



Prognostic factors in patients treated with second-line chemotherapy for advanced gastric cancer: results from the randomized prospective phase III FFCD-0307 trial

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Abstract

Aim The aim of this study was to determine prognostic factors in patients treated with second-line therapy (L2) for locally advanced or metastatic gastric and gastro-esophageal junction (GEJ) adenocarcinoma in a randomized phase III study with predefined L2.

Methods In the FFCD-0307 study, patients were randomly assigned to receive in L1 either epirubicin, cisplatin, and capecitabine (ECX arm) or fluorouracil, leucovorin, and irinotecan (FOLFIRI arm). L2 treatment was predefined (FOLFIRI for the ECX arm and ECX for the FOLFIRI arm). Chi square tests were used to compare the characteristics of patients treated in L2 with those of patients who did not receive L2. Prognostic factors in L2 for progression-free survival (PFS) and overall survival (OS) were analyzed using a Cox model.

Results Among 416 patients included, 101/209 (48.3%) patients in the ECX arm received FOLFIRI in L2, and 81/207 (39.1%) patients in the FOLFIRI arm received ECX in L2. Patients treated in L2, compared with those who only received L1 had: a better ECOG score (0–1: 90.4% versus 79.7%; $p=0.0002$), more frequent GEJ localization (40.8% versus 27.6%; $p=0.005$), and lower platelet count (median: 298000 versus 335000/mm³; $p=0.02$). In multivariate analyses, age < 60 years at diagnosis (HR 1.49, 95% CI 1.09–2.03, $p=0.013$) and ECOG score 2 before L2 (HR 2.62, 95% CI 1.41–4.84, $p=0.005$) were the only significant poor prognostic factors for OS.

Conclusion Age ≥ 60 years at diagnosis and ECOG score 0/1 before L2 were the only favorable prognostic factors for OS.

Keywords Gastric neoplasm · Survival · Prognosis · Second-line chemotherapy

Introduction

Worldwide, gastric cancer is the third leading cause of cancer-related mortality. Though the incidence has decreased over the last 20 years, the prognosis remains poor [1]. In patients with advanced or metastatic disease, 5-year overall survival remains less than 5%. In first-line, chemotherapy, regimens can improve overall survival. Doublets or triplet chemotherapy regimen, and trastuzumab in patients with human epidermal growth factor receptor (HER)-2 positive tumors, have demonstrated clinical benefits on overall

survival and quality of life [2–5]. Other studies have also demonstrated the potential benefits on overall survival of a second-line treatment, with irinotecan, taxanes, ramucirumab alone or combined with paclitaxel, and more recently nivolumab in third-line therapy and beyond [6–11]. In published clinical trials evaluating first-line treatments without pre-planned second line, the percentage of patients receiving a second line, when reported, is heterogenous, e.g., 14% in the REAL-2 trial, 45% in the ToGA trial, 75% in the SPIRITS trial; with a higher proportion in Asian trials compared to non-Asian trials [2–4]. Thus, few data are available to help the selection of patients for a second-line treatment. The aim of our study was to evaluate the prognostic factors in patients who received second-line therapy in a randomized prospective trial in which the first- and second-line treatments were planned [12].

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Materials and methods

Patients and study design

Patients from the FFCD-0307 trial had locally advanced or metastatic gastric or gastro-esophageal junction (GEJ) locally advanced or metastatic adenocarcinoma and were randomly assigned (1:1) to receive either epirubicin, cisplatin, and capecitabine (ECX) chemotherapy in the first line (ECX arm) with a predefined second-line therapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI) or to receive FOLFIRI in the first line (FOLFIRI arm) with a predefined ECX second-line therapy. Other inclusion criteria were: age 18 years or older, measurable and/or assessable lesions according to RECIST criteria, WHO performance score (PS) ≤ 2 , ability to take oral medications, no previous palliative chemotherapy (≥ 6 months from adjuvant chemotherapy was allowed), ≥ 3 weeks from previous radiotherapy, sufficient bone marrow function, creatinemia ≤ 110 $\mu\text{mol/l}$, and bilirubinemia ≤ 35 $\mu\text{mol/l}$.

