



ORIGINAL ARTICLE

Real-world treatment patterns and survival outcomes in HER2-positive metastatic gastric cancer

HER2-pozitif metastatik mide kanserinde gerçek yaşam tedavi yaklaşımları ve sağkalım sonuçları

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ABSTRACT • Background and Aims: Despite the evolution in management of metastatic human epidermal growth factor receptor-2 gastric cancer over the past decade, challenges remain in accessing new therapies in some parts of the world. We aimed to describe real-world treatment patterns, attrition, and survival outcomes in patients with human epidermal growth factor receptor 2-positive metastatic gastric cancer. **Materials and Methods:** This retrospective cohort study included patients aged ≥ 18 years with human epidermal growth factor receptor 2-positive metastatic gastric cancer who received at least one line of systemic antineoplastic therapy between January 1, 2015, and December 30, 2024. The primary outcome of the study was to define treatment choices and attrition rates in real-world clinical practice. Secondary endpoints were progression-free survival across treatment lines and overall survival. **Results:** Thirty-nine patients were included; median age was 65.5 years (min - max, 24.2 - 82.9), and 74.4% were male. The most common first-line regimens were oxaliplatin + 5-fluorouracil plus trastuzumab (38.5%) and docetaxel + cisplatin + 5-fluorouracil plus trastuzumab (25.6%); 15.4% did not receive trastuzumab, and no patient received pembrolizumab as first-line treatment. Median first-line progression-free survival was 7.49 months (95% CI 5.56 - 9.42), and median overall survival was 16.53 months (95% CI 12.56 - 20.49). Overall, 68.4% of patients received second-line therapy, 41.0% received third-line therapy, and 10.3% proceeded to fourth-line treatment. Second-line treatment was predominantly irinotecan + 5-fluorouracil-based, while paclitaxel was the most frequent third-line regimen. Median progression-free survival was 3.35 months (95% CI 3.02 - 3.68) in the second line and 2.69 months (95% CI 2.28 - 3.10) in the third-line setting. Disease progression was the leading cause of treatment discontinuation across all lines. **Conclusion:** Human epidermal growth factor receptor-2-positive metastatic gastric cancer remains associated with poor survival and limited real-world access to novel agents. There is an ongoing need for more effective therapies and better implementation of new treatments in routine practice.

Keywords: Gastric cancer, HER2, trastuzumab

ÖZET • Giriş ve Amaç: Son dekatta insan epidermal büyüme faktörü reseptörü-2-pozitif metastatik mide kanserinin tedavisinde önemli gelişmeler kaydedilmiş olmasına rağmen, dünyanın bazı bölgelerinde yeni tedavilere erişimde hâlen güçlükler bulunmaktadır. Bu çalışmada, insan epidermal büyüme faktörü reseptörü-2-pozitif metastatik mide kanseri olan hastalarda gerçek yaşamda uygulanan tedavi seçimleri, sonraki basamak tedaviye ulaşma oranları ve sağkalım sonuçlarını tanımlamayı amaçladık. **Gereç ve Yöntem:** Bu retrospektif kohort çalışmasına, 1 Ocak 2015 ile 30 Aralık 2024 tarihleri arasında insan epidermal büyüme faktörü reseptörü-2-pozitif metastatik mide kanseri tanısı ile en az bir basamak sistemik antineoplastik tedavi almış, ≥ 18 yaşındaki hastalar dahil edildi. Çalışmanın birincil sonlanım noktası, gerçek yaşam klinik pratiğinde tedavi seçimlerini ve sonraki basamak tedaviye ulaşma oranlarını tanımlamaktır. İkincil sonlanım noktaları ise tedavi basamaklarına göre progresyonsuz sağkalım ve genel sağkalım idi. **Bulgular:** Toplam 39 hasta çalışmaya dahil edildi; medyan yaş 65,5 yıl (min - max: 24,2 - 82,9) olup hastaların %74,4'ü erkekti. En sık uygulanan birinci basamak tedaviler oksaliplatin + 5-fluorourasil + trastuzumab (%38,5) ve dosetaksel + sisplatin + 5-fluorourasil + trastuzumab (%25,6) idi. Hastaların %15,4'ü trastuzumab almamış olup, hiçbir hasta birinci basamakta pembrolizumab tedavisi almamıştı. Medyan birinci basamak progresyonsuz sağkalım 7,49 ay (%95 GA 5,56 - 9,42), medyan genel sağkalım ise 16,53 ay (%95 GA 12,56 - 20,49) olarak saptandı. Hastaların %68,4'ü ikinci basamak, %41,0'ı üçüncü basamak ve %10,3'ü dördüncü basamak tedavi almıştı. İkinci basamakta tedaviler çoğunlukla irinotekan + 5-fluorourasil temelli iken, üçüncü basamakta en sık kullanılan rejim paklitaksel idi. Medyan progresyonsuz sağkalım ikinci basamakta 3,35 ay (%95 GA: 3,02 - 3,68), üçüncü basamakta ise 2,69 ay (%95 GA 2,28 - 3,10) olarak bulundu. Tüm tedavi basamaklarında tedavi kesilmesinin en sık nedeni hastalık progresyonu idi. **Sonuç:** İnsan epidermal büyüme faktörü reseptörü-2-pozitif metastatik mide kanseri, gerçek yaşam verilerinde hâlen kötü sağkalım ile ilişkilidir ve yeni ajanlara erişim sınırlıdır. Daha etkili tedavilere ve yeni tedavi yaklaşımlarının rutin klinik pratiğe daha iyi entegre edilmesine yönelik önemli bir gereksinim devam etmektedir.

