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Research Article

Comparison of FOLFIRI and Paclitaxel as Second-Line Chemotherapy in Metastatic HER2-Negative Gastric Cancer: A Real-World Retrospective Analysis

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Abstract

Objectives: Gastric cancer is among the leading causes of cancer-related deaths worldwide, and outcomes in the metastatic setting remain poor. While FOLFIRI and weekly paclitaxel are widely used as second-line options for HER2-negative disease, head-to-head comparative data are largely absent.

Methods: We retrospectively reviewed the records of 68 patients with metastatic HER2-negative gastric adenocarcinoma who received either FOLFIRI (n=55) or paclitaxel (n=13) as second-line chemotherapy at a single center between August 2013 and March 2023. Survival outcomes were estimated using the Kaplan-Meier method, and independent prognostic factors were identified using Cox regression analysis.

Results: The median PFS numerically favored FOLFIRI over paclitaxel (3.9 vs. 2.8 months; log-rank p=0.052) without reaching statistical significance; on multivariate Cox analysis, FOLFIRI independently predicted longer PFS (HR, 0.474; 95% CI, 0.245–0.918; p=0.027). OS was comparable between the two arms (8.5 vs. 5.5 months; log-rank p=0.580). Multivariate analysis revealed that intestinal-type Lauren classification (HR, 0.378; p=0.006), elevated CEA (HR, 4.879; p<0.001), and metachronous metastatic disease (HR, 2.313; p=0.012) emerged as independent prognostic factors for OS.

Conclusion: FOLFIRI was associated with longer PFS than paclitaxel and independently predicted PFS on multivariate analysis, although overall survival was similar between groups. These hypothesis-generating findings suggest that both regimens are reasonable second-line options, and prospective randomized trials with adequate power and standardized biomarker profiling are required to define the optimal approach.

Keywords: FOLFIRI, Metastatic Gastric Cancer, Overall Survival, Real-World Data, Retrospective Analysis, Paclitaxel, Progression-Free Survival, Second-Line Chemotherapy

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GLOBOCAN 2020 data reveal that gastric cancer ranks fourth in cancer incidence and fifth in cancer-related mortality worldwide.[1,2] At the time of diagnosis, nearly half of all cases are at an advanced or metastatic stage.[1] The prognosis for metastatic gastric adenocarcinoma remains poor, with a five-year overall survival rate of <5%.[2] This situation is a key focus in the investigation of effective treatments for this patient group. In patients with metastatic gastric adenocarcinoma, the median progression-free survival (PFS) with standard first-line plus platinum-based combination chemotherapy regimens ranges from 3.1 to 6 months. Recent phase 3 randomized trials have shown that adding targeted agents or immune checkpoint inhibitors to chemotherapy contributes to survival. However, the median progression-free survival reported in these studies ranged from 6.7 to 12.4 months, with most patients progressing rapidly and requiring second-line treatment.[3-10] Phase 3 evidence supports a meaningful overall survival benefit with second-line chemotherapy compared to the best supportive care in this population.[11] However, there is no clear international consensus on the preferred regimen for second-line treatment.[12,13] Clinicians make their choices at this stage, considering various factors such as the patient's general condition, comorbidities, and access to medication. In this context, FOLFIRI and weekly paclitaxel represent the most widely adopted cytotoxic options in the second-line setting. Although both regimens have been evaluated in various phase II trials, prospective randomized data based on direct comparisons are limited to date.[14,15] Against this background, we conducted a retrospective single-center study to evaluate and compare the efficacy of FOLFIRI and paclitaxel in the second-line treatment of metastatic gastric adenocarcinoma.

Methods

Study Design

We retrospectively identified 68 patients with metastatic HER2-negative gastric adenocarcinoma who received either FOLFIRI (5-fluorouracil, leucovorin, irinotecan) or paclitaxel as second-line chemotherapy between August 2013 and March 2023.

Patient Population

This study included patients diagnosed with metastatic gastric adenocarcinoma who received FOLFIRI or paclitaxel as second-line systemic therapy at our institution between August 2013 and March 2023. Patients with histopathologically confirmed gastric adenocarcinoma who received FOLFIRI or paclitaxel as second-line therapy and had sufficient clinical and laboratory follow-up data were included. Patients with insufficient medical records, those receiving a treatment regimen different from either of these two in the second line, and those with different secondary primary tumors were excluded. The histopathological and molecular characteristics of the tumor, including mismatch repair (MMR) status, the presence of a ring cell component, and a mucinous component, were retrospectively recorded. MMR status was assessed by immunohistochemical staining for MLH1, MSH2, MSH6, and PMS2. Loss of nuclear expression in any protein defined dMMR, while intact staining across all four markers defined pMMR. Additionally, serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) tumor marker values were collected before the initiation of second-line treatment. These parameters were analyzed only among patients with available data, and the corresponding subgroup sizes are reported separately in the Results section of this manuscript.

Data Collection

Clinicopathological data were obtained from institutional databases and medical records. The following variables were collected: patient demographic information (age and sex), histopathological and molecular features (tumor differentiation, diffuse or intestinal type, signet ring cell component, mucinous component, MMR), history of gastrectomy, tumor location, Eastern Cooperative Oncology Group (ECOG) performance status, and metastatic sites.

Outcome

The PFS endpoint spanned from second-line therapy commencement to documented progression or death from any cause, with censoring applied at the last known follow-up for event-free individuals. OS was computed from the same index date through death by any etiology, censoring survivors at the data cutoff date.