Treatment and evaluation

The ECX regimen consisted of epirubicin 50 mg/m^2 [15-min intravenous (IV) infusion] plus cisplatin 60 mg/m^2 (1-h IV infusion) on day 1 followed by oral capecitabine 1 g/m^2 twice per day from day 2 to day 15 every 3 weeks; the maximum authorized cumulative dose of epirubicin was 900 mg/m^2 . The FOLFIRI regimen consisted of irinotecan 180 mg/m^2 (90-min IV infusion) and leucovorin 400 mg/m^2 (2-h IV infusion) followed by a fluorouracil 400 mg/m^2 IV bolus and then fluorouracil 2400 mg/m^2 as a 46-h continuous infusion every 2 weeks.

Tumor response was evaluated by investigators and classified according to RECIST criteria. CT scans were performed before the start of treatment and then every 8 weeks until disease progression for each treatment line and in each arm.

Statistical analyses

Progression-free survival (PFS) was defined as the time from the start of the second line to the first progression or death (all causes). Patients alive without progression were censored at the last follow-up. Overall survival (OS) was defined as the time between the start of the second line and death (all causes). The disease control rate (DCR) was defined as the proportion of patients with a complete or partial response, or stable diseases during the second line according to RECIST criteria.

Qualitative and continuous variables were described using the usual descriptive statistics: numbers and percentages and medians with min–max, respectively. Comparison

of baseline characteristics of the two arms was made with the χ^2 test or nonparametric Wilcoxon test, depending on the type and distribution of variables.

Survival analyses (OS, PFS) were done using the Kaplan–Meier method and described using medians with 95% two-sided confidence intervals (95% CI). Cox models were used to estimate hazard ratios (HR) and logistic regressions were performed for DCR. All variables significant at 10% in univariate analyses were included in the multivariate analyses. Two multivariate models were made: the first one with factors assessed before the start of first-line therapy and the second one with factors assessed before the start of second-line therapy. Analyses were performed using SAS software 9.4 (SAS Institute, Cary, NC).

Results

Probability of receiving a second-line chemotherapy according to baseline characteristics

Among the 416 patients included in the FFCD-0307 trial, 182 patients received the preplanned second-line chemotherapy, 101/209 (48.3%) patients in the ECX arm received FOLFIRI in L2, and 81/207 (39.1%) of patients in the FOLFIRI arm received ECX in L2. No other second-line regimen was administered.

The baseline (before first line) clinical characteristics of patients are presented in Table 1. At baseline, patients with GEJ tumors (versus gastric tumors, $p=0.005$), ECOG 0–1 (versus ECOG 2, $p=0.0002$) were more likely to receive the second-line chemotherapy. There was no significant difference according to the first-line regimen (55.5% ECX, 44.5% FOLFIRI, $p=0.06$).

The baseline biological results were analyzed. The group of patients who received the second-line treatment had a lower baseline-platelet count (median 298,000/ mm^3 versus 335,000/ mm^3 , $p=0.02$). There were no significant differences according to the hemoglobin and neutrophils counts, and to serum levels of bilirubin, alkaline phosphatase, carcinoembryonic antigen (CEA) and carbohydrate antigen 19.9 (CA19.9) (Table 2).

Prognostic factors for disease control from the start of second line

The disease control rate (DCR) was assessable in 150 patients. The DCR was 45/83 (54.2%) for patients treated with FOLFIRI L2 versus 31/67 (46.3%) for patients treated with ECX L2.