Anahtar kelimeler: Gastrik kanser, HER2, trastuzumab

INTRODUCTION

Gastric cancer remains a major global health burden and is the fifth most common cancer worldwide, with an estimated 968,350 new cases and 659,853 deaths annually (1). Non-cardia gastric cancer, which constitutes approximately 80% of cases worldwide, is associated with *Helicobacter pylori* infection and dietary factors, whereas cardia gastric cancer is primarily linked to obesity and gastroesophageal reflux (2). Human epidermal growth factor receptor-2 (HER2) is one of the biomarkers, along with programmed death-ligand 1 (PD-L1) combined positive score (CPS) and claudin 18.2, recommended for evaluation in patients with metastatic gastric cancer to tailor first-line treatment selection (3-5). The prevalence of HER2 overexpression ranges from 10% to 20%, with a higher prevalence observed in proximal tumors. Intratumoral heterogeneity of HER2 expression may exist; therefore, it is recommended to provide a quantitative assessment of the proportion of tumor cells exhibiting positive HER2 staining by immunohistochemistry (IHC) and the gene amplification ratio (3). Chemotherapy regimens that include both a fluoropyrimidine and oxaliplatin are recommended as first-line treatment for metastatic gastric cancer. Based on the phase III Trastuzumab for Gastric Cancer (ToGA) trial, which showed higher response rates and longer survival with chemotherapy plus trastuzumab compared with chemotherapy alone, adding trastuzumab to chemotherapy is recommended for patients with HER2-overexpressing gastric cancer (6). Recently, adding pembrolizumab to chemotherapy plus trastuzumab improved progression-free survival (PFS) and overall survival (OS) in patients whose tumors had a CPS ≥ 1 ; therefore, chemotherapy, trastuzumab, and pembrolizumab are recommended as first-line treatment in this population (7,8).

Clinical phase III trials play a pivotal role in defining the efficacy and safety profile of new thera-

pies and often drive changes in standard oncology practice. Due to the stringent design of phase III trials, patients enrolled in these studies typically differ from those treated in routine care in terms of comorbidities, performance status, and access to therapies, and therefore may experience different outcomes. Moreover, national socioeconomic status is a determinant of drug access, and in low- and middle-income countries guideline-recommended treatments are not always accessible (9,10). Therefore, real-world practice does not always align with guideline recommendations. In this study, we aimed to characterize real-world treatment patterns, clinical outcomes, and attrition rates among patients with HER2-positive metastatic gastric cancer treated at a tertiary referral center in Türkiye.

MATERIALS and METHODS

This study was designed as a retrospective single-center cohort study. We retrospectively evaluated patients diagnosed with metastatic HER2-positive gastric cancer between January 1, 2015, and December 30, 2024. Patients aged ≥ 18 years with metastatic HER2-positive gastric cancer who received at least one line of systemic antineoplastic therapy for metastatic disease were included in the study. Patients with HER2-negative or inconclusive HER2 test results, a diagnosis of any other primary malignancy within the 5 years before the first gastric cancer diagnosis, as well as those with insufficient clinical data to perform survival analyses, were excluded. Patients were defined as HER2-positive if they had either immunohistochemical 3+ positivity or immunohistochemical 2+ positivity with fluorescence in situ hybridization (FISH) positivity or FISH positivity according to available pathology reports when the IHC score was unavailable.

