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The Prognostic Impact of HER2 Status and Survival Outcomes in Metastatic Triple Negative Breast Cancer

ALPER TURKEL[1], ECE BAYDAR[2], RÜMEYSA ÇOLAK[3], AHMET EMİN ÖZTÜRK[4], TEOMAN ŞAKALAR[5], SİNEM AKBAŞ[6], HASİBE BİLGE GÜR[7], EYYÜP ÇAVDAR[8], MESUT YILMAZ[3], DEVRİM ÇABUK[2], FATİH SELÇUKBİRİCİK[6], İLHAN HACIBEKİROĞLU[7] and MUTLU DOGAN[1]

[1]Department of Medical Oncology, University of Health Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Research and Treatment Hospital, Ankara, Türkiye;
[2]Department of Medical Oncology, Kocaeli University, Faculty of Medicine, Kocaeli, Türkiye;
[3]Department of Medical Oncology, Bakırköy Dr. Sadi Konuk Research and Treatment Hospital, Istanbul, Türkiye;
[4]Department of Medical Oncology, University of Health Sciences, Prof. Dr. Cemil Taşçıoğlu City Hospital, Istanbul, Türkiye;
[5]Department of Medical Oncology, Kahramanmaraş Sütçü İmam University, Faculty of Medicine, Kahramanmaraş, Türkiye;
[6]Department of Medical Oncology, Koç University, Faculty of Medicine, Istanbul, Türkiye;
[7]Department of Medical Oncology, Sakarya Research and Treatment Hospital, Sakarya, Türkiye;
[8]Department of Medical Oncology, Adıyaman University Research and Treatment Hospital, Adiyaman, Türkiye

Abstract

Background/Aim: This study investigated the prognostic impact of human epidermal growth factor-2 receptor (HER2) status on the survival of patients with metastatic triple-negative breast cancer (TNBC).

Patients and Methods: This multicenter, retrospective study included 168 patients diagnosed with recurrent or *de novo* metastatic TNBC between April 2013 and September 2024. Patients were categorized into two groups: HER2-negative (n=121, 72%) and HER2-low (n=47, 28%). Clinicopathological features and survival outcomes were compared between groups.

Results: The median follow-up was 44 months [95% confidence interval (CI)=35.7-52.2]. All patients received systemic chemotherapy as part of their first-line treatment. The median progression-free survival (PFS) in all patients was 9 months (95%CI=7.7-10.3 months). The median overall survival (OS) in all patients was 22 months (95%CI=17.4-26.5 months). Higher Ki67 value at diagnosis was a significant poor prognostic factor for median OS (29 months *vs.* 15 months, $p<0.001$). HER2-negative patients had significantly worse median OS than HER2-low

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Alper Türkel (ORCiD: 0000-0001-5071-9679), Vatan Street No. 91 Yenimahalle/Ankara, 06200 Turkey. Tel: +90 3123360909, Fax: +90 3123340352, e-mail: turkelalperr@gmail.com

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patients (19 months *vs.* 33 months, p=0.026). In multivariate analysis, the HER2-low group had significantly longer median OS than the HER2-negative group [hazard ratio=0.64 (95%CI=0.42-0.98), p=0.040].
Conclusion: HER2-low expression was associated with significantly improved survival compared with HER2-negative status in metastatic TNBC. These findings highlight HER2 status as a potential prognostic factor, particularly relevant in settings with limited access to novel therapies such as immunotherapy or antibody-drug conjugates.

Keywords: Metastatic, HER2-low, HER2 status, survival, triple-negative breast cancer.

Introduction

Breast cancer is the most common malignancy in women worldwide and remains the leading cause of cancer-related mortality (1). It is a heterogeneous disease comprising subtypes with distinct biological behaviors and prognostic characteristics (1, 2). Triple-negative breast cancer (TNBC) constitutes approximately 15-20% of all breast cancers (3). It is defined as a subgroup with an aggressive course and poor prognosis. Treatment options for TNBC, especially for metastatic ones, were quite limited until the 2000s. Immunotherapy and targeted treatments have emerged as transformative treatment strategies in TNBC. Immune checkpoint inhibitors such as programmed death-1 (PD-1) inhibitors (4) and antibody-drug conjugates (ADCs) such as sacituzumab govitecan (5) and trastuzumab deruxtecan (T-DXd) have been shown to provide better survival outcomes in TNBC, including human epidermal growth factor receptor-2 (HER2)-low cases (6). All of these significant advances have lighted a new era in the treatment of metastatic TNBC.

