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PHASE II STUDIES

Multicenter phase II study of oxaliplatin and sorafenib in advanced gastric adenocarcinoma after failure of cisplatin and fluoropyrimidine treatment. A gemcad study

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Summary *Background* Cisplatin and fluoropyrimidine (CF) are standard first- line treatment in advanced gastric cancer, but no second-line treatment has yet been established. We present a phase II study in which we evaluated the efficacy and toxicity of the combination of Sorafenib (S), and Oxaliplatin as second-line therapy. *Methods* Patients with progressive gastric adenocarcinoma after CF- first-line, ECOG 0–2, and measurable disease were included. The primary objective was PFS. Treatment doses were Oxaliplatin 130 mg/m^2/3 weeks and Sorafenib 800 mg/bid/d. *Results* We included 40 patients. CR was 2.5 % and SD was 47.2 %. Grade 3–4 toxic effects were neutropenia (9.8 %), thrombocytopenia (7.3 %), neurotoxicity (4.9 %) and diarrhea (4.9 %). Median PFS was 3 months (95 %CI: 2.3–4.1) and median OS was 6.5 months (95 % CI: 5.2–9.6). Time to progression (TTP) to first line therapy was a prognosis factor. Median OS was 9.7 months when time-to-progression during first-line chemotherapy was >6 months and 5.6 m when it was <6 months (p =0.04). *Conclusions* Time-to-progression under a CF-based first-line therapy determines subgroups of GC patients with different prognosis. The combination of Oxaliplatin-Sorafenib in advanced GC patients previously treated with CF appears safe, but our results do not support the implementation of a phase III trial.

Keywords Advanced gastric adenocarcinoma · Second-line treatment · Antitarget therapies · Oxaliplatin · Sorafenib

Introduction

Gastric cancer (GC) is the second most common cause of cancer–related death worldwide. In the U.S, the estimated number of new cases of GC in 2012 was 21,320 and the estimated number of associated deaths was 10,540 [1]. Several studies have shown the benefit of chemotherapy in terms of improved quality of life and overall survival in advanced GC [2, 3]. The

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combination of Cisplatin and a fluoropyrimidine (CF) is considered standard care for first-line treatment. The best therapeutic approach after progression following first-line chemotherapy has not been clearly established. Several phase II studies have yielded results compatible with a clinical benefit and radiologic responses that range from 14 % to 35 % [4–7]. These results parallel those obtained using second-line chemotherapy in others tumors, such as NSCLC or bladder carcinoma, where salvage treatment is considered good practice [8–11]. For these reasons, although no phase III trial has set the standard of care for the second line therapy in GC; several combinations are used after progression to first line chemotherapy.

Although little is known about the preferential pathways implicated in gastric cancer, the Ras/Raf/MERK/ERK pathway seems to play a major role, as observed in other tumours . Activated ERK overexpression (pERK) has been related with more advanced stages and lymph node positivity in gastric adenocarcinomas [12]. Data concerning other tumours that have hyperactivation of this pathway have shown that this could be due to mutation of any of the pathway members or to over activation of upstream factors. Interestingly, VEGF and VEGFR overexpression have been correlated with more advanced disease and worse survival in several series of resected gastric cancers [13, 14].

Sorafenib is a multitarget inhibitor of BRAF, VEGF and PDGFR, and thereby a selective Ras/Raf/MERK/ERK pathway inhibitor. It has shown to improve progression free survival (PFS) and overall survival (OS) in hepatocellular carcinoma and renal carcinoma [15, 16]. The chemotherapeutic drug Oxaliplatin has been evaluated in gastric cancer in combination with a fluoropyrimidine, yielding similar results to Cisplatin plus fluoropyrimidine as first-line treatment [17]. Interestingly, Oxaliplatin has shown non-cross resistance with Cisplatin and it displays a different toxicity profile [18, 19]. In view of the characteristics of these two drugs, their combination seems interesting. Furthermore, a phase I study in solid tumours reported that this association at a dose of Oxaliplatin of 130 mg/m2 was safe [20].

.In the present study, we report the results of a phase II study performed to assess the combination of Oxaliplatin plus Sorafenib as second-line therapy for advanced GC after progression to Cisplatin plus fluoropyrimidine-based first-line treatment.