Demographic and pathological characteristics, performance status, treatment details, treatment

start and end dates, and dates of progression and death were retrospectively collected from medical records. The primary outcome of the study was to define treatment choices and attrition rates in real-world clinical practice. Secondary endpoints were PFS across treatment lines and OS. PFS was defined as the time from treatment initiation to the date of disease progression or death from any cause. OS was defined as the time from the initiation of first-line treatment to the date of death from any cause. Disease progression was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria.

This retrospective study was conducted in accordance with the Declaration of Helsinki. It was ap-

proved by the Ankara University Faculty Ethics Committee, approval number: I11-1068-25.

All statistical analyses were performed using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were summarized as medians (min - max), and categorical variables were expressed as percentages. The chi-square test was used to compare categorical variables, while the Mann–Whitney U test or Student's t-test was applied to compare continuous variables, as appropriate. Survival curves and survival rates were estimated using the Kaplan-Meier method. All reported p-values were two-sided, and a p-value < 0.05 was considered statistically significant.

Table 1 Baseline characteristics of patients

Variables		N = 39
Age, years (median, min-max)		65.54 (24.2 - 82.9)
Age, years (n = 39)	< 65	19 (48.7)
	≥ 65	20 (51.3)
Gender (n = 39)	Female	10 (25.6)
	Male	29 (74.4)
ECOG-PS (n = 37)	0	3 (8.1)
	1	28 (75.7)
	2	6 (16.2)
Primary location (n = 38)	Cardia	17 (44.7)
	Non-cardia	21 (55.3)
Histologic subtype (n = 38)	Adenocarcinoma	35 (92.1)
	Signet ring	3 (7.9)
Metastatic disease type (n = 39)	Metachronous	12 (30.8)
	De novo	27 (69.2)
LN metastasis (n = 39)	No	10 (25.6)
	Yes	29 (74.4)
Liver metastasis (n = 39)	No	9 (23.1)
	Yes	30 (76.9)
Peritoneal metastasis (n = 39)	No	31 (79.5)
	Yes	8 (20.5)
Lung metastasis (n = 39)	No	33 (84.6)
	Yes	6 (15.4)
HER2 positivity (n = 37)	2	13 (35.1)
	3	24 (64.9)

ECOG: Eastern Cooperative Oncology Group; HER2: Human epidermal growth factor receptor 2; LN: Lymph node; PS: Performance status.

RESULTS

A total of 39 patients were included in the study. The median age was 65.5 years (range, 24.2 - 82.9), and 29 patients (74.4%) were male. Thirty-one patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1. The primary tumor location was non-cardia in 21 patients (53.8%), and histology was adenocarcinoma in 35 patients (92.1%). Twenty-seven patients (69.2%) had de novo metastatic disease. The most common site of metastasis was the liver (76.9%), followed by lymph nodes (74.4%) and the peritoneum (20.5%). HER2 positivity was observed in 13 patients (35.1%) with an IHC score of 2+ and in 24 patients (64.9%) with an IHC score of 3+. In two patients, the degree of IHC positivity was not available. The clinical and demographic characteristics of the patients are presented in Table 1. Although age ≥ 65

years and ECOG performance status of 2 were associated with shorter OS in univariable analysis, these associations were not retained after multivariable adjustment (Supplementary Table 1).

The median follow-up time was 15.67 months (min-max 4.73 - 52.40). The most used first-line treatment regimens were oxaliplatin + 5-fluorouracil (FOLFOX) plus trastuzumab (38.5%) and docetaxel + cisplatin + 5-fluorouracil (DCF) plus trastuzumab (25.6%) (Figure 1). Six patients (15.4%) did not receive trastuzumab in the first-line setting, and none of the patients received pembrolizumab as first-line therapy. Median PFS in the first-line setting was 7.49 months (95% CI 5.56 - 9.42) (Figure 2A). Median OS was 16.53 months (95% CI 12.56-20.49) (Figure 2B).

