EJMI

DOI: 10.14744/ejmi.2023.22720
EJMI 2023;7(2):153–161

Research Article

Second-line Therapy after Trastuzumab Failure in HER2-Positive Metastatic Gastric Cancer: A Real-life Data

Atakan Topcu,[1] Mehmet Besiroglu,[1] Muhammed Mustafa Atci,[2] Saban Secmeler,[2] Murat Ayhan,[3] Metin Ozkan,[4] Oktay Bozkurt,[4] Zuhat Urakci,[5] Seval Ay,[6] Caglayan Geredeli,[2] Ayse Irem Yasin,[1] Ozge Pasin,[7] Haci Mehmet Turk[1]

[1]Department of Medical Oncology, Bezmialem Vakif University, Istanbul, Türkiye
[2]Department of Medical Oncology, University of Health Sciences, Prof. Dr Cemil Tascioglu City Hospital, Istanbul, Türkiye
[3]Department of Medical Oncology, University of Health Sciences, Kartal Dr. Lutfi Kirdar Training and Research Hospital, Istanbul, Türkiye
[4]Department of Medical Oncology, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[5]Department of Medical Oncology, Dicle University Faculty of Medicine, Diyarbakir, Türkiye
[6]Department of Medical Oncology, Medeniyet University Faculty of Medicine, Istanbul, Türkiye
[7]Department of Biostatistics, Bezmialem Vakif University Faculty of Medicine, Istanbul, Türkiye

Abstract

Objectives: To compare the second-line treatments on survival after trastuzumab failure in HER2-positive metastatic gastric cancer.

Methods: We retrospectively included 57 patients. Of whom, 32 (56%) received paclitaxel, whereas 25 (44%) received 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI). We analyzed the patient characteristics, and survival outcomes of the second-line treatment.

Results: The median PFS was 3.5 months in the paclitaxel-group and 4.8 months in the FOLFIRI-group (p=0.569). The median overall survival (OS) was 6.0 months in paclitaxel-group and 11.0 months in FOLFIRI-group (p=0.410). FOLFIRI provided a significant OS advantage over paclitaxel in patients with grade 3 tumors or who did not have an objective first-line treatment response.

Conclusion: FOLFIRI may be recommended as a preferred option over paclitaxel in patients with these identified risk factors.

Keywords: FOLFIRI, Gastric cancer, HER2, paclitaxel, second-line therapy, trastuzumab failure

Cite This Article: *Topcu A, Besiroglu M, Atci MM, Secmeler S, Ayhan M, Ozkan M, et al. Second-line Therapy after Trastuzumab Failure in HER2-Positive Metastatic Gastric Cancer: A Real-life Data. EJMI 2023;7(2):153–161.*

Gastric cancer is one of the worst-prognosis cancers. Patients are usually diagnosed in advanced stages, with relatively low chances of cure. The primary goals of systemic therapy for metastatic gastric cancer are to provide symptom palliation and prolong survival.[1] Human epidermal growth factor receptor-2 (HER2) is a transmembrane tyrosine kinase receptor, with 6–30% HER2-positivity rate in gastric cancer. Trastuzumab is a monoclonal antibody-targeting HER2. The standard treatment for HER2-positive metastatic gastric cancer is now accepted worldwide, and

Address for correspondence: Atakan Topcu, MD. Tıbbi Onkoloji Bilim Dalı, Bezmialem Vakıf Üniversitesi, 34093, İstanbul, Türkiye
Phone: +90 212 523 22 88 **E-mail:** atakantopcu@hotmail.com

Submitted Date: December 11, 2022 **Accepted Date:** January 29, 2023 **Available Online Date:** March 21, 2023

trastuzumab is generally added to chemotherapy as first-line therapy. Unfortunately, most patients with HER2-positive metastatic gastric cancer fail the first-line treatment in <1 year.[2, 3] Moreover, no substantial evidence has supported the continuation of trastuzumab in the case of progression.[4, 5] In addition, many agents against HER2 were tried in the second-line treatment of HER2-positive metastatic gastric cancer but failed.[6, 7] Despite the negative trials, in a phase 2 trial, trastuzumab deruxtecan was reported as an antibody-drug conjugate composed of an anti-HER2 antibody and might be effective in patients with HER2-positive metastatic gastric cancer who have previously received at least two-line therapies in the advanced stage, including trastuzumab.[8]

Regardless of HER2 expression, a survival benefit has been demonstrated for irinotecan, 5-fluorouracil [5-FU], and leucovorin and irinotecan (FOLFIRI), paclitaxel, or ramucirumab as second-line treatment in metastatic setting.[9-14] For economic reasons, most patients in low-income countries cannot access ramucirumab and trastuzumab deruxtecan, so in clinical practice, most patients can only receive chemotherapy. Therefore, FOLFIRI and paclitaxel are still preferred as frequently used agents in the second-line, although these agents vary between clinicians and countries.