In univariate analysis, the neutrophil count $< 5000/\text{mm}^3$ ($p=0.028$) and ECOG score 0/1 before L2 ($p=0.008$) were the only significant good prognostic factor (Table 3). There was no correlation between the response rates in first and second

Table 1 Clinical characteristics of the population at baseline

	Second line			
	Yes		No	
	Number of patients, <i>n</i> = 182	%	Number of patients, <i>N</i> = 234	%
First-line treatment				
ECX	101	55.49	108	46.15
FOLFIRI	81	44.51	126	53.85
Sex				
Male	134	73.63	175	74.79
Female	48	26.37	59	25.21
Median age (min–max) in years				
< 60 years	93	51.10	103	44.21
≥ 60 years	89	48.90	130	55.79
	<i>n</i> = 178		<i>n</i> = 227	
ECOG score				
0	75	42.13	57	25.11
1	86	48.31	124	54.63
2	17	9.55	46	20.26
Body mass index (kg/m²)				
< 18.5	19	10.44	37	15.81
18.5–25	100	54.95	126	53.85
25–30	51	28.02	58	24.79
≥ 30	12	6.59	13	5.56
	<i>n</i> = 179		<i>n</i> = 228	
Localization				
Gastro-esophageal junction	73	40.78	63	27.63
Stomach	106	59.22	165	72.37
	<i>n</i> = 180		<i>n</i> = 227	
Linitis plastica				
Yes	42	23.33	56	24.67
No	138	76.67	171	75.33
	<i>n</i> = 177		<i>n</i> = 224	
Metastases				
Yes	157	88.70	192	85.71
No	20	11.30	32	14.29
	<i>n</i> = 178		<i>n</i> = 227	
Primary tumor resection				
Yes	40	22.47	62	27.31
No	138	77.53	165	72.69
	<i>n</i> = 179		<i>n</i> = 225	
Previous treatment				
Yes	19	10.61	24	10.67
No	160	89.39	201	89.33

ECX epirubicin, cisplatin and capecitabine, FOLFIRI irinotecan, leucovorin, fluorouracil bolus and 46-h continuous infusion every 2 weeks

Table 2 Biological characteristics at baseline

	Second Line	
	Yes, <i>N</i> =182	No, <i>N</i> =234
Hemoglobin (g/dl)		
<i>n</i>	179	228
Minimum	7.00	7.10
Median	12.20	12.05
Maximum	16.50	16.30
Creatinine (μmol/l)		
<i>n</i>	175	227
Minimum	32.00	5.50
Median	76.00	71.00
Maximum	115.00	118.00
Neutrophils (/mm ³)		
<i>n</i>	178	224
Minimum	2109.00	10.00
Median	5410.50	5698.50
Maximum	18737.00	22404.00
Platelets (×1000/mm ³)		
<i>n</i>	179	228
Minimum	141.00	108.00
Median	298.00	335.00
Maximum	922.00	1080.00
Total bilirubin (μmol/l)		
<i>n</i>	175	223
Minimum	1.70	1.70
Median	8.60	8.00
Maximum	108.00	85.00
Alkaline phosphatase		
<i>n</i>	176	219
≤1.5× normal value	130 (76.8%)	151 (68.9%)
>1.5× normal value	46 (26.1%)	68 (31.0%)
CEA		
<i>n</i>	167	205
≤2× normal value	105 (62.9%)	134 (65.4%)
>2× normal value	62 (37.1%)	71 (34.6%)
CA 19.9		
<i>n</i>	167	203
≤2× normal value	99 (59.3%)	120 (59.1%)
>2× normal value	68 (40.9%)	83 (40.9%)

lines (*p* (Fisher)=0.156 for patients treated with FOLFIRI L2, *p* (Fisher)=0.687 for patients treated with ECX L2).

Prognostic factors for PFS from the start of the second-line therapy

Median PFS was 2.8 months with FOLFIRI L2 and 2.1 months with ECX L2 (Fig. 1a). In univariate analysis, age ≥ 60 years and ECOG score 0/1 before L2 were the only significant good prognostic factors (Table 4).

