappeared entirely, with medians of 47.1 and 45.8 months. We regard the choice of index date as the substantive issue here rather

than a technical one, and we would suggest that comparisons of de novo versus recurrent presentation are interpretable only when the clock starts at a common event for both groups.

The seven blood-based indices need to be read against what the published estimates actually are, because our results agree with the literature in one place and contradict it in three. Only the prognostic nutritional index survived adjustment for performance status and disease extent, retaining an association with progression-free survival (hazard ratio, 1.88; 95 percent CI, 1.10 to 3.20) and falling just short for overall survival (1.86, 0.92 to 3.78). That direction matches a meta-analysis of 2,322 patients in which low pre-treatment index values were associated with worse overall survival,^[13] and the biological reading is straightforward: the index combines serum albumin with the absolute lymphocyte count, so it measures nutritional reserve alongside immune status, and in a population on prolonged antibody therapy, that composite may carry information that the pure ratios do not.^[24] The neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index separated overall survival before adjustment but not after it ($p=0.212$ and $p=0.260$), against pooled literature estimates for overall survival of 1.87 (1.41 to 2.48) and 1.97 (1.54 to 2.52), respectively.^[12,25] Our adjusted point estimates of 1.57 and 1.49 sit below those figures, with confidence intervals that include them, so a cohort of 110 patients and 37 deaths lacks the power to resolve an effect of that size, and this is not a contradiction of it. Two features of the comparison deserve stating: the median cut-off for a high neutrophil-to-lymphocyte ratio across the pooled studies was 3.0, while our cohort median was 2.52,^[11] so our high stratum is less extreme than the pooled one, and the two indices agree on stratum in 88 of 110 patients, with a Spearman correlation of 0.824, so they are near-duplicates here and should not be counted as independent signals.

Three indices ran opposite to the literature. Pooled estimates put a high pan-immune-inflammation value at 2.63 (1.46 to 4.74) and 2.045 (1.355 to 3.086) for overall survival, and a high C-reactive protein-to-albumin ratio at 1.95 (1.71 to 2.22),^[12,26,27] yet in our data, the strata predicted to fare worse had the longer medians. It is worth noting where those thresholds come from: the pan-immune-inflammation value was derived in operable breast cancer,^[28] and cut-offs established in patients with resectable disease need not transfer to a metastatic population receiving continuous antibody therapy, in whom counts are shaped by treatment as much as by tumour burden. This was baseline imbalance rather than biology, and it is the kind of confounding a cohort of this size invites: the apparently adverse strata contained fewer patients with impaired performance

status and fewer with three or more involved sites, and all three associations vanished once those two variables entered the model. Since seven indices were tested against two endpoints, with cut-offs taken from our own medians rather than the published ones and no correction for multiple testing, we treat the whole set, the prognostic nutritional index included, as hypotheses for a larger series with prespecified thresholds, and we propose none of them for clinical use. Two quantitative statements make the limits of this analysis explicit. Applying a Benjamini-Hochberg correction across the 14 tests in Table 1 leaves no index with a false discovery rate below 0.05, the smallest being 0.126 for the prognostic nutritional index against progression-free survival, so none of these associations would survive formal control of multiplicity. Separately, 37 deaths give 80 percent power only for hazard ratios of about 2.51 or larger, whereas the pooled literature estimates lie between 1.87 and 1.97 and would need roughly 70 to 80 deaths; our null results for the neutrophil-to-lymphocyte ratio and the systemic immune-inflammation index are therefore uninformative rather than contradictory, and the prognostic nutritional index finding, although the most robust in our data, must be read as a hypothesis rather than a validated prognostic marker.