At present, optimal second-line therapy is not established after the failure of first-line trastuzumab-based chemotherapy for HER2-positive subgroup disease. In addition, real-life data is missing and is still necessary for investigation. Moreover, many of these patients may not be suitable for second-line treatment due to poor performance status, impaired organ functions, advanced age, or comorbidities. Therefore, choosing an effective treatment for this subgroup may be essential. In real-life data, we retrospectively researched the second-line chemotherapic agent with better survival outcomes after the first-line trastuzumab failure in HER2-positive gastric cancer.

Methods

Study Design and Patients

Data of patients who were histopathologically diagnosed with HER2-positive metastatic gastric cancer between 2013 and 2020 were retrospectively analyzed in study centers, including patients who received first-line trastuzumab-based chemotherapy followed by second-line paclitaxel or FOLFIRI in metastatic gastric cancer. The HER2-positive criteria were defined as fluorescence in situ hybridization (FISH)+ with either immunohistochemistry (IHC2)+ or IHC3+. Patients who did not meet the HER-2 positivity criteria were HER2-positive and did not receive trastuzumab as first-line therapy, who received trastuzumab in the second-line, who received other chemotherapeutic agents other than FOLFIRI or paclitaxel in the second-line, Eastern Cooperative Oncology Group Performance Status (ECOG PS) of >2, and were under 18 years of age, as well as histological subtypes other than adenocarcinoma and signet ring cell carcinoma, were excluded from the study (Fig. 1).

Patient Evaluation

Clinic and demographic characteristics of the included patients were retrospectively noted. Trastuzumab was used in standard doses and schema in the first-line. Chemotherapeutic agents, paclitaxel (80 mg/m^2) was intravenously (IV) administered on days 1, 8, and 15, every 28 days, and FOLFIRI (irinotecan IV at 180 mg/m^2, 5 FU IV push at 400 mg/m^2, leucovorin at 400 mg/m^2, and 5-FU continuous IV infusion at 2400 mg/m^2) were administered on days 1 and 15, every 28 days, were used in same standard doses in all patients. Disease evaluations were assessed with computed tomography as a standard in all centers. Treatment response was evaluated by Response Evaluation Criteria in Solid Tumors version 1.1 criteria. The primary endpoint includes median overall survival (OS), which is considered as time from the initiation date of the second-line treatment until the death for any reason or the last date the patient was known to be alive. The secondary endpoint includes PFS, which was defined as the time from the initiation date of the second-line treatment to the date of disease progression or death. The hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for survival outcomes based on patient characteristics at baseline as second-line therapy were determined. The Local Ethics Committee reviewed and approved this study with the decision number: 16/329.

Statistical Analysis

Statistical data were obtained using the Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA). Qualitative variables were described by frequen-

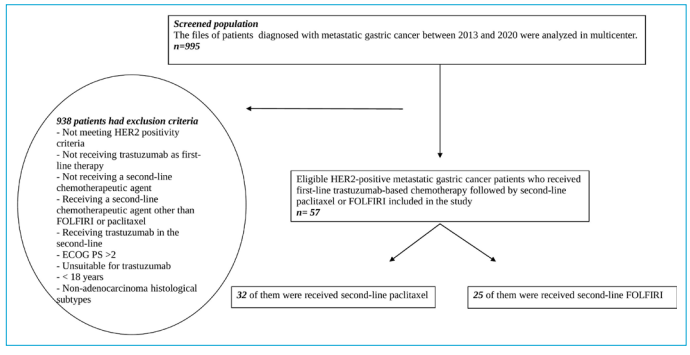

Figure 1. Flowchart of the patient selection.

cies and percentages, continuous and ordinal variables by mean, standard deviation, and median and range. The Kolmogorov–Smirnov test was applied to determine the normal distribution range. The Pearson χ^2 test was used to compare qualitative variables. The characteristics of patients were evaluated with descriptive analysis. Survival analysis was performed using the Kaplan–Meier survival curves and the log-rank test. Identified risk factors for death risk were determined by univariate Cox regression analysis. Forest plot applied HRs and corresponding 95% CIs were estimated using univariate Cox proportional-hazards regression models, stratified according to subgroups, for the analyses of OS and PFS. HRs of >1.0 indicated an increased likelihood of death. Statistical significance was set at $p<0.05$.

Results

This study included 57 patients with HER2-positive metastatic gastric cancer who received first-line trastuzumab-based chemotherapy followed by second-line paclitaxel or FOLFIRI. Of whom, 32 (56%) received paclitaxel, whereas 25 (44%) received FOLFIRI as second-line therapy. The mean age of patients for paclitaxel and FOLFIRI was 57.8±12.1 and 54±11.8 years, respectively. Of the patients, 75% had an ECOG PS of 0–1 and 25% had an ECOG PS of 2. The IHC was 3+ in 77% of patients and 2+ in 23%, whereas the FISH test was positive in all groups. Frequently, cisplatin and capecitabine/5-FU or capecitabine and oxaliplatin/5-FU and leucovorin and oxaliplatin (FOLFOX) regimens had been used with trastuzumab in the first-line therapy. The most common metastatic sites were the liver, peritoneum, and lungs at the initiation of the second-line therapy. No lethal toxicity that led to drug discontinuation was reported in either group receiving second-line therapy. Moreover, our study reported deaths in 27 patients (84%) in the paclitaxel group and 20 (80%) in the FOLFIRI group. All deaths were reported to be associated with disease progression. No statistical differences were determined at the initiation of second-line therapy in baseline characteristics of both groups such as previous chemotherapy regimens and trastuzumab cycles, first-line therapy response, HER2 IHC expression, grade, primer site, the number of metastatic lesions and organs, mean age, ECOG PS, comorbidity status, and gender. The baseline characteristics of the 57 patients are listed in Table 1.