Table 3 Prognostic factors for disease control rate in second-line therapy, univariate analysis

	Disease control (yes/no)	Odd ratio	95% Confidence interval	<i>p</i> value
Factors from the start of first-line therapy				
Treatment				
ECX second line	31/67	0.73	0.38 1.39	0.334
FOLFIRI second line	45/83	Ref	– –	
Sex				
Male	53/105	0.97	0.48 1.98	0.940
Female	22/43	Ref	– –	
Tumor localization				
GEJ	29/62	0.75	0.39 1.44	0.380
Stomach	46/85	Ref	– –	
ECOG score				
1–2	43/80	1.31	0.68 2.52	0.415
0	31/66	Ref	– –	
Body mass index (kg/m ²)				
<18.5	7/14	1.45	0.44 4.78	0.221
18.5–25	37/85	1.88	0.92 3.84	
≥25	29/49	Ref	– –	
Linitis plastica				
No	58/117	0.81	0.37 1.79	0.602
Yes	17/31	Ref	– –	
Metastasis				
No	10/16	1.67	0.57 4.85	0.349
Yes	65/130	Ref	– –	
Primary tumor resection				
No	56/113	0.93	0.43 2.01	0.843
Yes	17/33	Ref	– –	
Age				
<60 years	35/72	0.85	0.45 1.62	0.625
≥60 years	40/76	Ref	– –	
Hemoglobin				
<12 g/dl	31/65	0.81	0.42 1.55	0.521
≥12 g/dl	44/83	Ref	– –	
Neutrophils				
<5000/mm ³	37/60	2.12	1.08 4.14	0.028
≥5000/mm ³	38/88	Ref	– –	
Platelets				
<300,000/mm ³	42/73	1.72	0.90 3.31	0.101
≥300,000/mm ³	33/75	Ref	– –	
Alkaline phosphatases				
≤1.5× normal value	53/109	1.37	0.66 2.85	0.405
>1.5× normal value	22/39	Ref	– –	
CEA				
≤2× normal value	41/85	1.16	0.58 2.31	0.676
>2× normal value	27/52	Ref	– –	

Table 3 (continued)

	Disease control (yes/no)	Odd ratio	95% Confidence interval		p value
CA 19.9					
≤2× normal value	45/82	0.69	0.35	1.36	0.283
>2× normal value	26/57	Ref	–	–	
Factors from the start of second-line therapy					
ECOG score					
≥2	8/26	0.14	0.04	0.49	0.008
1	21/39	0.37	0.12	1.12	
0	19/25	Ref	–	–	
Body mass index (kg/m²)					
< 18.5	11/18	1.85	0.59	5.82	0.576
18.5–25	44/87	1.20	0.56	2.60	
≥25	17/37	Ref	–	–	
CEA					
≤2× normal value	30/52	0.79	0.34	1.82	0.576
>2× normal value	26/41	Ref	–	–	
CA 19.9					
≤2× normal value	31/51	1.27	0.55	2.94	0.579
>2× normal value	22/40	Ref	–	–	

Bold—p value < 0.05

Prognostic factors for OS from the start of second-line therapy

The median OS was 5.4 months with FOLFIRI L2 and 4.8 months with ECX L2 (Fig. 1b). The median OS in the third quartile (subgroup of longer survivors), was 10.48 months (95% CI 8.84–12.39) for FOLFIRI in L2, and

8.02 months (95% CI 6.80–10.25) for ECX in L2. In univariate analysis, platelet count < 300,000/mm³ (p = 0.025), age ≥ 60 years (p = 0.008) and ECOG score before L2 were the only significant good prognostic factors (Table 5). In multivariate analyses, in the first model, age < 60 years at diagnosis (versus ≥ 60 years) (HR 1.49, 95% CI 1.09–2.03, p = 0.013) and in the second model ECOG score ≥ 2 before L2 (HR 2.62, 95% CI 1.41–4.84, p = 0.005) were the only significant poor prognostic factors (Table 6).