The number of taxane cycles delivered strongly separated survival on univariate analysis, and we do not interpret that as a treatment effect. Cycles accumulate while a patient remains alive and fit, so the variable partly encodes observation time; in this cohort, it correlated with follow-up at a Spearman coefficient of 0.379, and in a landmark analysis restricted to patients alive at six months, the association fell to non-significance.^[17,18] (hazard ratio, 2.57; 95 percent CI, 0.86 to 7.68; $p=0.090$). The most direct external check on this comes from CLEOPATRA itself, in which a post hoc analysis grouped the 804 patients by the number of docetaxel cycles received into fewer than six ($n=119$), exactly six ($n=210$), and more than six ($n=475$), and applied time-dependent multivariate Cox regression, which is the same correction our landmark analysis approximates.^[29] After accounting for the pertuzumab effect (progression-free survival hazard ratio, 0.61; 95 percent CI, 0.51 to 0.74; overall survival, 0.60; 95 percent CI, 0.49 to 0.74), receiving more than six cycles rather than exactly six conferred no significant advantage in either progression-free survival (0.80; 95 percent CI, 0.63 to 1.01; $p=0.0640$) or overall survival (0.88; 95 percent CI, 0.69 to 1.12; $p=0.3073$), and the benefit of pertuzumab held at every duration. Randomised evidence outside the HER2 setting points the same way, with a meta-analysis of chemotherapy-duration trials finding only a marginal overall survival gain (0.91; 95 percent CI, 0.84 to 0.99) and the MANTA1 trial finding no difference at all.

^[30,31] Against a trial that made the same comparison in the same regimen and found nothing, the large separation in our univariate data is most plausibly due to bias rather than benefit. One difference in delivery deserves reporting: our cohort was concentrated at exactly six cycles (75 of 110, 68.2 percent), with only 18 patients (16.4 percent) receiving more, whereas 59.1 percent of CLEOPATRA patients received more than six, a markedly different distribution ($p<0.001$). We therefore report the variable as a marker of tolerability and clinical course, not as an argument for prolonging taxane exposure, and we note that the trial evidence gives no reason to expect benefit from doing so.

Cardiac tolerability was as expected for the regimen: median ejection fraction was unchanged at 60 percent, a fall of ten points or more occurred in 3 patients, and 4 patients had a value below 50 percent during treatment. One patient had a fall to 25 percent, which illustrates that clinically important cardiac events do occur even where group medians are unchanged and that reporting the median alone would be misleading. The toxicity profile we can report was otherwise mild, with all documented events being grade 1 or 2, but this must be read alongside the documentation limitations described below.

The limitations of this study are substantial, and we set them out explicitly. It is retrospective, conducted at two centres, and its 110 patients provide limited power for subgroup analysis; the confidence intervals around the subgroup medians are correspondingly wide. Follow-up is immature for overall survival, as discussed. Toxicity was documented for between 51 and 65 patients, depending on the event, so the toxicity denominators are smaller than the cohort, and the percentages describe only those patients in whom the event was recorded; diarrhoea and neutropenia were not captured as fields at all, and their absence from our results should not be read as absence from the cohort. The subsequent therapy fields were similarly incomplete, which is why we report those proportions against explicit denominators. Response was assessed by RECIST version 1.1 in routine imaging at approximately three-month intervals rather than at protocol-defined times, so progression dates carry the ascertainment uncertainty inherent in real-world imaging schedules, and objective response could not be reconstructed retrospectively for the whole cohort from the available records. Histological grade was not recorded in 9.1 percent of patients, and no imputation was performed. Finally, the cut-off values for the inflammatory indices were derived from this cohort, so they are internally optimal by construction and require external validation before any clinical use. Brain metastasis was recorded in only 7 patients (6.4 percent), which is well below the 30 to 50 percent lifetime incidence described for HER2-positive

disease.^[32] Because brain imaging was performed for symptoms rather than by protocol screening, and screening of asymptomatic patients is not currently recommended,^[32] our figure should be read as the proportion with clinically detected brain metastasis at any point during follow-up and not as the true cumulative incidence.

Conclusion

In conclusion, first-line pertuzumab-based therapy in routine practice produced outcomes broadly consistent with the registration trial for progression-free survival, with an overall survival estimate that remains immature. Performance status and metastatic burden were the dominant prognostic factors, and the prognostic nutritional index emerged as an inexpensive candidate marker for progression-free survival that warrants prospective evaluation. Our data also indicate that the apparent prognostic advantage of de novo presentation is a function of how survival time is measured, and we would encourage the use of a treatment-based index date in studies that include both de novo and recurrent patients.