The concept of "HER2-low" in breast cancer has led to significant developments and new treatment approaches in recent years. The prevalence of HER2-low expression is relatively high, occurring in 45-55% of all breast cancer cases and in approximately 30-35% of TNBC cases (7, 8). Clinical trial outcomes suggest that HER2-low breast cancer may represent a distinct entity with unique clinical and prognostic features compared to HER2-negative disease. However, no consensus has yet been reached. Moreover, most published studies have focused on early-stage breast cancer, with relatively few addressing the metastatic setting.

This study aimed to compare the clinical, prognostic factors, and survival outcomes of HER2-negative and HER2-low subgroups in metastatic TNBC.

Patients and Methods

Study design. This is a multicenter retrospective study that included 168 patients with *de novo* metastatic or recurrent metastatic TNBC diagnosed between April 2013 and September 2024. The study was approved by the Ethics Committee of the University of Health Sciences Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital (2024-05/72). In *de novo* metastatic patients, the diagnosis of TNBC was confirmed based on the results of the initial biopsy. In recurrent metastatic patients, the diagnosis was confirmed based on the initial biopsy and biopsy taken from the metastatic region. TNBC was defined as estrogen receptor-negative (ER <1%), progesterone receptor-negative (PR <1%), and human epidermal growth factor receptor-2 (HER2) negative or HER2-low. HER2 negativity was defined as CerbB2 immunohistochemical (IHC) score 0. HER2-low status was defined as patients with a CerbB2 IHC score of 1 or 2, in whom HER2 amplification could not have been demonstrated by in situ hybridization (ISH). The inclusion criteria for the study were: age over 18 years, metastatic disease, and more than one line of systemic treatment at an advanced stage. Patients with a secondary primary malignancy and inadequate complete access to past medical records were excluded from the study.

Survival analyses. Descriptive statistical methods were used to analyze the clinical and histopathological

characteristics of the patients. The chi-square test was used to compare categorical data. The unpaired student's *t*-test was used to compare two groups for data normally distributed. The Kolmogorov-Smirnov test was also used for normality.

The Kaplan-Meier method was used for survival analysis [median progression-free survival (PFS) and median overall survival (OS)]. PFS was defined as the time from diagnosis to recurrence, metastasis, or the last contact date. OS was defined as the interval between the date of diagnosis and the date of death or last contact. The reverse Kaplan-Meier test was used to determine the median follow-up.

A *p*-value less than 0.05 was considered as statistically significant. All statistical analyses were performed using the Statistical Package for Social Science (SPSS) for personal computers, version 21.0, Chicago, IL, USA.

Results

Patient baseline characteristics. A total of 168 patients were included in the study. All patients were female. The mean age of the patients was 50.2 (±11.3). Sixty-nine (41.1%) patients were premenopausal, 15 (8.9%) were perimenopausal, and 84 (50%) were postmenopausal. Forty-two (28%) patients had hypertension, 31 (18.5%) had diabetes mellitus, and 10 (6%) had heart disease as comorbid diseases. Upon examination of the pathological features, 121 (72%) patients were HER2-negative, and 47 (28%) patients were classified as HER2-low. Forty-one (24.4%) patients had grade 2 disease, and 127 (75.6%) had grade 3. The mean Ki67 value was 52.7% (±24.7), and the median Ki67 value was 50%. Fifty-eight (34.5%) of the patients had *de novo* metastatic disease, while 110 (65.5%) had recurrent metastatic disease (Table I).

The most common sites of metastasis were the bone, lung, and liver. The patients' *de novo* metastasis and recurrence sites are detailed in Table II and Table III. Baseline characteristics of HER2-negative and HER2-low patients were similar in terms of demographic and clinicopathological features (Table I).