Supplementary Table 1 Univariate and multivariate analysis for predictors of overall survival

Variable		Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age	< 65	1		1	
	≥ 65	2.22 (1.06 - 4.64)	0.034	2.14 (0.95 - 4.84)	0.067
Gender	Female	1		-	
	Male	0.83 (0.34 - 2.05)	0.692	-	-
ECOG-PS	0-1	1		1	
	2	3.21 (1.11 - 9.25)	0.031	2.17 (0.72 - 6.61)	0.171
Lung metastasis	No	1		-	
	Yes	1.67 (0.62 - 4.47)	0.306	-	-
Liver metastasis	No	1		-	
	Yes	1.33 (0.51 - 3.48)	0.555	-	-
Lymph node metastasis	No	1		-	
	Yes	0.67 (0.31 - 1.48)	0.326	-	-
Peritoneal metastasis	No	1		-	
	Yes	1.11 (0.48 - 2.61)	0.803	-	-
HER2 positivity	2	1		-	
	3	1.11 (0.51 - 2.40)	0.790	-	-
Trastuzumab treatment in first line	No	1		-	
	Yes	0.99 (0.35 - 2.88)	0.999	-	-

ECOG: Eastern Cooperative Oncology Group; HER2: Human epidermal growth factor receptor 2; PS: Performance status.

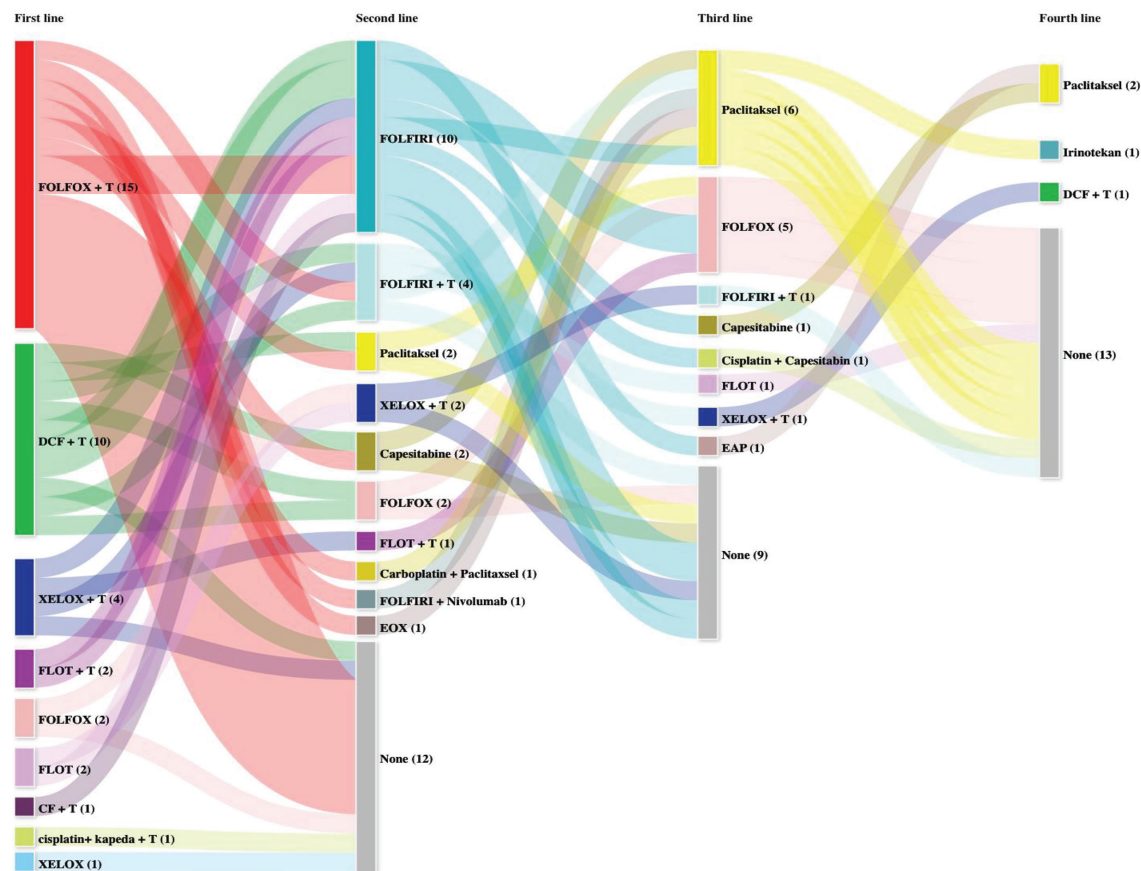


Figure 1 First- to fourth-line treatment patterns*

The patient who is still receiving first-line treatment has not been shown.