In all groups, the median follow-up time was 5.9 months (1.2–41.3). The median PFS was 3.8 months (95% Confidence Intervals [CI]: 2.9–4.7), the 6-month PFS rate was 30.3%, and the 1-year PFS rate was 10.7%. The median OS was 6.9 months (95% CI: 3.7–10.1), the 6-month OS rate was 58.8%, and the 1-year OS rate was 23.2%. The median PFS was 3.5 months (95% CI: 3.1–3.9) in the paclitaxel group and 4.8 months (95% CI: 3.7–5.9,) in the FOLFIRI group (p=0.569) (Fig. 2). The median OS was 6.0 months (95% CI: 3.9–8.2) in the paclitaxel group and 11.0 months (95% CI: 7.6–14.3) in the FOLFIRI group (p=0.410) (Fig. 2). A numerical difference was found in PFS and OS in favor of FOLFIRI; however, it did not reach statistical significance between all the groups.

The HRs and 95% CIs of the second-line therapy for the PFS and OS analysis were evaluated in prespecified subgroups (Figs. 3 and 4). FOLFIRI treatment was determined to be associated with improved OS over paclitaxel in patients with grade 3 tumors or who did not have an objective response to the first-line treatment. In patients with grade 3 tumors, the median OS was 9.0 months in the FOLFIRI group and 4.2 months in the paclitaxel group. The OS was statistically longer in the FOLFIRI group than in the paclitaxel group (Hazard Ratio: 0.42, 95% CI: 0.18–0.96, p=0.040). In patients who did not have an objective response to the first-line treatment, the median OS was 10.8 months in the FOLFIRI group and 4.4 months in the paclitaxel group. Similarly, the OS was statistically longer in the FOLFIRI group than in the paclitaxel group (HR: 0.33, 95% CI: 0.11–0.95, p=0.040). It was detected that FOLFIRI treatment was associated with more prolonged PFS than paclitaxel in patients who have lung metastasis or >4 metastatic lesions. Patients with lung metastases have a median PFS of 4.8 months in the FOLFIRI group and 2.6 months in the paclitaxel group. The PFS was statistically longer in the FOLFIRI group than in the paclitaxel group (HR: 0.28, 95% CI: 0.08–0.99, p=0.047). Patients with >4 metastatic lesions have a median PFS which was 6 months in the FOLFIRI group and 2.8 months in the paclitaxel group. In addition, the PFS was statistically longer in the FOLFIRI group than in the paclitaxel group (HR: 0.28, 95% CI: 0.10–0.82, p=0.021).

Identified risk factors for death risk were determined by univariate Cox regression analysis (Fig. 4). In the presence of Grade 3 alone (HR: 0.42) and did not have a first-line objective response alone (HR: 0.33), which were defined as identified risk factors alone, there was a significant reduction in the risk of death with FOLFIRI compared to paclitaxel. Of the 18 patients with these two risk factors, ten patients received paclitaxel, and eight received FOLFIRI. The median OS was 3.9 months (95% CI: 2.7–5.19) in the paclitaxel group and 5.2 months (95% CI: 5.2–5.3) in the FOLFIRI group. The median OS of patients with both identified risk factors was statistically longer in the FOLFIRI group than in the paclitaxel group (p=0.047) (Fig. 5).

Table 1. The baseline characteristics of all patients (n=57)