Ethical Considerations

Ethical conduct of the study was ensured through adherence to institutional review board standards and applicable national regulatory requirements. Ethics committee approval was obtained from the Institutional Non-Interventional Clinical Research Ethics Committee (details withheld for peer review). As this was a retrospective chart review, formal informed consent was not required per the ethics committee waiver. Patient data were de-identified before analysis to ensure confidentiality.

Treatment

FOLFIRI (irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 400 mg/m^2 bolus plus 2400 mg/m^2 over 46 hours, every two weeks) and weekly paclitaxel (80 mg/m^2

on days 1, 8, and 15 of a 28-day cycle) were administered until progression, unacceptable toxicity, or patient/physician decision, with dose modifications per institutional practice. Regimen selection was at the treating physician's discretion, based on performance status, comorbidities, and prior tolerance. Response and progression were assessed by routine clinical and radiological evaluation during standard institutional follow-up.

Statistical Analysis

Analyses were performed using IBM SPSS Statistics v27.0 (IBM Corp., Armonk, NY, USA). Between-group differences in categorical variables were evaluated using Fisher's exact test or the Pearson chi-square test, as appropriate. Standardized mean differences (SMDs) were additionally calculated to assess the magnitude of baseline imbalance between the two treatment groups, as p-values from significance testing are strongly influenced by sample size; an absolute SMD greater than 0.1 was considered indicative of a meaningful between-group imbalance. Survival distributions were visualized with Kaplan-Meier plots, and intergroup comparisons were made using the log-rank test. The prognostic impact of clinical and pathological variables on PFS and OS was analyzed sequentially through univariate and multivariate Cox regression. In the multivariate analysis, backward stepwise Cox regression based on the likelihood-ratio method was used, and hazard ratios (HRs) with 95% confidence intervals were reported. Variables with a p-value <0.20 in the univariate analysis were included in the multivariate model. This liberal inclusion threshold was preferred, particularly given the limited sample size, to avoid excluding potential prognostic factors; accordingly, the resulting models are interpreted as hypothesis-generating rather than confirmatory. The PFS model included 68 patients with 65 progression events, and the OS model included 68 patients with 64 deaths. The proportional hazards assumption was assessed using log-minus-log survival plots and was satisfied, as the curves remained approximately parallel without crossing throughout follow-up (Supplementary Fig. S1). As a sensitivity analysis, the two covariates showing meaningful baseline imbalance (CA 19-9 level and number of metastatic sites) were forced into the multivariable PFS model to evaluate the robustness of the treatment effect. All hypothesis tests were two-tailed, and a p-value below 0.05 was considered statistically significant.

Language polishing was carried out with the aid of Paperpal (Cactus Communications), limited strictly to grammar and phrasing improvements. The tool played no part in shaping the study methodology, analytical approach, or scientific output. Final editorial decisions rested entirely with the authors, who assume complete accountability for the presented work.

Results

Patient Characteristics

The cohort comprised 68 patients with metastatic HER2-negative gastric adenocarcinoma who received paclitaxel (n=13) or FOLFIRI (n=55) as second-line therapy between August 2013 and March 2023. The median age of the entire cohort was 58.5 years (range: 24–80). Most of the cohort was male (65.9%), and almost all patients had an ECOG performance score of 0–1 (95.5%). The primary tumor location was the stomach in 75% of patients and the gastroesophageal junction in 25% of patients. A total of 36.8% of patients had undergone previous gastrectomy, with subtotal and total gastrectomy rates of 7.4% and 29.4%, respectively. When the histopathological characteristics of the tumors were evaluated, diffuse-type tumors constituted the predominant group in the entire cohort according to the Lauren classification (54.4%), while intestinal-type tumors were detected in 26.5% of the patients. In terms of histological differentiation, poorly differentiated tumors constituted the largest subgroup (64.7%), followed by moderately differentiated (20.6%), well-differentiated (5.9%), and undifferentiated tumors (2.9%). Histological differentiation could not be assessed in 5.9% of patients. The ring cell component was present in 52.9% of patients, absent in 39.7%, and undetectable in 7.4%. The mucinous component was detected in 39.7% of patients, absent in 52.9%, and undetectable in 7.4%. MSI/MMR status could be assessed in only 22.1% of the patients, and in all these patients, DNA repair (pMMR/MSI) status was adequately matched. MMR status could not be assessed in 77.9% of patients.

When laboratory parameters at the start of second-line treatment were examined, CEA levels were normal in 52.9% of patients, elevated in 36.8%, and unavailable in 10.3%. CA 19-9 levels were normal in 36.8% of patients, elevated in 52.9%, and unavailable in 10.3%. Regarding the number of metastatic sites, 1–2 metastatic sites were detected in most patients (69.1%), while more than 2 metastatic sites were detected in 30.9% of patients. De novo metastatic disease was present in 75% of patients, and metachronous metastatic disease in 25%. The baseline characteristics of all patients are presented in Table 1.