Discussion

Second-line treatment is seldom administered and results in all studies in limited efficacy on tumor growth. In the FFCD-0307 trial, only 43% of patients received a second-line therapy. From baseline, patients more likely to receive this second line more frequently had GEJ tumors and an ECOG score 0–1. Nonetheless, the clinical benefits were still limited, with median overall survival following the second line of around 5 months. For the second line, age ≥ 60 years and ECOG score 0/1 were the only significant good prognostic factors for OS in multivariate analyses.

The proportion of patients receiving a second line was closer to that observed in the ToGA trial (45%), than in the REAL-2 trial (14%), which illustrates the differences in clinical approaches in different centers [3, 5]. A planned second-line therapy in the FFCD-0307 may have favored the prescription of the second-line therapy. Median PFS (2.8 months with FOLFIRI L2 and 2.1 months with ECX L2) are in the same range as other published data: 2.3 months with irinotecan and 3.6 months with docetaxel [13], 2.1 months with ramucirumab alone in the REGARD

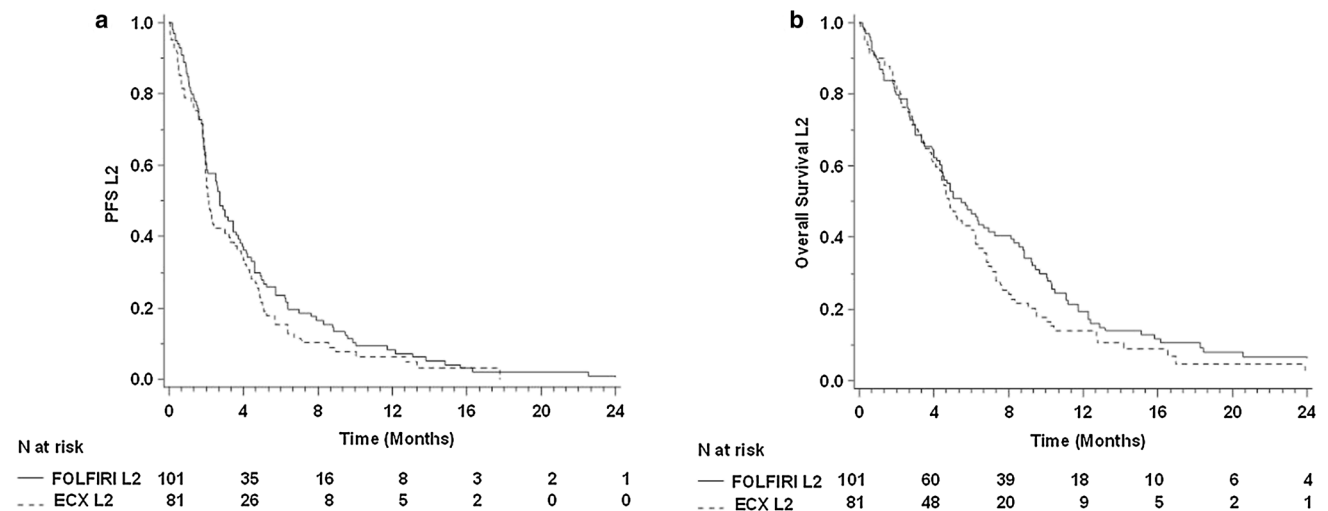


Fig. 1 a Progression-Free Survival from the start of the second-line treatment (PFS L2). b Overall Survival from the start of the second-line treatment (L2)

Table 4 Prognostic factors for PFS after second-line therapy, univariate analysis