Characteristic	FOLFIRI (n=25)	Paclitaxel (n=32)
Age, years (mean±SD)	54±11.8	57.8±12.1	p=0.354
Age			
≤60	18/25 (72%)	20/32 (62.5%)	p=0.450
>60	7/25 (28%)	12/32 (37.5%)	
Gender			
Female	8/25 (32%)	8/32 (25%)	p=0.559
Male	17/25 (68%)	24/32 (75%)	
ECOG PS			
0-1	20/25 (80%)	23/32 (71.9%)	p=0.479
2	5/25 (20%)	9/32 (28.1%)	
Smoking			
No	11/25 (44%)	22/32 (68.8%)	p=0.060
Yes	14/25 (56%)	10/32 (31.3%)	
High level of CEA*			
No	10/25 (40%)	11/32 (34.4%)	p=0.662
Yes	15/25 (60%)	21/32 (65.6%)	
High level of CA 19-9*			
No	15/25 (60%)	17/32 (53.1%)	p=0.604
Yes	10/25 (40%)	15/32 (46.9%)	
At least ≥1 comorbidity			
No	17/25 (68%)	25/32 (78.1%)	p=0.389
Yes	8/25 (32%)	7/32 (21.9%)	
Previous gastrectomy			
Yes	4/25 (16%)	13/32 (40.6%)	p=0.044
No	21/25 (84%)	19/32 (59.4%)	
Localization			
GEJ	14/25 (56%)	10/32 (31.3%)	p=0.060
Gastric	11/25 (44%)	22/32 (68.7%)	
Lauren's classification			
Intestinal	16/20 (80%)	21/29 (72.4%)	p=0.544
Diffuse	4/20 (20%)	8/29 (27.6%)	
Histologic classification			
Adenocarcinoma	23/25 (92%)	25/32 (78.1%)	p=0.154
Signet ring cell carcinoma	2/25 (8%)	7/32 (21.9%)	
Grade			
Grade 1&2	6/22 (27.3%)	10/26 (38.5%)	p=0.413
Grade 3	16/22 (72.7%)	16/26 (61.5%)	
De novo metastatic			
No	3/25 (12%)	12/32 (37.5%)	p=0.030
Yes	22/25 (88%)	20/32 (62.5%)	
Liver metastasis			
No	11/25 (44%)	7/32 (21.9%)	p=0.075
Yes	14/25 (56%)	25/32 (78.1%)	
Lung metastasis			
No	19/25 (76%)	25/32 (78.1%)	p=0.850
Yes	6/25 (24%)	7/32 (21.9%)	
Peritoneal metastasis			
No	16/25 (64%)	19/32 (59.4%)	p=0.722
Yes	9/25 (36%)	13/32 (40.6%)	

Table 1. CONT.

Characteristic	FOLFIRI (n=25)	Paclitaxel (n=32)
Number of metastatic organs		
1	14/25 (56%)	19/32 (59.4%)	p=0.798
>1	11/25 (44%)	13/32 (40.6%)	
Number of metastatic lesions		
1-4	16/25 (64%)	21/32 (65.6%)	p=0.898
>4	9/25 (36%)	11/32 (34.4%)	
HER2 expression		
IHC3+/FISH+	20/25 (80%)	24/32 (75%)	p=0.655
IHC2+/FISH+	5/25 (20%)	8/32 (25%)	
First-line treatment with trastuzumab		
Cisplatin + Capecitabine/5-FU	7/19 (36.8%)	5/29 (17.2%)	p=0.125
CAPOX/FOLFOX	12/19 (63.2%)	24/29 (82.8%)	
First-line treatment objective response		
Yes	14/25 (56%)	18/32 (56.3%)	p=0.985
No	11/25 (44%)	14/32 (43.7%)	
First-line treatment clinical response		
Yes	21/25 (84%)	25/32 (78.1%)	p=0.577
No	4/25 (16%)	7/32 (21.9%)	
First-line trastuzumab cut-off		
>6 cycles	9/25 (36%)	18/32 (56.2%)	p=0.129
≤6 cycles	16/25 (64%)	14/32 (43.8%)	

* The accepted high level for CEA and CA19-9 was >5 ng/ml and >37 U/ml, respectively; ** Abbreviation: ECOG PS; Eastern Cooperative Oncology Group Performance Status, GEJ; Gastroesophageal junction; FOLFIRI, 5-FU and leucovorin and irinotecan; CAPOX, capecitabine and oxaliplatin; FOLFOX, 5-FU and leucovorin and oxaliplatin.

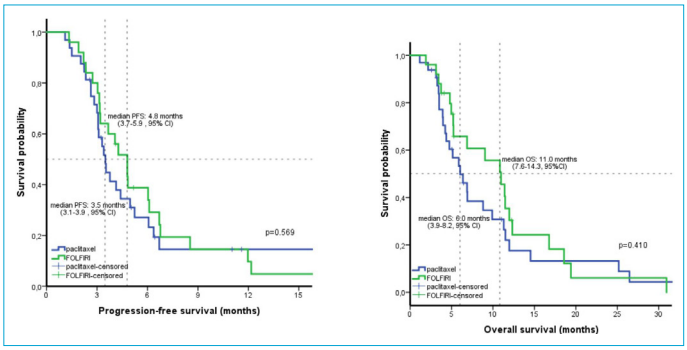

Figure 2. Kaplan–Meier curves of PFS and OS for paclitaxel and FOLFIRI in the second-line treatment of metastatic gastric cancer.

Discussion

Our study evaluated the survival difference in paclitaxel and FOLFIRI, the commonly used agents in the second-line treatment of metastatic gastric cancer, in HER2-positive patients and compare with subgroup analyses. The present study revealed no major difference in the basal characteristics of patients, which means that patients were a homogeneous group. Our real-life results revealed that the median PFS was 3.5 months with paclitaxel and 4.8 months with FOLFIRI, and the median OS was 6.0 months with paclitaxel and 11.0 months with FOLFIRI. A numerical difference was found in favor of FOLFIRI either the PFS or OS; however, no statistically significant differences were observed between paclitaxel and irinotecan in all groups. In addition, FOLFIRI provided a significant OS advantage over paclitaxel in patients with grade 3 tumors or did not have an objective first-line treatment response.