When the entire cohort was evaluated, the most frequently administered first-line chemotherapy regimen was 5FU-oxaliplatin-folinic acid (FOLFOX) (54.5%), followed by cisplatin-5FU (5-fluorouracil) (30.9%) and capecitabine-oxaliplatin (CAPOX) (8.8%). Cisplatin-5FU-pembrolizumab combinations were administered as first-line treatments in 1.5% of patients, whereas FOLFIRI was administered in 1.5% of patients. The distribution of first-line regimens ac-

Table 1. Baseline characteristics of the patients

Age (median, min-max)	**58.5 (24-80)**	
	n	**%**
Age		
<65	50	73.5
≥65	18	26.5
Sex		
Female	26	38.2
Male	42	61.8
BMI		
<18.0	10	14.7
18.0-34.9	56	82.4
≥35	2	2.9
Tumor Location		
GEJ	17	25.0
Gastric	51	75.0
Gastrectomy		
No	43	63.2
Yes	25	36.8
Gastrectomy Type		
Subtotal Gastrectomy	5	7.4
Total Gastrectomy	20	29.4
Lauren Classification		
Diffuse Type	37	54.4
Intestinal Type	18	26.5
Not available	13	19.1
Tumor Differentiation		
Well-differentiated	4	5.9
Moderately differentiated	14	20.6
Poorly differentiated	44	64.7
Undifferentiated	2	2.9
Not available	4	5.9
Signet ring cell component		
No	27	39.7
Yes	36	52.9
Not available	5	7.4
Mucinous component		
No	36	52.9
Yes	27	39.7
Not available	5	7.4
MSI		
No	15	22.1
Not determined	53	77.9
ECOG		
0	19	27.9
1	45	66.2
2	4	5.9
CEA Level		
Normal	36	52.9
High	25	36.8
Not available	7	10.3
CA 19-9 Level		
Normal	25	36.8
High	36	52.9
Not available	7	10.3
1-2	47	69.1
>2	21	30.9
Metastatic Timing		
Synchronous	51	75.0
Metachronous	17	25.0

BMI: Body mass index; dMMR: Deficient Missmatch repair; GEJ: Gastroesophageal junction; ECOG: Eastern cooperative oncology group; MMR: Missmatch repair; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9.

cording to the paclitaxel and FOLFIRI groups is presented in Table 2.

Third-line treatment was not administered in 66.2% of the cohort, as these patients either maintained disease control on second-line therapy or had died prior to further treatment. Third-line treatment was available to 33.8% of patients; the most frequently used regimens in this group were paclitaxel (20.6%), FOLFOX (7.4%), and FOLFIRI (5.9%). Fourth-line and subsequent treatments were administered to 5.9% of patients. When the entire cohort was evaluated, the most frequent sites of metastatic involvement were the lymph nodes (64.7%), peritoneum (38.2%), liver (33.8%), lungs (14.7%), and bone (13.6%). No brain metastases were observed in any patient. Metastatic site distribution did not differ significantly between the paclitaxel and FOLFIRI arms. Liver (p=0.796), lung (p=0.673), peritoneum (p=0.173), lymph node (p=0.362), bone (p=1.000), and ovarian (p=1.000) involvement were included in the analysis. The detailed distribution of metastatic involvement by organ is presented in Table 3.

Most baseline characteristics were comparable between groups by chi-square testing (Table 4). However, standardized mean differences revealed meaningful imbalances (SMD > 0.1) in several covariates, most notably CA

Table 2. Distribution of chemotherapy regimens by line of therapy according to patient cohorts

	All cohorts		Paklitaxel (n=13)		FOLFIRI (n=55)	
	n	%	n	%	n	%
First line therapy						
FOLFOX	37	54.4	8	61.5	29	52.7
CAPOX	6	8.8	2	15.4	4	7.3
Cisplatin-5FU-Pembrolizumab	1	1.5	1	7.7	0	0.0
Cisplatin-5FU	21	30.9	1	7.7	20	36.4
FOLFIRI	1	1.5	1	7.7	0	0.0
DCF	2	2.9	0	0.0	2	3.6
Third line therapy						
No therapy (ongoing second-line therapy/death)	45	66.2	9	69.2	36	65.5
Paklitaxel	14	20.6	0	0.0	14	25.5
FOLFIRI	4	5.9	4	30.8	0	0.0
FOLFOX	5	7.4	0	0.0	5	9.1
Fourty line therapy						
No therapy (ongoing third-line therapy/death)	64	94.1	12	92.3	52	94.5
FOLFOX	2	2.9	1	7.7	1	1.8
DCF	1	1.5	0	0.0	1	1.8
Paklitaxel	1	1.5	0	0.0	1	1.8

CAPOX: Capecitabine, oxaliplatin; FOLFIRI: Folinic acid, 5-fluorouracil, irinotecan; FOLFOX: Folinic acid, 5-fluorouracil, oxaliplatin; DCF: Docetaxel, cisplatin, 5-fluorouracil; 5-FU: 5-fluorouracil

19-9 level (SMD 0.90) and the number of metastatic sites (SMD −0.74), as well as age, tumor differentiation, and ECOG performance status. Consistent with this, the paclitaxel group had a significantly higher rate of elevated CA 19-9 (92.3% vs. 43.6%; p=0.006), and the FOLFIRI group more frequently had ≥2 metastatic sites (36.4% vs. 7.7%; p=0.044).

Survival Outcomes

At a median follow-up of 8.1 months (range: 1.3–47.4; last follow-up, December 2024), 94.1% of patients (n=64) had experienced the primary endpoint of death. Median PFS numerically favored FOLFIRI over paclitaxel (3.9 months. [95% CI: 3.4–4.4] vs. 2.8 months.[95% CI: 1.7–3.9]; log-rank p=0.052), although this did not reach statistical significance (Fig. 1).

Although FOLFIRI yielded an approximately 3-month longer median OS, this difference was not statistically significant (8.5 months.[95% CI: 7.0–10.0] vs. 5.5 months.[95% CI: 0.0–15.1]; log-rank p=0.580) (Fig. 2). These findings indicate that although FOLFIRI offers a statistically significant advantage in PFS, this gain is not reflected in overall survival.