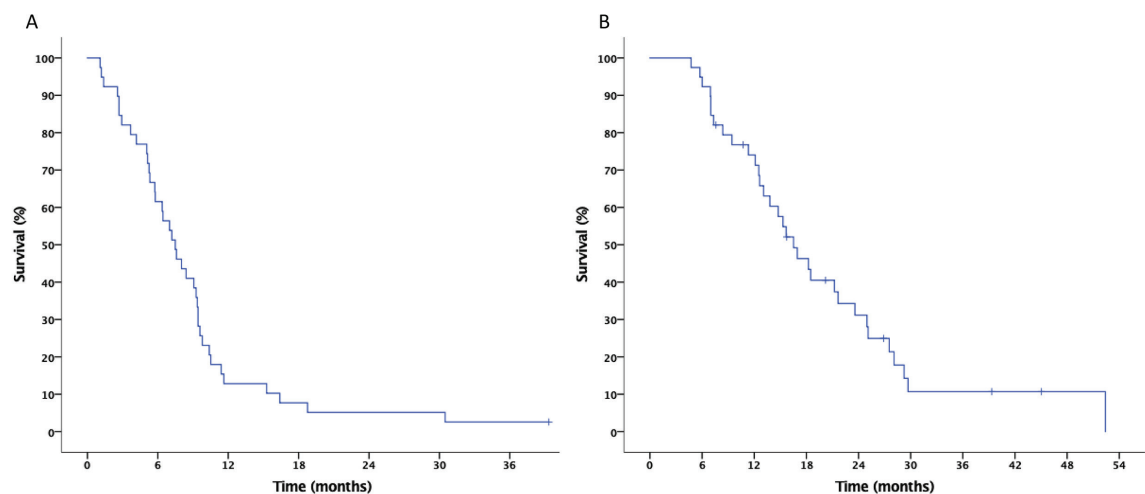


Figure 2 Kaplan-Meier curve for progression free survival (A) and overall survival for first-line treatment.

One patient was still receiving first-line therapy at the time of analysis. Of the remaining 38 patients, 26 (68.4%) received second-line treatment. In the second-line setting, the most commonly used regimens were irinotecan + 5-fluorouracil (FOLFIRI) (42.3%) and FOLFIRI plus trastuzumab (15.4%) (Figure 3A). The median PFS in the second-line setting was 3.35 months (95% CI, 3.02 - 3.68). Sixteen patients (41.0%) received third-line treatment, while only four patients (10.3%) received fourth-line therapy. In the third-line setting, paclitaxel (31.3%), FOLFOX (18.8%), and FOLFIRI

(12.5%) were the commonly utilized regimens. The median progression-free survival with third-line treatment was 2.69 months (95% CI, 2.28 - 3.10) (Figure 3B).

For the first-line setting, the main cause of treatment discontinuation was disease progression (73.4%), followed by completion of the planned treatment (15.8%), treatment-related toxicity (7.9%), and decline in performance status (2.6%). Disease progression remained the primary reason for treatment discontinuation across all subsequent treatment lines (Figure 4).

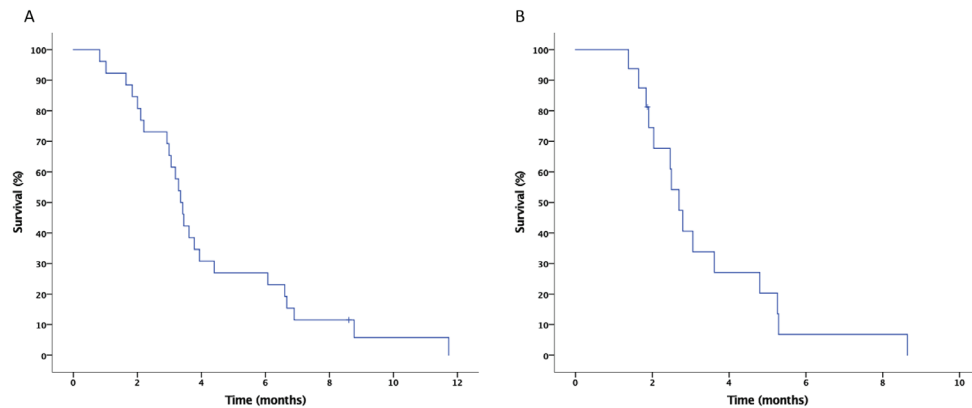


Figure 3 Kaplan-Meier curve for progression free survival for second-line (A) and third-line treatment (B).