To the best of our knowledge, this was the first study that compared paclitaxel and FOLFIRI in second-line treatment in patients with metastatic HER2-positive gastric cancer who failed after first-line trastuzumab-based chemotherapy. At present, data on which agent can be given in the second-line after the failure of first-line trastuzumab-based chemotherapy is unclear. No strong recommendation was determined for continuing trastuzumab beyond progression or the administration of other anti-HER therapies such as pertuzumab, trastuzumab emtansin, or lapatinib.[5, 7, 15-17] In addition, real-life data in this area is insufficient and still needs investigation.

Gastric cancer is a highly heterogeneous disease. For example, in terms of metastasis, it has been shown that the T1 stage, which is detected at an earlier stage, may cause more frequent visceral metastases, such as lung and liver,

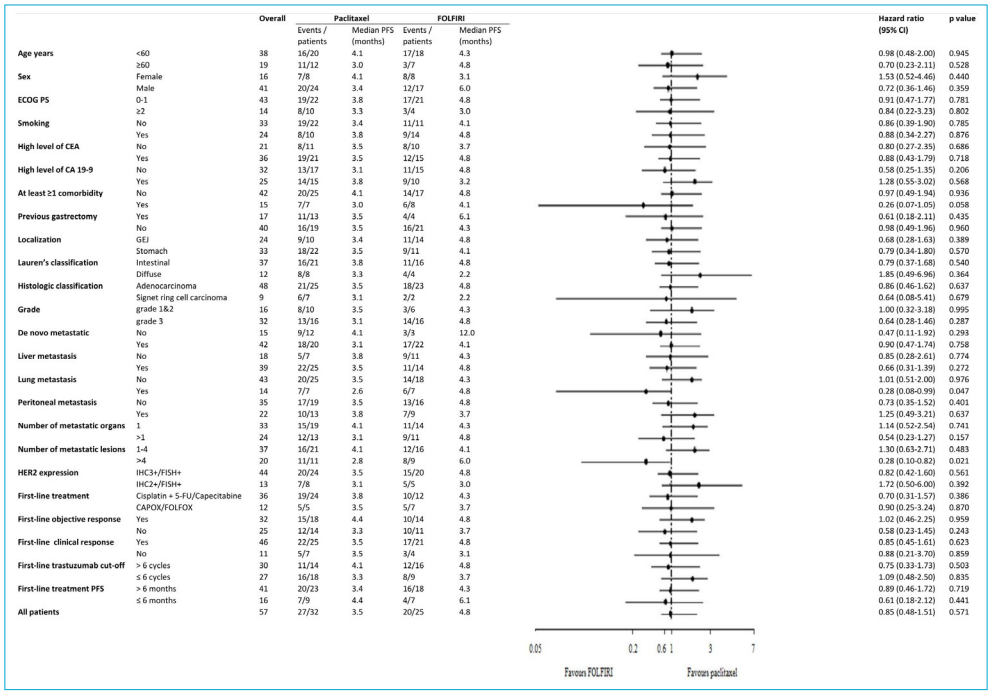

Figure 3. Forest plot of HRs for the PFS according to participant characteristics at baseline.

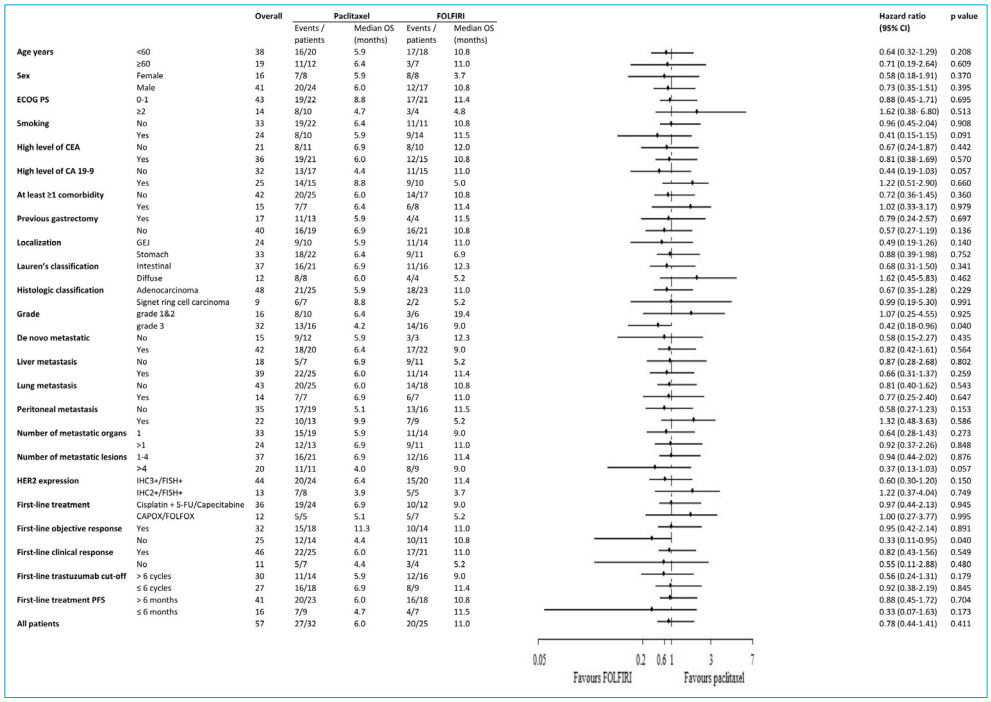

Figure 4. Forest plot of HRs for the OS according to participant characteristics at baseline.