Progression-Free Survival (PFS) - Cox Regression Analysis

Variables with p<0.20 on univariate analysis (BMI, prior gastrectomy, CEA level, and second-line treatment) were entered into the multivariate model. On univariate analysis, the second-line regimen showed a trend toward longer PFS with FOLFIRI (p=0.057), which reached significance on multivariate analysis (HR 0.474; 95% CI 0.245–0.918; p=0.027). A body mass index <18 was associated with a higher risk of progression than a body mass index ≥18 (HR, 0.385; 95% CI, 0.185–0.843; p=0.017) (Table 5). In a sensitivity analysis in which the two imbalanced covariates (CA 19-9 level and number of metastatic sites) were forced into the multivariable model together with the second-line regimen, FOLFIRI remained independently associated with longer PFS (HR 0.533; 95% CI 0.307–0.927; p=0.026), while neither CA 19-9 (p=0.846) nor the number of metastatic sites (p=0.519) was significantly associated with PFS. This indicates that the PFS advantage of FOLFIRI was robust to these baseline imbalances.

Overall Survival (OS) - Cox Regression Analysis

For overall survival, variables showing p<0.20 on univariate analysis, including sex, BMI, Lauren classification, CEA

Table 3. Distribution and comparison of metastatic ınvolvement sites in paclitaxel and FOLFIRI groups

	All cohorts		Paklitaxel (n=13)		FOLFIRI (n=55)		p	
	n	%	n	%	n	%		
Liver								
No	45	66.2	9	69.2	36	65.5	0.796	X^2
Yes	23	33.8	4	30.8	19	34.5		
Lung								
No	58	85.3	12	92.3	46	83.6	0.673	FET
Yes	10	14.7	1	7.7	9	16.4		
Peritoneal								
No	42	61.8	10	76.9	31	56.4	0.173	X^2
Yes	26	38.2	3	23.1	24	43.6		
Lymph node								
No	24	35.3	6	46.2	17	30.9	0.362	X^2
Yes	44	64.7	7	53.8	38	69.1		
Adrenal								
No	66	97.1	13	100.0	53	96.4		
Yes	2	2.9	0	0.0	2	3.6		
Pleural								
No	65	95.6	12	92.3	53	96.4		
Yes	3	4.4	1	7.7	2	3.6		
Bone								
No	58	85.3	11	84.6	47	85.5	1.000	FET
Yes	10	14.7	2	15.4	8	14.5		
Ovarian								
No	63	92.6	12	92.3	51	92.7	1.000	FET
Yes	5	7.4	1	7.7	4	7.3		
Cutaneous								
No	67	98.5	13	100.0	54	98.2		
Yes	1	1.5	0	0.0	1	1.8		
Splenic								
No	67	98.5	13	100.0	54	98.2		
Yes	1	1.5	0	0.0	1	1.8		
Renal								
No	67	98.5	13	100.0	54	98.2		
Yes	1	1.5	0	0.0	1	1.8		

FET: Fisher's exact test; X2: Chi-square

level, metastatic site count, and metastatic timing, were carried forward into a multivariate model, which identified Lauren classification, CEA level, and metastatic timing as independent prognostic factors. Patients with intestinal-type tumors had a significantly lower risk of death than those with diffuse-type tumors (HR 0.378; 95% CI 0.188–0.760; p=0.006), whereas elevated CEA levels were associated with a markedly higher risk of death (HR 4.879; 95% CI 2.223–10.705; p<0.001). Metachronous metastatic disease was also linked to a higher risk of death than synchronous disease (HR 2.313; 95% CI 1.204–4.445; p=0.012), whereas second-line treatment did not reach statistical significance as a predictor of overall survival (Table 6).

Discussion

In this retrospective single-center study of 68 patients with metastatic gastric adenocarcinoma, FOLFIRI was associated with a numerically longer median PFS than paclitaxel (3.9 vs. 2.8 months; log-rank p=0.052), which reached significance on multivariate analysis (HR 0.474; p=0.027), with no significant difference in OS (8.5 vs. 5.5 months; log-rank p=0.580). Unfortunately, almost all patients with metastatic gastric cancer experience disease progression after first-line therapy and require second-line therapy or palliative supportive care. Phase 3 studies have shown that second-line chemotherapy is superior to supportive care in patients who have progressed on first-line therapy and have a good performance status.[11,16,17] Many phase 2 and phase 3.[15,18-26] studies have tested chemotherapy and targeted therapies in patients who are candidates for second-line treatment; however, a standard approach at this stage is still lacking.