Disclosure

Ethical Committee Approval: The study was approved by the Manisa Celal Bayar University Faculty of Medicine Health Sciences Ethics Committee (no: 20.478.486/4049, date: 08.04.2026).

Informed Consent: The study used data collected in the course of routine care with no additional intervention, the requirement for individual informed consent was waived.

Conflict of Interest: The authors declare no conflict of interest.

Funding: The authors declare that they received no external funding.

Use of AI for Writing Assistance: The authors used ChatGPT (OpenAI) solely for language editing, grammar correction, and improvement of manuscript readability. The authors reviewed and edited all outputs and take full responsibility for the content of the manuscript. No artificial intelligence tool was used for data collection, data analysis, interpretation of results, or generation of scientific conclusions.

Author contributions: Concept – SG, EBE; Design – MU, İTÜ, APE; Supervision – İTÜ, MU, FE, APE; Fundings – MU, ÖY, EBE, İTÜ; Materials – FE, HSS; Data Collection or Processing: SG, EBE, ÖY; Analysis or Interpretation: FE, APE, HSS; Literature Search: SG, MU, ÖY; Writing: SG, Critical Review: İTÜ, HSS.

Peer-review: Externally peer-reviewed.

References

- Slamon DJ, Clark GM, Wong SG, Levin WJ, Ullrich A, McGuire WL. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235(4785):177–82. [\[CrossRef\]](#)
- Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM, Dowsett M. HER2 Testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update Summary. *J Oncol Pract* 2018;14(7):437–41. [\[CrossRef\]](#)
- 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(11):783–92. [\[CrossRef\]](#)
- Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, et al; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. *N Engl J Med* 2012;366(2):109–19. [\[CrossRef\]](#)
- Swain SM, Kim SB, Cortés J, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA study): overall survival results from a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2013;14(6):461–71. [\[CrossRef\]](#)
- Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al; CLEOPATRA study group. 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(4):519–30.
- Miles D, Ciruelos E, Schneeweiss A, Puglisi F, Peretz-Yablonski T, Campone M, et al; PERUSE investigators. Final results from the PERUSE study of first-line pertuzumab plus trastuzumab plus a taxane for HER2-positive locally recurrent or metastatic breast cancer, with a multivariable approach to guide prognostication. *Ann Oncol* 2021;32(10):1245–55.
- Polito L, Shim J, Hurvitz SA, Dang CT, Knott A, Du Toit Y, et al. Real-World first-line use of pertuzumab with different taxanes for human epidermal growth factor receptor 2-positive metastatic breast cancer: a comparative effectiveness study using US electronic health records. *JCO Oncol Pract* 2023;19(7):435–45. [\[CrossRef\]](#)
- Mehta S, Xie J, Ionescu-Iltu R, Nie X, Kwong WJ. Real-world treatment patterns and outcomes following first-line pertuzumab and trastuzumab among patients with HER2+ metastatic breast cancer. *Oncol Ther* 2023;11(4):481–93. [\[CrossRef\]](#)
- Dai WF, Beca JM, Nagamuthu C, Liu N, de Oliveira C, Earle CC, et al. Comparative effectiveness and safety of pertuzumab and trastuzumab plus chemotherapy vs trastuzumab plus chemotherapy for treatment of metastatic breast cancer. *JAMA Netw Open* 2022;5(2):e2145460. [\[CrossRef\]](#)
- Ethier JL, Desautels D, Templeton A, Shah PS, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in breast cancer: a systematic review and meta-analysis. *Breast Cancer Res* 2017;19(1):2. [\[CrossRef\]](#)