than T2 and higher stage.[18, 19] It is also a molecularly very heterogeneous tumor. Intratumoral and inter-patient heterogeneity in gastric cancer remains a significant barrier to drug improvement for targeted therapies.[20] Besides, the heterogeneity of immunostaining for HER2 is greater in gastric tumors than breast carcinomas, and the possibility of false-result testing is higher. Due to this intratumoral heterogeneity, analyzing HER2 positivity in both IHC and FISH tests may lead to more precise outcomes. In our study, all patients were verified by FISH.[21] Gastric cancer patients who are previously treated with trastuzumab may develop resistance to this agent and may decrease HER2 expression, which has been reported in 16–69% of such patients. Thus, the efficacy of anti-HER2 therapies is cur-

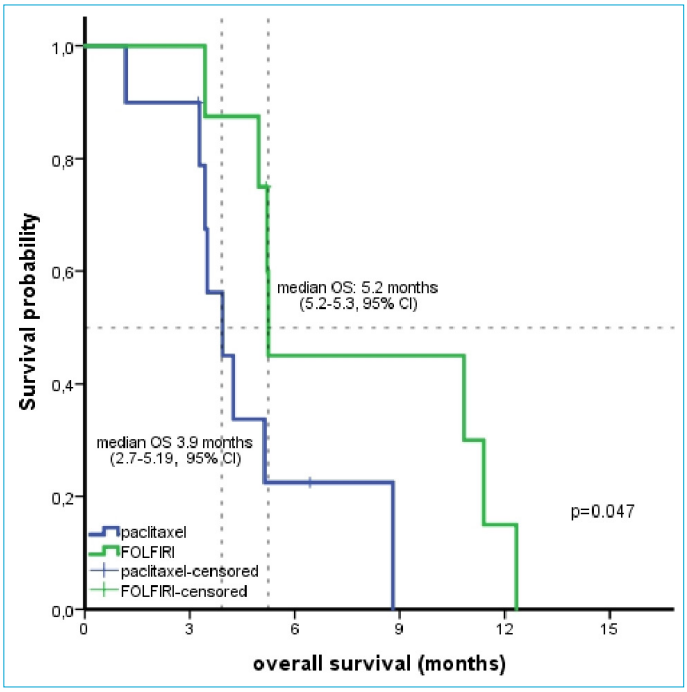

Figure 5. Kaplan–Meier curves of OS for paclitaxel and FOLFIRI in patients with both identified risk factors, which a grade 3 and did not have an objective response to the first-line treatment.

rently limited in the second-line contrary to breast cancer.[5, 22, 23] In addition, new researches are still needed to understand how to control these challenges. Therefore, current chemotherapeutic agents are currently the most preferred treatments in clinical practice.[1, 24] However, in a recent study, trastuzumab deruxtecan treatment contributed to an OS advantage over standard chemotherapy among patients with third-line or later therapy in HER2-positive advanced gastric cancer (12.5 months vs. 8.4 months, p=0.01).[8] This phase 2 study may recommend the third-line treatment and beyond in gastric cancer. However, all patients in this study had an ECOG PS of 0–1, which may indicate a relatively good patient population. The RAINBOW is the largest study for the second-line treatment that reported a survival benefit of ramucirumab in combination with paclitaxel compared with paclitaxel (9.6 months vs. 7.6 months).[13] The subgroup analysis of the RAINBOW study revealed an increased OS by 4.4 months in the combination of ramucirumab with paclitaxel compared with paclitaxel in the second-line treatment of HER2-positive gastric cancer (11.4 months vs. 7.0 months). The median PFS was 2.7 months with paclitaxel and 4.2 months with combination therapy. This study shows that ramucirumab and paclitaxel combination could be effective and safe in the second-line treatment with patients who received trastuzumab as first-line therapy.[25] In addition, a limited analysis described the efficacy of ramucirumab for this subgroup of patients. Moreover, ramucirumab and trastuzumab derutexan are currently unavailable in many low-income countries.

Chemotherapeutic agents, such as irinotecan, FOLFIRI, and paclitaxel, are shown to provide an OS advantage regardless of HER2 status. These regimens are widely used in many countries, and evidence of a difference between chemotherapeutic agents is unavailable in the effects on OS and PFS outcomes.[1, 9, 11] However, these agents' efficacy, subgroup analysis, and comparison in the HER2-positive subgroup are unknown. Our study found a median OS of 11 months with FOLFIRI and 6 months with paclitaxel and provided notable survival results and information in this subgroup.