The evidence supporting the inclusion of the FOLFIRI regimen in guidelines for second-line treatment of metastatic gastric cancer largely comes from phase 2 studies. One such trial evaluated the combination of irinotecan with 5-FU/leucovorin in patients with primary refractory or relapsed esophageal and gastric cancer, reporting a median PFS of 3.7 months and a median OS of 6.4 months.[23] In a phase 2 study testing irinotecan plus 5FU plus leucovorin in patients with metastatic gastric cancer previously refractory to cisplatin and taxane therapies, mPFS was 2.5 months and mOS was 7.6 months.[15] In another phase 2 study, median progression-free survival (mPFS) was 2.3 months, and median overall survival (mOS) was 5.1 months with the FOLFIRI regimen in patients previously treated with 5FU who experienced recurrence.[20] A randomized phase 2 study comparing irinotecan monotherapy against a modified FOLFIRI regimen in patients with metastatic gastric cancer who had progressed following first-line treatment found no significant difference in either median PFS (2.2 vs. 3.0 months) or median OS (5.8 vs. 6.7 months), leading the authors to conclude that the addition of 5-FU/leucovorin did not meaningfully improve clinical outcomes.[24] The 3.9-month mPFS and 8.5-month mOS results with FOLFIRI

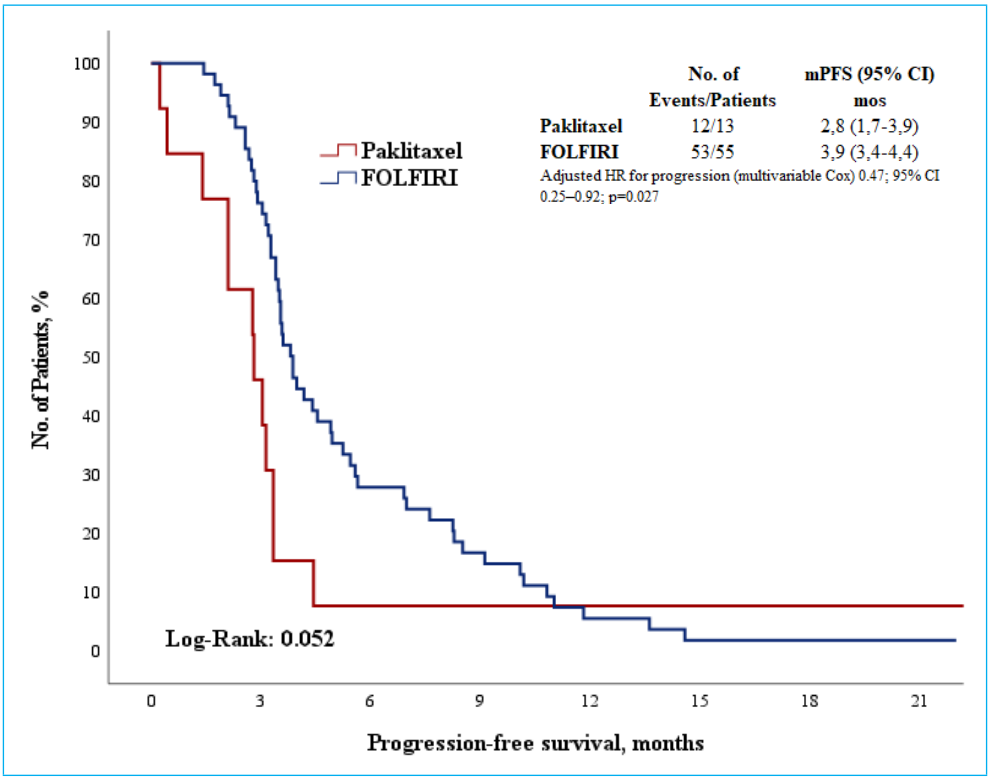

Figure 1. Progression-free survival comparison between FOLFIRI and paclitaxel as second-line treatment in metastatic gastric cancer.

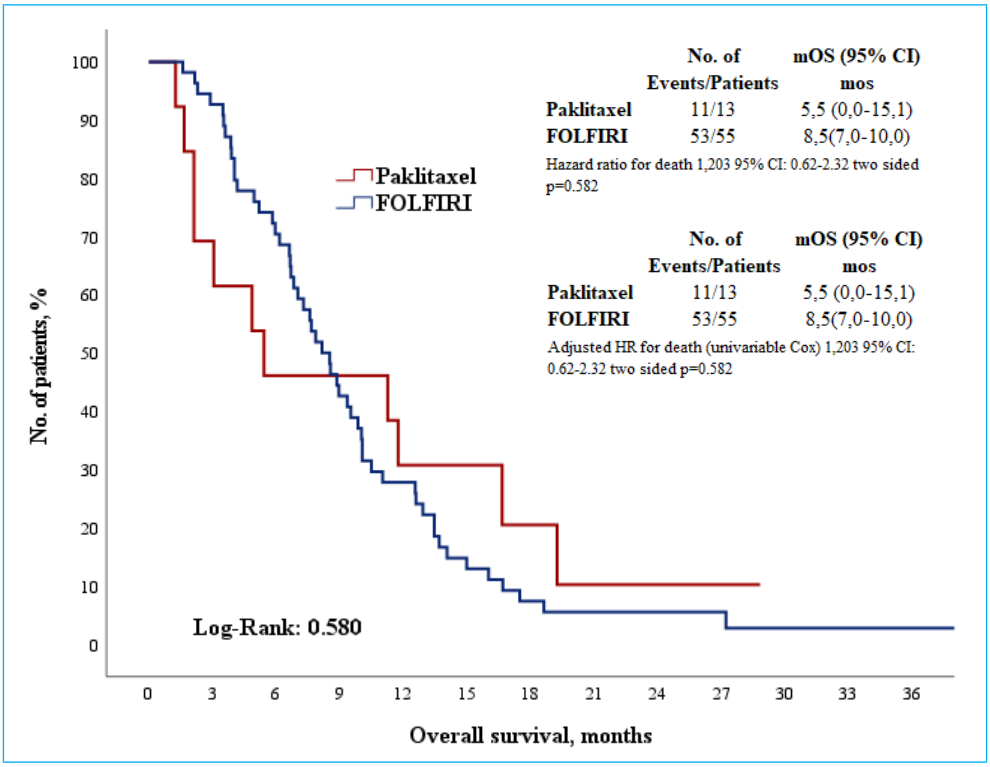

Figure 2. Overall survival comparison between FOLFIRI and paclitaxel as second-line treatment in metastatic gastric cancer.