	<i>N</i> events/ <i>N</i>	Hazard ratio	95% Confidence interval	<i>p</i> value
From the start of first-line therapy				
Treatment				
ECX second line	77/81	1.17	0.86 1.58	0.312
FOLFIRI second line	97/101	Ref	– –	
Sex				
Male	127/134	1.12	0.80 1.57	0.502
Female	47/48	Ref	– –	
Tumor localization				
GEJ	71/73	1.17	0.87 1.59	0.302
Stomach	100/106	Ref	– –	
ECOG score				
1–2	99/103	0.93	0.69 1.27	0.658
0	71/75	Ref	– –	
Body mass index (kg/m ²)				
< 18.5	19/19	0.85	0.51 1.43	0.674
18.5–25	94/100	0.87	0.63 1.21	
≥ 25	61/63	Ref	– –	
Linitis plastica				
No	132/138	0.99	0.69 1.41	0.944
Yes	40/42	Ref	– –	
Metastasis				
No	20/20	0.86	0.54 1.38	0.540
Yes	149/157	Ref	– –	
Primary tumor resection				
No	133/138	1.23	0.86 1.77	0.255
Yes	38/40	Ref	– –	
Age				
< 60 years	91/93	1.38	1.03 1.87	0.034
≥ 60 years	83/89	Ref	– –	
Hemoglobin				
< 12 g/dl	76/81	1.19	0.88 1.61	0.268
≥ 12 g/dl	95/98	Ref	– –	
Neutrophils				
< 5000/mm ³	70/75	0.82	0.60 1.12	0.209
≥ 5000/mm ³	100/103	Ref	– –	
Platelets				
< 300,000/mm ³	87/91	0.74	0.54 1.00	0.051
≥ 300,000/mm ³	84/88	Ref	– –	
Alkaline phosphatases				
≤ 1.5× normal value	126/130	0.94	0.66 1.34	0.737
> 1.5× normal value	42/46	Ref	– –	
CEA				
≤ 2× normal value	101/105	1.04	0.75 1.45	0.799

Table 4 (continued)

	<i>N</i> events/ <i>N</i>	Hazard ratio	95% Confidence interval	<i>p</i> value
> 2× normal value	58/62	Ref	– –	
CA 19.9				
≤ 2× normal value	96/99	1.12	0.81 1.53	0.506
> 2× normal value	63/68	Ref	– –	
From the start of second-line therapy				
PFS in the first line				
≤ 6 months	98/100	Ref	– –	0.559
> 6 months	76/82	0.91	0.68 1.24	
ECOG score				
≥ 2	36/36	3.18	1.85 5.47	< 0.001
1	44/45	1.53	0.91 2.58	
0	24/27	Ref	– –	
Body mass index (kg/m ²)				
< 18.5	23/24	0.94	0.56 1.58	0.403
18.5–25	102/105	1.21	0.84 1.75	
≥ 25	41/45	Ref	– –	
CEA				
≤ 2× normal value	59/62	0.85	0.56 1.28	0.431
> 2× normal value	42/45	Ref	– –	
CA 19.9				
≤ 2× normal value	53/56	0.76	0.51 1.14	0.184
> 2× normal value	46/48	Ref	– –	

Bold—*p* value < 0.05

trial [9], 2.9 months with paclitaxel and 4.4 months with paclitaxel combined with ramucirumab in the RAINBOW trial [10]. Median OS was 5.4 months with FOLFIRI L2 and 4.8 months with ECX L2. In other trials, median OS was 4–8.4 months with irinotecan and 9.5 months with docetaxel, 5.3 months with ramucirumab alone in the REGARD trial, 7.4 months with paclitaxel and 9.4 months with paclitaxel combined with ramucirumab in the RAINBOW trial.

Other studies have investigated prognostic factors in patients with metastatic gastric adenocarcinoma treated in the first or second line. In a large retrospective analysis, ECOG ≥ 2, bone metastases, ascites, alkaline phosphatase > 85UI/l, albumin < 3.6 g/dl and no resected primary tumor were identified as poor prognostic factors for OS for patients receiving first-line chemotherapy [14]. In a pooled analysis of three randomized trials, ECOG ≥ 2, liver metastases, peritoneal metastases, and alkaline phosphatase ≥ 100UI/l were poor prognostic factors [15]. In

Table 5 Prognostic factors for overall survival after second-line therapy, univariate analysis