Insufficient efficacy in the second-line treatment and poor HER2-positive gastric cancer prognosis highlights the need for optimal treatment decision-making in the second-line treatment. Various accepted factors may influence the survival of patients with second-line therapy, which may help the clinicians with the decisions. PFS of <6 months for the first-line therapy, the response to first-line treatment, poor ECOG PS, poorly differentiated tumor, and disease extent are important risk factors for survival in the second-line treatment.[13, 26-29] Our study revealed that, in patients who had grade 3 (poorly differentiated) tumors and/or did not have an objective first-line treatment response, FOLFIRI provided a significant OS advantage over paclitaxel. Therefore, it might be primarily recommended with these identified risk factors. In addition, FOLFIRI was numerically better OS advantage than paclitaxel in PFS <6 months, the extent of disease (metastasis lesions and sites), or poor ECOG PS; however, no statistical significance was found in our study. In our study, although there was no significant difference in most factors between the groups in baseline characteristics, there was a statistical difference between only two groups: previous gastrectomy (p=0.044) and de novo metastasis (p=0.030). Although it may be conceivable that exposure to chemotherapy before it has metastasized may cause resistance, the effect of these conditions on survival is unclear in the second-line. In our study, no significant impact on survival was observed for these two conditions (univariate Cox regression analysis, Figs. 3 and 4). Therefore, it did not affect the primary outcome of our study.

With the known poor prognosis of gastric cancer and limited treatment options in the second-line treatment, FOLFIRI might be recommended rather than paclitaxel in patients who had a grade 3 tumor or did not have an objective response to the first-line treatment or had both risk factors. In addition, our study might contribute significant real-life

results for this particular area as there is no strong recommendation for the HER2-positive subgroup in the second-line treatment. We also know that different treatment options may be preferred for the second-line options in many countries, but many patients cannot access ramucirumab or trastuzumab deruxtecan. Therefore, this study may provide significant contributions for clinicians who choose paclitaxel or FOLFIRI treatments, which can be used frequently among existing chemotherapy agents. Study limitations include the retrospective data and relatively small sample size. There were no patients using ramucirumab in our study. Access to ramucirumab is limited in many countries that are not economically strong, such as ours. However, due to this situation, this study provides crucial information, especially for many patients who cannot reach ramucirumab in the second-line. The clinicians in our study reported no lethal toxicity that leads to drug discontinuation in either group; thus, we did not include detailed information regarding adverse events. This study should be evaluated in a prospective longitudinal design in a larger group of patients.

Conclusion

The present study provided considerable real-life results in survival outcomes for FOLFIRI and paclitaxel in the second-line HER2-positive metastatic gastric cancer treatment. Paclitaxel and FOLFIRI have provided comparable results and could be used for the second-line treatment. Moreover, FOLFIRI provided a significant OS advantage over paclitaxel in patients with grade 3 tumors and/or did not have an objective first-line treatment response. Therefore, we advocate that FOLFIRI may be recommended as a preferred option rather than paclitaxel in patients with these identified risk factors. This study provides essential contributions, especially for many patients who cannot reach ramucirumab or trastuzumab deruxtecan treatments in the second-line of HER2-positive metastatic gastric cancer. Prospective new studies are needed to provide more information on this subject.

Disclosures

Ethics Committee Approval: The Clinical Research Ethics Committee of Bezmialem Vakif University approved this study with the decision number: 16/329.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.T., M.B., H.M.T.; Design – A.T., M.B.; Supervision – A.T., M.B.; Materials – A.T., C.G., S.A.; Data collection &/or processing – A.T., M.M.A., S.S., M.A., O.B., Z.U, S.A.; Analysis and/or interpretation – A.T., M.B., O.P.; Literature search – A.T., A.I.Y.; Writing – A.T., A.I.Y.; Critical review – A.T., M.B., M.O., H.M.T.

References

1. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396:635–48.
2. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687–97. Erratum in: Lancet 2010;376:1302.
3. Parisi A, Porzio G, Ficorella C. Multimodality treatment in metastatic gastric cancer: From past to next future. Cancers (Basel) 2020;12:2598.
4. Ter Veer E, van den Ende T, Creemers A, de Waal L, van Oijen MGH, et al. Continuation of trastuzumab beyond progression in HER2-positive advanced esophagogastric cancer: a meta-analysis. Acta Oncol 2018;57:1599–604.
5. Makiyama A, Sukawa Y, Kashiwada T, Kawada J, Hosokawa A, Horie Y, et al. Randomized, Phase II Study of Trastuzumab Beyond Progression in Patients With HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: WJOG7112G (T-ACT Study). J Clin Oncol 2020;38:1919–27.
6. Lorenzen S, Riera Knorrenschild J, Haag GM, Pohl M, Thuss-Patience P, Bassermann F, et al. Lapatinib versus lapatinib plus capecitabine as second-line treatment in human epidermal growth factor receptor 2-amplified metastatic gastro-oesophageal cancer: a randomised phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Eur J Cancer 2015;51:569–76.
7. Thuss-Patience PC, Shah MA, Ohtsu A, Van Cutsem E, Ajani JA, Castro H, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncol 2017;18:640–53.
8. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al; DESTINY-Gastric01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419–30.
9. Sym SJ, Hong J, Park J, Cho EK, Lee JH, Park YH, et al. A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy. Cancer Chemother Pharmacol 2013;71:481–8.
10. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. J Clin Oncol 2013;31:4438–44.