Table I. *Comparison of baseline characteristics of HER2-negative and HER2-low groups.*

	Total (n=168)	HER2-negative (n=121)	HER2-low (n=47)	*p*-Value
Age (years) (±SD)	50.2 (±11.3)	50.6 (±11.4)	49.2 (±11.1)	0.635
Sex F/M (n)	168/0	121 / 0	47 / 0	
Menopausal status, n (%)				
Premenopausal	69 (41.1)	53 (43.8)	16 (34)	0.864
Perimenopausal	15 (8.9)	8 (6.6)	7 (14.9)	
Postmenopausal	84 (50)	60 (49.6)	24 (51.1)	
Hypertension, n (%)	47 (28)	38 (31.4)	9 (19.1)	0.112
Diabetes mellitus, n (%)	31 (18.5)	21 (17.4)	10 (21.3)	0.556
Heart disease, n (%)	10 (6)	7 (5.8)	3 (6.4)	0.883
Grade, n (%)				
Grade 2	41 (24.4)	25 (20.7)	16 (34)	0.070
Grade 3	127 (75.6)	96 (79.3)	31 (66)	
Ki67 (%), (±SD)	52.7 (±24.7)	54.2 (±24.7)	48.9 (±24.4)	0.396
De novo metastasis, n (%)				
Yes	58 (34.5)	40 (33.1)	18 (38.3)	0.521
No	110 (65.5)	81 (66.9)	29 (61.7)	

HER2: Human epidermal growth factor receptor-2; HER2 negative: IHC score 0; HER2-low: IHC 1+ or 2+/ISH negative; IHC: immunohistochemistry; ISH: in situ hybridization.

Table II. *Metastasis sites in patients with de novo metastasis.*

De novo metastasis sites	Number of patients (n)	Percent (%)
Bone	11	19
Lung	9	15.6
Bone and liver	9	15.6
Liver and lung	5	8.6
Liver	4	6.9
Bone and lung	4	6.9
Bone, liver, and lung	4	6.9
Mediastinal lymph nodes	4	6.9
Abdominal lymph nodes	2	3.4
Brain	1	1.7
Bone and brain	1	1.7
Liver and brain	1	1.7
Bone, liver, and brain	1	1.7
Neck lymph nodes	1	1.7
Skin	1	1.7
Total	58	100

Treatment regimens. Systemic treatment regimens in the first-line setting were examined. Thirty-four (20.2%) of the patients received capecitabine, 29 (17.3%) carboplatin

Table III. *Metastasis sites in patients with recurrent metastasis.*

Recurrence sites	Number of patients (n)	Percent (%)
Lung	22	20
Bone	19	17.3
Liver	17	15.5
Bone and lung	9	8.2
Bone, liver, and lung	7	6.4
Brain	7	6.4
Ipsilateral/contralateral breast	5	4.5
Bone and liver	5	4.5
Mediastinal lymph nodes	4	3.6
Liver and lung	4	3.6
Skin	3	2.8
Lung and brain	2	1.8
Bone, liver, lung, and brain	2	1.8
Bone, liver, and brain	1	0.9
Bone and brain	1	0.9
Liver and brain	1	0.9
Leptomeningeal	1	0.9
Total	110	100

Table IV. *First-line treatment regimens.*

Treatment regimens	Number of patients (n)	Percent (%)
Capecitabine	34	20.2
Carboplatin plus paclitaxel	29	17.3
Paclitaxel	24	14.3
Cisplatin plus gemcitabine	21	12.5
Carboplatin plus gemcitabine	18	10.7
Adriamycin plus cyclophosphamide	16	9.5
Capecitabine plus docetaxel	10	6
Gemcitabine	4	2.3
Vinorelbine	3	1.8
Docetaxel	3	1.8
Carboplatin, gemcitabine, and atezolizumab	2	1.2
Cisplatin	1	0.6
Adriamycin	1	0.6
Gemcitabine plus paclitaxel	1	0.6
Intrathecal methotrexate	1	0.6
Total	168	100