	<i>N</i> death/ <i>N</i>	Hazard ratio	95% Confidence interval	<i>p</i> value
From the start of first-line therapy				
Treatment				
ECX second line	74/81	1.25	0.91 1.70	0.167
FOLFIRI second line	91/101	Ref	– –	
Sex				
Male	120/134	1.21	0.86 1.70	0.285
Female	45/48	Ref	– –	
Tumor localization				
GEJ	66/73	0.91	0.66 1.25	0.554
Stomach	97/106	Ref	– –	
ECOG score				
1–2	94/103	0.96	0.70 1.32	0.812
0	67/75	Ref	– –	
BMI (kg/m ²)				
< 18.5	18/19	0.90	0.53 1.53	0.779
18.5–25	89/100	0.89	0.64 1.24	
≥ 25	58/63	Ref	– –	
Linitis plastica				
No	125/138	0.96	0.67 1.39	0.843
Yes	38/42	Ref	– –	
Metastasis				
No	20/20	0.96	0.60 1.54	0.871
Yes	140/157	Ref	– –	
Primary tumor resection				
No	126/138	1.24	0.86 1.80	0.257
Yes	36/40	Ref	– –	
Age				
< 60 years	87/93	1.52	1.12 2.08	0.008
≥ 60 years	78/89	Ref	– –	
Hemoglobin				
< 12 g/dl	72/81	1.31	0.96 1.80	0.093
≥ 12 g/dl	90/98	Ref	– –	
Neutrophils				
< 5000/mm ³	67/75	0.80	0.59 1.10	0.174
≥ 5000/mm ³	94/103	Ref	– –	
Platelets				
< 300,000/mm ³	81/91	0.70	0.51 0.96	0.025
≥ 300,000/mm ³	81/88	Ref	– –	
Alkaline phosphatase				
≤ 1.5N	121/130	0.85	0.59 1.23	0.398
> 1.5N	38/46	Ref	– –	
CEA				
≤ 2× normal value	97/105	1.01	0.72 1.41	0.951
> 2× normal value	53/62	Ref	– –	
CA 19.9				
≤ 2× normal value	90/99	1.18	0.85 1.64	0.334

Table 5 (continued)

	<i>N</i> death/ <i>N</i>	Hazard ratio	95% Confidence interval	<i>p</i> value
> 2× normal value	60/68	Ref	– –	
From the start of second-line therapy				
PFS in first line				
≤ 6 months	95/100	Ref	– –	0.096
> 6 months	70/82	0.77	0.56 1.05	
ECOG score				
≥ 2	36/36	2.82	1.64 4.83	0.0003
1	40/45	1.36	0.81 2.29	
0	22/27	Ref	– –	
Body mass index (kg/m ²)				
< 18.5	22/24	0.94	0.56 1.58	0.593
18.5–25	95/105	1.15	0.79 1.67	
≥ 25	40/45	Ref	– –	
CEA				
≤ 2× normal value	55/62	0.88	0.57 1.34	0.536
> 2× normal value	38/45	Ref	– –	
CA 19.9				
≤ 2× normal value	47/56	0.69	0.46 1.06	0.088
> 2× normal value	44/48	Ref	– –	

Bold—*p* value < 0.05

Table 6 Multivariate analyses for overall survival (OS) from the start of the second-line therapy, investigating factors assessed before the first-line therapy and factors assessed before the second-line therapy

	Hazard ratio	95% Confidence interval	<i>p</i> value
Factors assessed before the start of first-line therapy (<i>n</i> = 179)			
Age at diagnosis			
< 60 years	1.49	1.09 2.03	0.013
≥ 60 years	Ref	– –	
Hemoglobin			
< 12 g/dl	1.20	0.87 1.66	0.268
≥ 12 g/dl	Ref	– –	
Platelets			
< 300,000/mm ³	0.73	0.53 1.01	0.056
≥ 300,000/mm ³	Ref	– –	
Factors assessed before the start of second-line therapy (<i>n</i> = 87)			
PFS in first line			
≤ 6 months	Ref	– –	0.372
> 6 months	0.81	0.51 1.29	
ECOG score			
≥ 2	2.62	1.41 4.84	
1	1.38	0.76 2.49	
0	Ref	– –	0.005
CA 19.9			
≤ 2× normal value	0.75	0.47 1.19	0.219
> 2× normal value	Ref	– –	