Table 4. Comparison of baseline characteristics between paclitaxel and FOLFIRI groups

	Second Line Therapy				p	SMD
	Paklitaxel (n=13)		FOLFIRI (n=55)			
Age (median, min-max)	61 (24-80)		58 (24-76)			
	n	**%**	**n**	**%**		
Age						
<65	7	53.8	43	78.2	0.074	0.53
≥65	6	46.2	12	21.8		
Sex						
Female	7	53.8	19	34.5	0.198	-0.40
Male	6	46.2	36	65.5		
Tumor Location						
GEJ	3	23.1	14	25.5	0.859	0.06
Gastric	10	76.9	41	74.5		
Gastrectomy						
no	8	61.5	35	63.6	0.888	0.04
yes	5	38.5	20	36.4		
Gastrectomy Type						
Subtotal Gastrectomy	2	15.4	3	5.5		
Total Gastrectomy	3	23.1	17	30.9		
Lauren Classification						
Diffuse Type	6	46.2	31	56.4	0.614	0.21
Intestinal Type	2	15.4	16	29.1		
Tumor Differentiation						
Well/Moderately differentiated	1	7.7	17	30.9	0.123	0.62
Poorly/ Undifferentiated	10	76.9	36	65.5		
Signet ring cell component						
no	4	30.8	23	41.8	0.459	0.23
yes	8	61.5	28	50.9		
Mucinous component						
no	7	53.8	29	52.7	0.926	-0.02
yes	5	38.5	22	40.0		
ECOG						
0-1	11	84.6	53	96.4	0.105	0.41
2	2	15.4	2	3.6		
BMI index						
<18,0	1	7.7	9	16.4	0.427	0.27
≥18,0	12	92.3	46	83.6		
CEA level						
normal	8	61.5	28	50.9	0.835	-0.22
high	5	38.5	20	36.4		
CA 19-9 level						
normal	1	7.7	24	43.6	***0.006***	0.90
high	12	92.3	24	43.6		
Number of metastatic sites						
0-1	12	92.3	35	63.6	***0.044***	-0.74
≥2	1	7.7	20	36.4		
Metastatic Timing						
Synchronous	9	69.2	42	76.4	0.593	0.16
Metachronous	4	30.8	23	41.8		

p values derived from chi-square test unless otherwise stated; SMD: Standardized mean difference (SMD > 0.1 indicates meaningful imbalance). ECOG: Eastern cooperative oncology group; BMI: Body mass index; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9.

in our study are largely consistent with those from these previous phase 2 studies.

Paclitaxel has been included in the guidelines as a second-line treatment for patients with metastatic gastric cancer, particularly based on data from phase 2 studies. In one phase 2 study, the mean survival among patients previously treated with weekly paclitaxel who experienced disease progression was approximately 5 months.[27] Another phase 2 study reported an mPFS of 2.6 months and an mOS of 7.8 months with paclitaxel.[18] In a phase 2 study of patients with metastatic gastric cancer who had disease progression under previous treatments and received paclitaxel every 3 weeks, mOS was reported to be 8 months.[21] The 2.8-month mPFS and 5.5-month mOS observed in the paclitaxel cohort of our study were consistent with results from phase 2 studies reported in the literature.

No prospective trial has yet directly compared weekly paclitaxel with FOLFIRI in this setting. The available comparative evidence is limited to randomized phase III trials comparing weekly paclitaxel with irinotecan monotherapy, neither of which demonstrated a statistically meaningful survival difference.[14,19] In the WJOG 4007 trial, Hironaka et al.[14] reported comparable median OS between the paclitaxel and irinotecan arms (9.5 vs. 8.4 months; HR, 1.13; p=0.38), with a similar pattern observed for median PFS (3.6 vs. 2.3 months; HR, 1.14; p=0.33). In the KCSG ST10-01 trial, Lee et al.[19] likewise found no statistically significant difference in PFS (3.5 vs. 2.1 months; p=0.234) or OS (8.6 vs. 7.0 months; p=0.126); however, the non-inferiority of irinotecan relative

Table 5. Univariate and Multivariate Cox Regression Analyses for Progression-Free Survival

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (≥65 vs. <65)	1.226	0.694 - 2.165	0.482			
Sex (male vs. female)	1.107	0.667 - 1.835	0.695			
BMI (≤18.5 vs. >18.5)	0.445	0.219 - 0.923	***0.030***	0.385	0.185 - 0.843	***0.017***
Tumor Location (Stomach vs. GEJ)	1.195	0.678 - 2.107	0.538			
Gastrectomy (yes vs. no)	0.695	0.418 - 1.158	***0.163***			
Lauren Classification (diffuse vs. intestinal)	0.927	0.514 - 1.675	0.803			
Tumor Differantiation (poorly/undiff. vs. well/moderately diff.)	1.359	0.780 - 2.365	0.279			
Signet ring cell component (yes vs. no)	0.876	0.526 - 1.460	0.612			
Musinous component (yes vs. no)	0.760	0.555 - 1.537	0.924			
ECOG (≥2 vs. <2)	1.187	0.429 - 3.289	0.741			
CEA level (>ULN vs <ULN)	1.436	0.843 - 2.447	***0.183***			
CA 19-9 level (>ULN vs <ULN)	1.272	0.749 - 2.159	0.374			
Number of Metastatic Sites (≥2 vs. 0-1)	1.039	0.617 - 1.750	0.885			
Metastatic Timing (Metachronous vs. Synchronous)	0.971	0.557 - 1.695	0.918			
Second Line Therapy (FOLFIRI vs. Paklitaxel)	0.537	0.283 - 1.019	***0.057***	0.474	0.245 - 0.918	***0.027***

BMI: Body mass index; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan.

to paclitaxel could not be formally established, largely owing to early trial termination resulting from lower-than-expected patient accrual.