plus paclitaxel, 24 (14.3%) single-agent paclitaxel, 21 (12.5%) cisplatin plus gemcitabine, 18 (10.7%) carboplatin plus gemcitabine, and 16 (9.5%) adriamycin plus cyclophosphamide. Less common treatment regimens and all first-line treatment regimens are detailed in Table IV. The mean number of treatment cycles in first-line treatment was 7.42 (±4.9). Of the 168 patients included in the study, 121 (72%) had any grade of treatment-related adverse events. Of these, 38 (31.4%) were grade 1, 56 (46.3%) were grade 2, 23 (19%) were grade 3, and three (2.4%) were grade 4. The most common treatment-related side effect was hematological toxicity (n=82, 48.8%), followed by neuropathy (n=36, 21.4%). Hepatotoxicity, nephrotoxicity, and pulmonary thromboembolism were observed less frequently as treatment-related side effects.

Of the patients who received first-line therapy, 115 (68.4%) also received second-line therapy. Twenty-two (19.1%) patients received capecitabine, 16 (14%) patients received paclitaxel, 14 (12.1%) patients received carboplatin plus gemcitabine, 14 (12.1%) patients received cisplatin plus gemcitabine, and 13 (11.3%) patients received sacituzumab govitecan as second-line therapy. The treatment regimens as second-line therapy are detailed in Table V. The mean number of treatment cycles in second-line therapy was 5.9 (±3.6). Of the 115 patients who received second-line therapy, 83 (72.1%) had treatment-related adverse events of any grade. The most common treatment-related adverse event was hematologic toxicity (n=50, 43.4%). The second most common treatment-

Table V. *Second-line treatment regimens.*

Treatment modalities	Number of patients (n)	Percent (%)
Capecitabine	22	19.1
Paclitaxel	16	14.0
Carboplatin plus gemcitabine	14	12.1
Cisplatin plus gemcitabine	14	12.1
Sacituzumab govitecan	13	11.3
Vinorelbine	10	8.7
Carboplatin plus paclitaxel	9	7.8
Gemcitabine	5	4.3
Docetaxel	3	2.6
Capecitabine plus docetaxel	3	2.6
Adriamycin plus cyclophosphamide	1	0.9
Gemcitabine plus capecitabine	1	0.9
Ixabepilone	1	0.9
Capecitabine plus ixabepilone	1	0.9
Cyclophosphamide, epirubicin, and 5-fluorouracil	1	0.9
Capecitabine plus pembrolizumab	1	0.9
Total	115	100.0