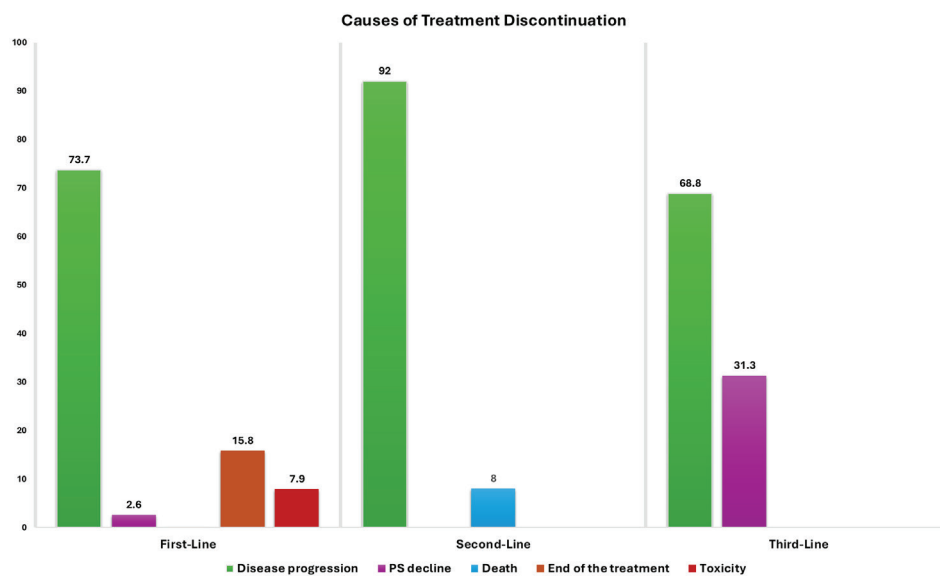


Figure 4 Causes of treatment discontinuation across treatment lines

DISCUSSION

Real-world data are important for understanding treatment patterns, attrition, toxicity, and outcomes in routine practice, thereby complementing trial results and informing guideline development and everyday clinical decision-making. Our study showed that patients with HER2-positive metastatic gastric cancer treated at our center had a median OS of 16.53 months. Median PFS was 7.49 months, 3.35 months, and 2.69 months in the first-, second-, and third-line settings, respectively. Overall, 68.4% of patients received second-line therapy, 41.0% received third-line therapy, and only 10.3% proceeded to fourth-line treatment.

FOLFOX plus trastuzumab (38.5%) and DCF plus trastuzumab (25.6%) were the most used first-line regimens, while FOLFIRI-based therapies were most frequently administered in the second-line setting (57.9%), and paclitaxel was the most common third-line agent (31.3%) in our study. Although the chemotherapy backbone varied by time and region, the preferred first-line approach in real-world practice was a chemotherapy doublet plus trastuzumab (11-13). In patients with gastric cancer, attrition rates are high, and in real-world practice more than half of patients typically do not proceed to second-line therapy. However, in our study, the proportions of patients receiving subsequent lines of therapy were higher than those reported in other real-world cohorts. In an England-based real-world cohort of HER2-positive metastatic gastric cancer treated with trastuzumab-based first-line therapy, only 33.3% of patients received second-line treatment and 6.6% proceeded to third-line therapy (11). In this real-world cohort, first-line treatment most frequently comprised capecitabine–cisplatin plus trastuzumab (54.9%), whereas subsequent lines were largely confined to taxane- and irinotecan-based regimens, with paclitaxel monotherapy the most common second-line option (36.4%) and FOLFIRI the most frequently

used third-line regimen (19.1%) (11). Among the 2,745 patients in China, 17.7% were HER2-positive, 69.3% received first-line therapy, and among those, 38.3% subsequently received second-line therapy and only 14.9% went on to receive third-line therapy (14). Irrespective of HER2 status, only 32.8% of patients who initiated first-line therapy reached second-line treatment, and 10.2% reached third-line therapy, in the German cohort (15). Similarly, in a real-world cohort from Latin America and Europe, only 14.4% of patients received second-line treatment and 3.0% received third-line therapy (16).