Retrospective comparisons are also available. In a cohort of 99 patients, no significant difference was observed between FOLFIRI and paclitaxel monotherapy in PFS (6

Table 6. Univariate and multivariate cox regression analyses for overall survival

	Univariate			Multivariate		
	HR	95% CI	p	HR	95% CI	p
Age (≥65 vs. <65)	0.873	0.495 - 1.547	0.646			
Sex (male vs. female)	1.444	0.855 - 2.439	***0.169***			
BMI (≤18.0 vs.>18.0)	0.583	0.291 - 1.168	***0.128***			
Tumor Location (Stomach vs. GEJ)	1.250	0.708 - 2.208	0.442			
Gastrectomy (yes vs. no)	0.864	0.515 - 1.450	0.580			
Lauren Classification (diffuse vs. intestinal)	0.624	0.339 - 1.148	***0.129***	0.378	0.188 - 0.760	***0.006***
Tumor Differantiation (poorly/undiff. vs. well/moderately diff.)	1.377	0.781 - 2.428	0.269			
Signet ring cell component (yes vs. no)	0.981	0.581 - 1.659	0.944			
Musinous component (yes vs. no)	0.900	0.535- 1.512	0.689			
ECOG (≥2 vs. <2)	1.067	0.385 - 2.957	0.901			
CEA level (>ULN vs <ULN)	1.939	1.107 - 3.396	***0.020***	4.879	2.223 - 10.705	***<0.001***
CA 19-9 level (>ULN vs <ULN)	1.178	0.688 - 2.015	0.551			
Number of Metastatic Sites (≥2 vs. 0-1)	1.412	0.833 - 2.393	***0.200***			
Metastatic Timing (Metachronous vs. Synchronous)	1.741	0.985 - 3.076	***0.057***	2.313	1.204 - 4.445	***0.012***
Second Line Therapy (FOLFIRI vs. Paklitaxel)	1.203	0.623 - 2.324	0.582			

BMI: Body mass index; CEA: Carcinoembryonic antigen; CA 19-9 level: Carbohydrate antigen 19-9; FOLFIRI: 5-fluorouracil, leucovorin, irinotecan.

months in both arms; p=0.793) or OS (10 vs. 8 months; p=0.162).[28] Real-world data from a Turkish cohort showed that carboplatin-paclitaxel and FOLFIRI yielded equivalent second-line outcomes in HER2-negative metastatic gastric cancer, with a median PFS of 3 months in both arms and OS of 7 versus 8 months, neither of which reached statistical significance.[29] The results obtained in this study, particularly in HER2-negative patients, are comparable; our findings, consistent with no difference in overall survival, suggest a possible progression-free survival advantage for FOLFIRI.

While OS was broadly similar between arms, FOLFIRI did pull ahead in terms of PFS, and this gap may not be entirely due to the regimen itself. The paclitaxel group entered treatment with a considerably heavier tumor burden, as suggested by the strikingly higher rate of elevated CA 19-9 in that arm (92.3% vs. 43.6%; p=0.006), which likely worked against them from the outset.[30-33]

Current guidelines endorse FOLFIRI and taxane-based regimens as viable second-line alternatives in settings where ramucirumab is inaccessible or contraindicated.[12,13] In our country, access to ramucirumab, which guidelines recommend as a second-line treatment for HER2-negative disease, remains limited due to cost and reimbursement restrictions. Therefore, a direct comparison of cytotoxic regimens is highly valuable in daily clinical practice.

In the multivariate analysis, FOLFIRI treatment was an independent predictor of PFS. Consistent with the literature, a low body mass index (<18) was associated with a higher risk of progression, likely reflecting the adverse prognostic impact of malnutrition and poor nutritional reserve in patients with metastatic gastric cancer.[34] This should be regarded as an exploratory finding and interpreted with caution, as it may reflect chance, residual confounding, or the small subgroup sizes inherent to our retrospective single-center design. Consistent with the literature, intestinal-type histology was associated with better overall survival than diffuse-type histology in our cohort. This association should nonetheless be interpreted with caution, given the small sample size and the substantial proportion of patients with an undetermined Lauren subtype (19.1%).[35] The strong association between elevated CEA levels and poor overall survival was not unexpected, given the consistent association between this marker, tumor burden, and prognosis in gastric cancer.[36] In our study, metachronous metastatic disease was identified as an independent factor for worse overall survival, consistent with previous studies.[37] This likely reflects the longer interval between the initial diagnosis and metastatic relapse, during which resistant clones can emerge and accumulate, leaving these patients with a more treatment-refractory disease by the time they reach the second-line setting.