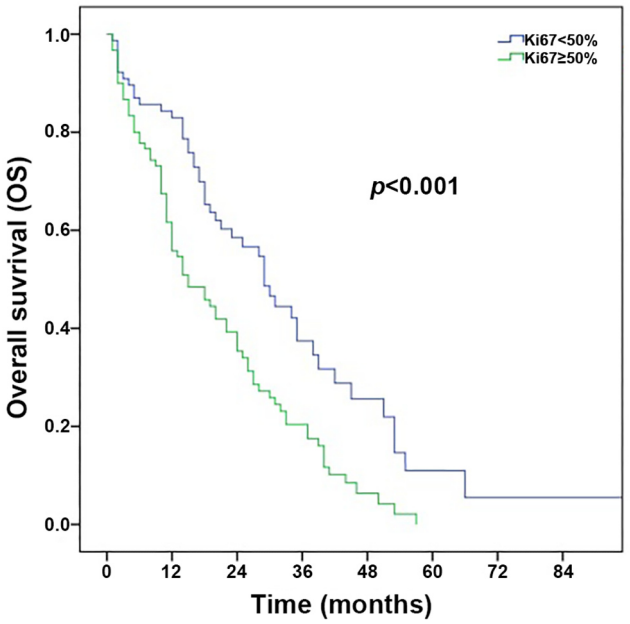


Figure 1. *Kaplan-Meier curve for overall survival according to Ki67 values.*

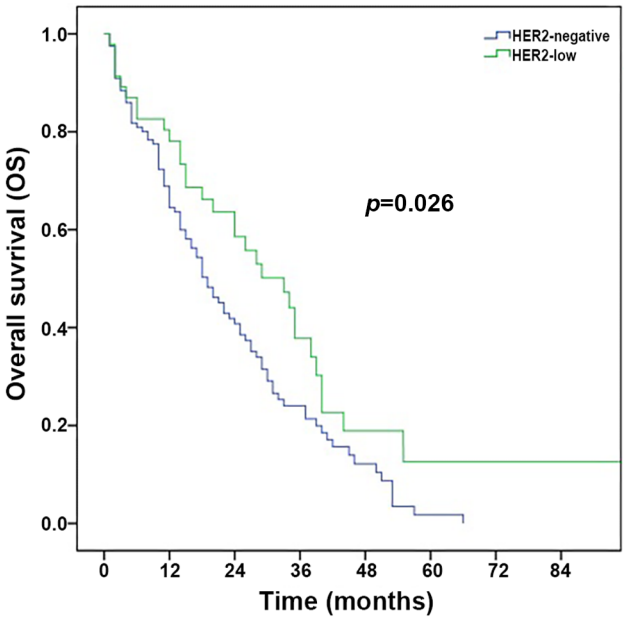


Figure 2. *Kaplan-Meier curve for overall survival according to HER2 status.*

related adverse event was neuropathy (n=24, 20.8%). Hepatotoxicity and nephrotoxicity were less common.

Survival analyses. The median follow-up was 44 months (95%CI=35.7-52.2). The median PFS in all patients was 9 months (95%CI=7.7-10.3 months). The median OS in all patients was 22 months (95%CI=17.4-26.5 months). Possible factors were age, menopausal status, *de novo* metastasis status, Ki67 value at diagnosis, grade at diagnosis, and HER2 status. In the univariate analyses, the median PFS was significantly worse in patients with *de novo* metastasis than in those with recurrent disease (8 months *vs.* 9 months, p=0.010). However, there was no difference in median OS between the two groups (22 months *vs.* 21 months, p=0.562). Higher Ki67 value at diagnosis was a significant poor prognostic factor for median OS (29 months *vs.* 15 months, p<0.001) (Figure 1).

When the groups were evaluated according to HER2 status, the median PFS for HER2-negative patients was eight months, and the median PFS for HER2-low patients was 11 months (p=0.167). HER2-negative patients had significantly worse median OS than HER2-low patients (19 months *vs.* 33 months, p=0.026) (Figure 2). Older age and postmenopausal status seemed to have numerically better OS; however, the differences were not statistically significant. Median OS was 25 months versus 19 months for age and 25 months versus 19 months for menopausal status (p=0.651 and p=0.654, respectively). Survival outcomes for other factors are detailed in Table VI.

Multivariate analysis was performed to examine the effects of age, menopausal status, Ki67 value, and HER2 status. Univariate analysis evaluated these factors as prognostic factors for median OS. The HER2 low group had significantly longer median OS than the HER2 negative group [HR=0.64 (95%Cl=0.42-0.98), p=0.040]. Other statistically significant prognostic factors are presented in Table VII.

Discussion

TNBC has an aggressive tumor biology. Until recently, the mainstay of treatment for metastatic TNBC was systemic chemotherapy. However, ADCs and immunotherapy have

Table VI. *Univariate analysis of possible prognostic factors for survival.*

	Median PFS (95%CI)	*p*-Value	Median OS (95%CI)	*p*-Value
Age (years)				
≤49	8.0 (6.63-9.36)	0.207	25.0 (18.73-31.26)	0.651
>49	9.0 (6.68-11.32)		19.0 (15.15-22.85)	
De novo metastasis				
Yes	8.0 (6.86-9.13)	**0.010**	22.0 (16.97-27.03)	0.562
No	9.0 (6.27-11.72)		21.0 (14.88-27.11)	
Ki67 (%)				
<50	11.0 (9.71-12.28)	0.109	29.0 (22.79-35.20)	**<0.001**
≥50	8.0 (6.46-9.53)		15.0 (8.46-21.53)	
HER2 status				
Negative	8.0 (6.87-9.12)	0.167	19.0 (14.79-23.20)	**0.026**
Low	11.0 (6.57-15.42)		33.0 (22.33-43.66)	
Grade				
Grade 2	10.0 (7.21-12.78)	0.137	24.0 (16.03-31.06)	0.115
Grade 3	9.0 (7.51-10.48)		20.0 (14.00-25.99)	
Menopausal status				
Pre(peri)menopausal	9.0 (7.59-10.40)	0.929	25.0 (17.68-32.31)	0.654
Postmenopausal	9.0 (7.22-10.77)		19.0 (15.13-22.86)	