11. Lee KW, Maeng CH, Kim TY, Zang DY, Kim YH, Hwang IG, et la. A phase III study to compare the efficacy and safety of paclitaxel versus irinotecan in patients with metastatic or recurrent gastric cancer who failed in first-line therapy (KCSG ST10-01). Oncologist 2019;24:18–e24.
12. Tomita Y, Moldovan M, Chang Lee R, Hsieh AH, Townsend A, Price T. Salvage systemic therapy for advanced gastric and oesophago-gastric junction adenocarcinoma. Cochrane Database Syst Rev 2020;11:CD012078.
13. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al; RAINBOW Study Group. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014;15:1224–35.
14. Kim SH, Lee GW, Go SI, Cho SH, Kim HJ, Kim HG, et al. A phase II study of irinotecan, continuous 5-fluorouracil, and leucovorin (FOLFIRI) combination chemotherapy for patients with recurrent or metastatic gastric cancer previously treated with a fluoropyrimidine-based regimen. Am J Clin Oncol 2010;33(6):572–6.
15. Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol 2018;29:2052–60.
16. Tabernero J, Hoff PM, Shen L, Ohtsu A, Shah MA, Cheng K, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): final analysis of a double-blind, randomised, placebo-controlled phase 3 study. Lancet Oncol 2018;19:1372–84.
17. Satoh T, Xu RH, Chung HC, Sun GP, Doi T, Xu JM, et al. Lapatinib plus paclitaxel versus paclitaxel alone in the second-line treatment of HER2-amplified advanced gastric cancer in Asian populations: TyTAN--a randomized, phase III study. J Clin Oncol 2014;32:2039–49.
18. Wang S, Feng Y, Swinnen J, Oyen R, Li Y, Ni Y. Incidence and prognosis of liver metastasis at diagnosis: a pan-cancer population-based study. Am J Cancer Res 2020;10:1477–1517.
19. Wang S, Chen L, Feng Y, Swinnen JV, Jonscher C, Van Ongeval C, et al. Heterogeneity of synchronous lung metastasis calls for risk stratification and prognostic classification: Evidence from a population-based database. Cancers (Basel) 2022;14:1608.
20. Roviello G, Aprile G, D'Angelo A, Iannone LF, Roviello F, Polom K, et al. Human epidermal growth factor receptor 2 (HER2) in advanced gastric cancer: Where do we stand? Gastric Cancer 2021;24:765–79.
21. Pectasides E, Stachler MD, Derks S, Liu Y, Maron S, Islam M, et al. Genomic heterogeneity as a barrier to precision medicine in gastroesophageal adenocarcinoma. Cancer Discov 2018;8:37–48.
22. Pietrantonio F, Caporale M, Morano F, Scartozzi M, Gloghini A, De Vita F, et al. HER2 loss in HER2-positive gastric or gastroesophageal cancer after trastuzumab therapy: Implication for further clinical research. Int J Cancer 2016;139:2859–64.
23. Grillo F, Fassan M, Sarocchi F, Fiocca R, Mastracci L. HER2 heterogeneity in gastric/gastroesophageal cancers: From benchside to practice. World J Gastroenterol 2016;22:5879–87.
24. Jin P, Li J, Pan H, Wu Y, Zhu F. Immunological surrogate endpoints of COVID-2019 vaccines: the evidence we have versus the evidence we need. Signal Transduct Target Ther 2021;6:48.
25. De Vita F, Borg C, Farina G, Geva R, Carton I, Cuku H, et al. Ramucirumab and paclitaxel in patients with gastric cancer and prior trastuzumab: subgroup analysis from RAINBOW study. Future Oncol 2019;15:2723–31. Erratum in: Future Oncol 2021;17:3409.
26. Pericay C, Rivera F, Gomez-Martin C, Nuñez I, Cassinello A, Imedio ER. Positioning of second-line treatment for advanced gastric and gastroesophageal junction adenocarcinoma. Cancer Med 2016;5:3464–74.
27. Catalano V, Graziano F, Santini D, D'Emidio S, Baldelli AM, Rossi D, Vincenzi B, et al. Second-line chemotherapy for patients with advanced gastric cancer: Who may benefit? Br J Cancer 2008;99:1402–7.
28. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al; REGARD Trial Investigators. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31–9.
29. Janowitz T, Thuss-Patience P, Marshall A, Kang JH, Connell C, Cook N, et al. Chemotherapy vs supportive care alone for relapsed gastric, gastroesophageal junction, and oesophageal adenocarcinoma: a meta-analysis of patient-level data. Br J Cancer 2016;114:381–7.