12. Cheng HW, Wang T, Yu GC, Xie LY, Shi B. Prognostic role of the systemic immune-inflammation index and pan-immune inflammation value for outcomes of breast cancer: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2024;28(1):180–90.
13. Hu G, Ding Q, Zhong K, Wang S, Wang S, Huang L. Low pre-treatment prognostic nutritional index predicts poor survival in breast cancer patients: A meta-analysis. *PLoS One* 2023;18(1):e0280669. [\[CrossRef\]](#)
14. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370(9596):1453–7. [\[CrossRef\]](#)
15. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45(2):228–47. [\[CrossRef\]](#)
16. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials* 1996;17(4):343–6. [\[CrossRef\]](#)
17. Suissa S. Immortal time bias in pharmaco-epidemiology. *Am J Epidemiol* 2008;167(4):492–9. [\[CrossRef\]](#)
18. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:b5087. [\[CrossRef\]](#)
19. Rimawi M, Ferrero JM, de la Haba-Rodriguez J, Poole C, De Placido S, Osborne CK, et al; PERTAIN Study Group. First-Line trastuzumab plus an aromatase inhibitor, with or without pertuzumab, in human epidermal growth factor receptor 2-positive and hormone receptor-positive metastatic or locally advanced breast cancer (PERTAIN): a randomized, open-label phase II trial. *J Clin Oncol* 2018;36(28):2826–35. [\[CrossRef\]](#)
20. Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012;367(19):1783–91. Erratum in: *N Engl J Med* 2013;368(25):2442. [\[CrossRef\]](#)
21. Cortés J, Kim SB, Chung WP, Im SA, Park YH, Hegg R, et al; DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N Engl J Med* 2022;386(12):1143–54. [\[CrossRef\]](#)
22. Dawood S, Broglio K, Ensor J, Hortobagyi GN, Giordano SH. Survival differences among women with de novo stage IV and relapsed breast cancer. *Ann Oncol* 2010;21(11):2169–74. [\[CrossRef\]](#)
23. Daily K, Douglas E, Romitti PA, Thomas A. Epidemiology of de novo metastatic breast cancer. *Clin Breast Cancer* 2021;21(4):302–8. [\[CrossRef\]](#)
24. Wang Y, Battseren B, Yin W, Lin Y, Zhou L, Yang F, et al. Predictive and prognostic value of prognostic nutritional index for locally advanced breast cancer. *Gland Surg* 2019;8(6):618–26. [\[CrossRef\]](#)
25. Liu X, Qu JK, Zhang J, Yan Y, Zhao XX, Wang JZ, et al. Prognostic role of pretreatment neutrophil to lymphocyte ratio in breast cancer patients: A meta-analysis. *Medicine (Baltimore)* 2017;96(45):e8101. Erratum in: *Medicine (Baltimore)* 2018;97(4):e9727. Erratum in: *Medicine (Baltimore)* 2017;96(52):e9526. [\[CrossRef\]](#)
26. Qi X, Qiao B, Song T, Huang D, Zhang H, Liu Y, et al. Clinical utility of the pan-immune-inflammation value in breast cancer patients. *Front Oncol* 2023;13:1223786. [\[CrossRef\]](#)
27. Cui X, Jia Z, Chen D, Xu C, Yang P. The prognostic value of the C-reactive protein to albumin ratio in cancer: An updated meta-analysis. *Medicine (Baltimore)* 2020;99(14):e19165. [\[CrossRef\]](#)
28. Lin F, Zhang LP, Xie SY, Huang HY, Chen XY, Jiang TC, et al. Pan-immune-inflammation value: a new prognostic index in operative breast cancer. *Front Oncol* 2022;12:830138. [\[CrossRef\]](#)
29. Miles D, Im YH, Fung A, Yoo B, Knott A, Heeson S, et al. Effect of docetaxel duration on clinical outcomes: exploratory analysis of CLEOPATRA, a phase III randomized controlled trial. *Ann Oncol* 2017;28(11):2761–7. [\[CrossRef\]](#)
30. Gennari A, Stockler M, Puntoni M, Sormani M, Nanni O, Amadori D, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol* 2011;29(16):2144–9. [\[CrossRef\]](#)
31. Gennari A, Amadori D, De Lena M, Nanni O, Bruzzi P, Lorusso V, et al. Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. *J Clin Oncol* 2006;24(24):3912–8. [\[CrossRef\]](#)
32. Garcia-Alvarez A, Papakonstantinou A, Oliveira M. Brain metastases in HER2-positive breast cancer: current and novel treatment strategies. *Cancers (Basel)* 2021;13(12):2927. [\[CrossRef\]](#)