Median OS in our cohort (16.53 months) was higher than the median OS reported for chemotherapy plus trastuzumab in the overall ToGA population (13.8 months) and was comparable to the outcome in the HER2-high subgroup (IHC 3+ or IHC 2+/FISH+), where median OS was 16.0 months (6). Median OS was also like that in the control arm of KEYNOTE-811 (chemotherapy plus trastuzumab), where median OS was 16.8 months (8). Median PFS with first-line treatment was 7.49 months in our study; however, 15.4% of patients did not receive trastuzumab. In comparison, median PFS was 6.7 months with chemotherapy plus trastuzumab in the ToGA trial and 8.1 months in the control arm of the KEYNOTE-811 trial (6,7). Survival times were slightly higher than those reported in previous real-world studies, possibly related to lower treatment attrition and greater access to post-progression therapies (11,12,14,16).

In our cohort, 15.4% of patients did not receive trastuzumab, and none received pembrolizumab in first-line treatment, highlighting ongoing limitations in drug accessibility. Many patients are unable to proceed to subsequent lines of therapy, making it crucial to deliver the most effective treatment available at each stage. In addition, there was

heterogeneity in second- and third-line regimens, and some patients continued trastuzumab beyond progression, emphasizing the need to provide more effective and accessible treatment options in this population. In the phase II DESTINY-Gastric01 trial, trastuzumab deruxtecan demonstrated superior efficacy to physician's choice of chemotherapy in patients who received at least two lines of therapy, with higher objective response rates (40.5% vs. 11%), longer PFS (5.6 vs. 3.5 months), and improved OS (12.5 vs. 8.4 months) (17). Similarly, the DESTINY-Gastric04 trial showed that, in the second-line setting, trastuzumab deruxtecan achieved higher overall response rate (ORR) (44.3% vs. 29.1%) and longer OS (14.7 vs. 11.4 months) compared with ramucirumab-paclitaxel combination (18). Based on these data, trastuzumab deruxtecan is now recommended as a preferred second-line option for patients who progress on trastuzumab-containing regimens; however, access to this agent remains limited, including in our practice. During the study period, pembrolizumab and trastuzumab deruxtecan were not reimbursed for these indications in Türkiye and were not widely accessible as part of routine treatment for metastatic gastric cancer. Therefore, country-specific regulatory and reimbursement barriers should be considered when interpreting real-world treatment patterns and outcomes in our cohort.

Our study had several limitations. Firstly, our data were collected retrospectively, making the analysis particularly susceptible to missing or incomplete information. Secondly, the sample size was relatively small, which may limit the statistical power and the robustness of some subgroup analyses. Furthermore, although multivariable analysis for OS was conducted, the limited number of patients and events rendered the results exploratory; there-

fore, these findings should be interpreted with caution. Finally, because treatment access and reimbursement policies differ substantially between countries, and our cohort included only patients from Türkiye, the generalizability of these findings to other healthcare settings may be limited. The strengths of the present study include the use of high-quality data derived from a single-center cohort, which allowed consistent patient evaluation, treatment assessment, and follow-up. In addition, the relatively long follow-up period enabled a more comprehensive evaluation of survival outcomes. Finally, the study reflects real-world clinical practice and may therefore provide clinically relevant information on treatment outcomes outside the controlled setting of prospective clinical trials.

In conclusion, HER2-positive metastatic gastric cancer continues to be associated with poor survival outcomes and limited treatment options in real-world practice. In our cohort, access to newly approved agents such as pembrolizumab and trastuzumab deruxtecan remained restricted, reflecting the slow implementation of novel therapies into routine care. These findings underscore the need for more effective and innovative treatment strategies, as well as health system-level efforts to improve drug accessibility and optimize treatment sequencing, with the ultimate goal of improving outcomes for patients.

Ethics: *This retrospective study was conducted in accordance with the Declaration of Helsinki. It was approved by the Ankara University Faculty Ethics Committee, approval number: İ11-1068-25.*

Conflicts of Interests: *All authors have declared no conflicts of interest.*

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