Bold—*p* value < 0.05

second-line therapy, a retrospective analysis identified ECOG ≥ 2 , hemoglobin ≤ 11.5 g/dl, CEA > 50 ng/ml, ≥ 3 metastatic sites, and time to progression ≤ 6 months under first-line treatment as independent poor prognostic factors [16]. Another retrospective study identified the following as prognostic factors in second-line chemotherapy: the PFS in the first-line chemotherapy, the performance status, serum levels of albumin and alkaline phosphatase and no resected primary tumor [17]. In a retrospective study that included 126 patients, a good performance status, a higher hemoglobin level and a longer time to progression in the first-line chemotherapy were good prognostic factors in the second-line chemotherapy [18]. More recently, a large retrospective multicenter analysis included 868 patients treated with second-line therapy. Median PFS was 2.8 months and median OS was 5.6 months. Patients received various treatments, but mostly single-agents or doublets with fluoropyrimidines, irinotecan, and taxanes. The ECOG score, an LDH level > 480 UI/l, a neutrophil/lymphocyte ratio ≥ 2.7 and PFS ≤ 6.8 months in the first line were the four independent factors for poor OS [19]. In our study, PFS in L1 was not a prognostic factor (HR 0.81 95% IC 0.51–1.29). The relative efficacy of the two investigated regimen may partly explain this result, an efficient second-line therapy may be able to counterbalance a short PFS in L1 in patients in good general condition. Age (≥ 60 years or as a continuous variable) was an independent good prognostic factor for PFS and OS. In a meta-analysis comparing elderly with young patients, elderly patients had more diffuse-type cancer, but better 5-year OS [20]. There are few data in the literature about age as a prognostic factor in L2. In the study investigating prognostic factors in L2 in 868 patients, patients ≥ 40 years had a 5.8 months median OS versus 3.9 for patients < 40 years ($p=0.001$ in univariate analysis), and patients ≥ 75 years had a 6.9 median OS versus 5.6 for patients < 75 ($p=0.08$). However, there were no significant differences in the multivariate analysis [19]. In our study, our hypothesis is that most patients ≥ 60 years died in L1 (51%, versus 40% of patients < 60 years), leading to the selection of particularly fit elderly patients in L2. The platelet count at baseline was borderline significant in the multivariate analysis for OS ($p=0.056$). The prognostic impact of thrombocytosis has also been suggested in other studies, as in the MRC-COIN trial. In this trial including patients with metastatic colorectal cancer, patients with raised baseline-platelet counts receiving intermittent chemotherapy had impaired survival and quality of life [21].

The main strength of our study is that the second-line therapy was planned in the protocol. Our study has some limits. Some data, such as lymphocyte counts and serum LDH levels, are missing from our database. The use of epirubicin in the treatment of gastric cancer is now controversial. A recent study that included 1002 patients from a

national registry did not demonstrate any benefit of adding epirubicin to a platinum-fluoropyrimidine doublet chemotherapy, but greater toxicity [22]. There is a need to identify patients who will benefit from antiangiogenic drugs, but no predictive factors have been identified so far.

In conclusion, the benefits of second-line chemotherapy remain limited, with age ≥ 60 years at diagnosis and ECOG score 0/1 before the start of L2 being the only good prognostic factors in this study. Robust prognostic and predictive factors still need to be confirmed in prospective trials.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

Ethical approval All participants gave their written informed consent before inclusion in the FFCO-0307 trial. The study was approved by relevant ethics committees.

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