Our study has several limitations. A retrospective single-center design, small paclitaxel cohort, and baseline group imbalances all work against definitive conclusions; selection bias and residual confounding are difficult to rule out in this setting. In addition, the limited number of events relative to the number of covariates resulted in a low events-per-variable ratio, particularly within the small paclitaxel subgroup. The multivariable models should therefore be regarded as exploratory and potentially subject to overfitting, and the identified associations require confirmation in larger prospective cohorts. Toxicity is another area where our data were lacking. Adverse events were not recorded systematically or consistently across patient files, making any meaningful comparison of tolerability between the two regimens essentially impossible, which is unfortunate, given how heavily side effect profiles weigh in real-world second-line treatment decisions. MMR/MSI status was unavailable in nearly four out of five patients, which meant we could not properly examine the prognostic role of a marker that is becoming increasingly important in gastric cancer management. However, real-world data directly comparing FOLFIRI with taxane-based regimens in this setting are still surprisingly scarce, and we hope our findings can at least help shape the questions that future prospective trials set out to answer. Given the small paclitaxel cohort (n=13), propensity-score matching was not feasible without prohibitive loss of statistical power. We therefore quantified baseline imbalance using standardized mean differences, which confirmed meaningful differences in several covariates despite non-significant p-values. These imbalances—particularly the higher CA 19-9 burden in the paclitaxel arm and the greater number of metastatic sites in the FOLFIRI arm—may have influenced the observed outcomes and cannot be excluded as sources of residual confounding.

Conclusion

In summary, FOLFIRI was associated with longer PFS than paclitaxel after adjustment, although this did not translate into an overall survival benefit. These findings are hypothesis-generating; both regimens remain reasonable second-line options in HER2-negative metastatic gastric cancer, and the optimal choice cannot be determined from this retrospective analysis. Confirmation in adequately powered prospective trials with proper molecular stratification is required.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and its amendments. Eth-

ical approval (approval number: 2025/145; approval date: March 5, 2025) for this study was obtained from the Non-Interventional Clinical Research Ethics Committee of Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Türkiye.

Informed Consent: The requirement for written informed consent was waived by the ethics committee owing to the retrospective design of the study.

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

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Abbreviations

5-FU: 5-Fluorouracil

BMI: Body mass index

CA 19-9: Carbohydrate antigen 19-9

CAPOX: Capecitabine, oxaliplatin

CEA: Carcinoembryonic antigen

CI: Confidence interval

DCF: Docetaxel, cisplatin, 5-fluorouracil

dMMR: Deficient mismatch repair

ECOG: Eastern Cooperative Oncology Group

FISH: Fluorescence in situ hybridization

FOLFIRI: Folinic acid, 5-fluorouracil, irinotecan

FOLFOX: Folinic acid, 5-fluorouracil, oxaliplatin

GEJ: Gastroesophageal junction

HER2: Human epidermal growth factor receptor 2

HR: Hazard ratio

IHC: Immunohistochemistry

MMR: Mismatch repair

MSI: Microsatellite instability

OS: Overall survival

PFS: Progression-free survival

pMMR: Proficient mismatch repair

ULN: Upper limit of normal

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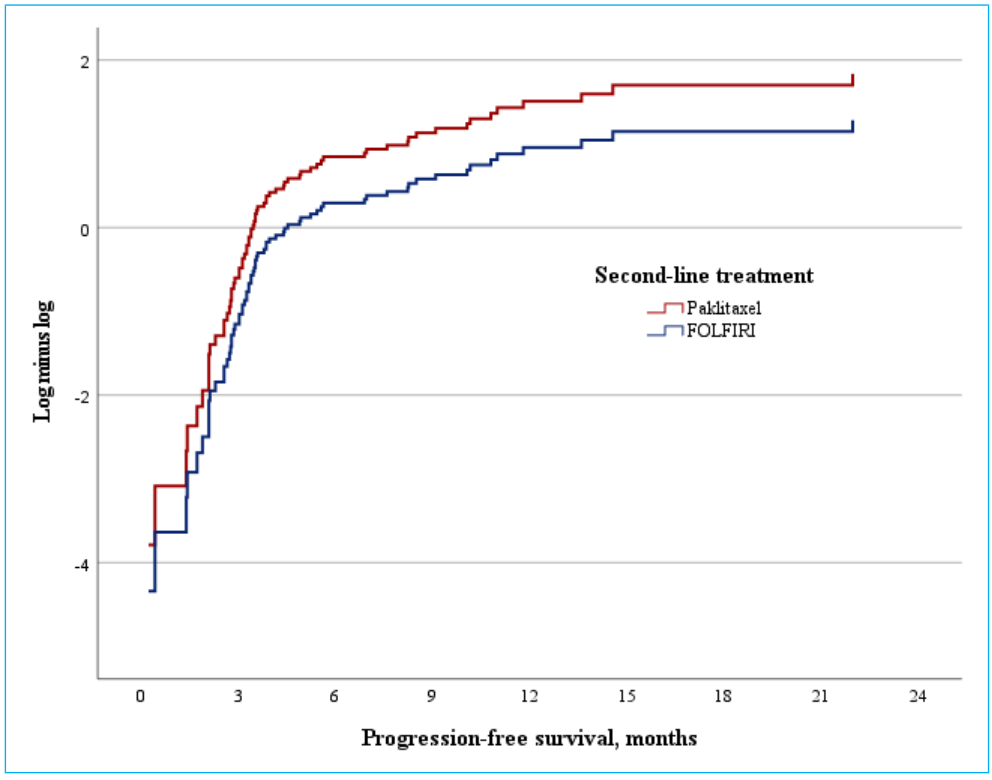

Supplementary Figure 1. Log minus log plot of progression-free survival (PFS) according to second-line treatment regimens.