PFS: Progression-free survival; OS: overall survival; HER2: human epidermal growth factor receptor-2; CI: confidence interval. Statistically significant *p*-values are shown in bold.

demonstrated improved survival outcomes, leading to a novel practice-changing strategy (4, 9)

There are several studies investigating the prognostic role of HER2-low status in both hormone receptor-positive (HR+) and HR-negative (HR-) patients with breast cancer, with different outcomes (10-14). However, there is no well-established consensus on this subject in the current literature.

In a study conducted using pooled analysis from three prospective clinical trials, including 350 patients with metastatic TNBC, the prognostic impact of HER2 status was investigated, and 34.9% of the patients were HER2-low (15). The HER2-low rate was lower in our study, at 28%. In a prior study, patients with HER2-low tumors were older and had fewer premenopausal patients than those with HER2-negative tumors. We found no difference between these two groups, regarding age and menopausal status in our study. In survival analysis, there was no significant difference in PFS and OS according to HER2 status (*i.e.*, HER2-low *vs.* HER2-), consistent with other studies in the literature (15). However, we found that HER2-low patients had significantly longer OS than HER2-negative ones (p=0.026). The survival advantage in HER2-low breast cancer patients is a novel addition to the literature, as there is currently no consensus on the effect of HER2 status. We believe that this study should be supported by prospective trials.

Table VII. *Multivariate analysis of clinical characteristics affecting overall survival.*

	HR (95%CI)	*p*-Value
Age (years)		
≤49	Ref	
>49	0.540 (0.296-0.988)	0.045
Ki67 (%)		
<50	Ref	
≥50	1.914 (1.334-2.767)	0.001
HER2 status		
Negative	Ref	
Low	0.648 (0.429-0.980)	0.040
Menopausal status		
Pre(peri)menopausal	Ref	
Postmenopausal	1.831 (1.009-3.322)	0.047

HR: Hazard ratio; HER2: human epidermal growth factor-2 receptor; CI: confidence interval.

Carsten *et al.* investigated the prognostic significance of HER2 status in patients with early-stage breast cancer

by pooling data of a total of 2,310 patients from four prospective trials (16). In this analysis, both HR+ and HR- patients were evaluated in subgroups, as HER2-low and HER2-negative. In the HR-/TNBC group (n=1,162), the HER2-low subgroup had longer DFS and OS than the HER2-negative subgroup. The 3-year DFS was 84.5% *vs.* 74.4%, and 3-year OS was 90.2% *vs.* 84.3% (p=0.0076, p=0.016), respectively (16). However, that study was conducted in patients with early-stage breast cancer, whereas all patients in our study had metastatic disease.

In another study conducted by Jiang *et al.* using the National Cancer Database in the United States, 30,929 patients with *de novo* metastatic HER2-low breast cancer were analyzed (17). Both HR+ and HR- patients were included, and 16.2% of the patients had TNBC. HER2-low rate in the TNBC group was 51.4%. It was higher than that in our study. The HER2-low group had longer OS than the HER2-negative group. Median OS for HR+/HER2 low patients was 39.0 months *vs.* 37.1 months (HR=0.95, 95%CI=0.91-0.98), and it was 15.8 months *vs.* 14.1 months for HR-/HER2 low ones (HR=0.92, 95%CI=0.86-0.98) (17). Li *et al.* compared the clinicopathological features and survival outcomes of patients with HER2-low and HER2-negative metastatic breast cancer (18). Three hundred eighty-eight (27.1%) of 1,433 patients had TNBC, and 35.3% of patients with TNBC were in the HER2-low group. The HER2-low group had longer OS, similar to the outcomes of our study. In our study, median OS was 19 months in the HER2-low group and 33 months in the HER2-negative group (p=0.026). Li *et al.* mentioned that the median OS was longer in both the overall population and HR+ patients, but there was no OS difference for either HER2-low or HER2-negative patients in the TNBC population (29.5 months *vs.* 29.9 months, p=0.718) (18).

Patients with '*de novo*' metastatic breast cancer, including TNBC, were reported to have better OS than relapsed ones (19). In our study, there was no difference in OS, but patients with '*de novo*' metastatic disease had significantly worse PFS (p=0.562, p=0.01).

There are novel therapeutic options, such as ADCs, for many solid tumors, including breast cancer. In the DESTINY-Breast04 study, trastuzumab deruxtecan (T-DXd), an ADC, was shown to have efficacy in patients with metastatic HER2-low breast cancer. Most (89%) of the patients had HR+/HER2 low breast cancer. T-DXd provided a significant OS improvement in both the whole population and the HR+/HER2 low subgroup (6). In this study, only 11.3% of the patients had HR-/HER2-low (TNBC) disease; therefore, there was no direct comparison of HR-/HER2-low patients with HR+/HER2-low ones due to the small number of HR-/HER2-low patients. However, the T-DXd survival advantage, observed in almost all populations, including HR+ and HR- HER2-low ones, supports its clinical utility in daily routine, as a recommended second-line treatment option in metastatic HER2-low TNBC.

In current clinical practice for metastatic TNBC, assessment of PD-L1 combined positive score (CPS), *BRCA* mutation status, and HER2-low expression for eligibility to trastuzumab deruxtecan (T-DXd) is recommended for second-line and later therapies. Although chemo-immunotherapy is the standard of care for patients with metastatic TNBC with a PD-L1 CPS score ≥10, systemic chemotherapy without immunotherapy is still used as a first-line treatment in many developing countries, including our own, due to limited access to immunotherapy, primarily because of reimbursement issues and/or other factors. Except for two patients who had chemotherapy with atezolizumab, almost all of the patients in our study received systemic chemotherapy as 1st-line treatment. The survival analyses determined that the HER2-low subgroup had a significantly longer OS than the HER2-negative subgroup (33 months *vs.* 19 months, p=0.026). As mentioned earlier, this outcome may inform treatment decisions for patients with limited access to current treatment options, such as immunotherapy or PARP inhibitors (PARPi), particularly for those with metastatic HER2-low disease.

The limitations of our study include its retrospective nature, small sample size, lack of knowledge regarding PDL1 status, and the addition of immunotherapy for possible PDL1 CPS >10, *BRCA* mutation status, and PARPi usage. PDL1 and *BRCA* mutation status have significant clinical implications here, as none of our patients received

immunotherapy, PARPi, and/or ADCs, including patients who could have potentially benefited from them. Despite all these limitations, we demonstrated a survival advantage with only systemic chemotherapy as the first-line treatment.

Conclusion

In our study, we evaluated the prognostic significance of HER2 status in patients with metastatic TNBC retrospectively. We found that the HER2-low subgroup had significantly longer OS than the HER2-negative subgroup. There is conflicting data for both HR+/HER2 negative and TNBC patients in the literature. Some of them agree with our study, showing a survival benefit with systemic chemotherapy, even without immunotherapy, for patients with a PDL1 CPS >10. Additionally, PARPi is recommended for patients with *BRCA* mutations and/or ADCs for those with HER2-low tumors. This may represent an advantage for patients with limited access to novel therapeutics such as immunotherapy or ADCs. Nevertheless, prospective randomized clinical trials are needed to validate these findings.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization: AT and MD; Data curation: AT; Formal analysis: AT and RM; Investigation: AT and SA; Methodology: MD and DÇ; Project administration: MD; Resources: all authors; Software: AT; Supervision: MD and FS; Roles/Writing – original draft: AT and MD; Writing – review & editing: all authors.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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