Patients and methods

- Patient Eligibility

This single-arm, single-step, multi-centre phase II trial was designed and developed by the Spanish Multidisciplinary Digestive Cancer Group (Grupo Español Multidisciplinar de Cáncer Digestivo- GEMCAD). Patients with metastatic and histologically confirmed adenocarcinoma of the gastro esophageal junction or stomach were eligible if they met the following inclusion criteria: progressive disease after first-line therapy based on cisplatin plus a fluoropyrimidine (either 5-Fluorouracil or Capecitabine); ECOG 0–2; age >18 years; measurable disease by RECIST criteria 1.1; life expectancy >12 weeks; adequate medullar, renal and hepatic function;. Major exclusion criteria were patients who received CF in a neoadjuvant or adjuvant setting, CNS metastases, significant gastrointestinal bleeding or obstruction, symptomatic peripheral sensitive neuropathy, major surgery in the last 4 weeks, and severe or uncontrolled medical conditions (e.g., impaired heart and lung function, diabetes, active infections, or liver disease).

All patients provided written inform consent before the initiation of any study procedure and this study was conducted according to the ethical principles of the Declaration of Helsinki and approved by the institutional review board of each participant center The trial was registered at Clinical Trials-gov as “A Phase 2 Trial of Oxaliplatin and Sorafenib Combination in Patients With Locally Advanced or Metastatic Gastric or Gastro esophageal Junction Adenocarcinoma, Relapsed After a Cisplatin Based Treatment” (NCT-01262482) and to EudraCT (registration number: 2008-004223-27).

- Study treatment and assessment

Study medication consisted of intravenous administration of Oxaliplatin 130 mg/m2 over 2 h on day 1 and Sorafenib 400 mg twice daily in a 21-day cycle. Treatment was administered until progression of disease, unacceptable toxicity, or treatment discontinuation for any other reason. Baseline assessment included full medical history, physical examination, ECG, and a chest-abdomen-pelvis CT scan within 28 days of inclusion. Assessments of vital signs, ECOG performance status, creatinine clearance, and a routine blood analysis were performed within 7 days of inclusion. A negative serum pregnancy test was also required for women of childbearing potential,.

Clinical evaluation and hematologic and biochemistry analyses were repeated every 3 weeks, before starting a new cycle. Tumor assessments were performed every 3 cycles. If complete or partial response was reached, a confirmatory CT scan was performed in the next 4 weeks.

Adverse events and toxicity were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0.

A new cycle of therapy was started only if the neutrophil count was ≥1,500/mm3, platelet count was ≥100 000/mm3, and all relevant non-hematological toxic effects were grade 1 or lower. Otherwise, Oxaliplatin administration was delayed until blood parameters returned to normal range and/or non-hematological toxicity resolved. If recovery did not occur within 3 weeks, Oxaliplatin was discontinued and patients continued with Sorafenib alone until disease progression.

Oxaliplatin was reduced to 100 mg/m2 if neutropenia ≥ grade 2 or thrombopenia ≥ 2 were observed on day one, grade ≥ 3 febrile neutropenia, or grade > 3 non-hematological toxicity. A second reduction to 85 mg/m2 was permitted in case of a new event. A specific dose reduction was planned for Oxaliplatin neurotoxicity and only one reduction was allowed. Oxaliplatin was reduced to 100 mg/m2 in case of grade 3 neuropathy lasting > 7 days but resolving before the next treatment cycle, or in case of grade 2 neuropathy continuing on day one.

Sorafenib was discontinued in case of grade ≥2 hand-foot syndrome or grade ≥3 hypertension. After recovery to a grade ≤1, Sorafenib was reintroduced at a dose of 200 m/m2 twice daily.

- Statistical considerations

The primary endpoint in this phase II trial was progression-free survival (PFS), defined as the time from inclusion in the study to progression or death, whichever occurred first. Patients lost to follow-up and/or alive and free of progression at the time of study closure (August 2011) were censored. Secondary endpoints were response rate (RR) as assessed by RECIST criteria [21] and overall survival (OS) defined as the time from inclusion in the study to death. Sample size was initially computed using a single-step Fleming design and assuming a bilateral alpha of 0.1, power of 90 %, and median PFS of 4.3 months if the experimental treatment was not effective [22]. Under these assumptions the required sample size was 43 evaluable patients to detect an increase in PFS of 17 % at 12 months, and the study would be considered as positive if 10 or more patients were free of progression and alive at 12 months. Patient recruitment rate was slower than expected and study coordinators decided to stop patient inclusion when 40 patients were recruited. Under the same assumptions, if 38 of these 40 patients were evaluable, the study would yield a power of 87 %. The study was considered positive if 9 or more patients were alive and free of progression after 12 months' follow-up. PFS and OS were calculated by the Kaplan-Meier method. Cox proportional hazards regression with Efron method for ties was used to perform the survival analysis. The proportional hazards assumption was verified by plotting the cumulative martingale residuals and assessing for significance. SAS V9.2 (SAS Institute, Cary, NC) was used for the analysis.

Results

- Patients' characteristics

From January 2009 to August 2011, 40 patients were enrolled at ten Spanish centers. All were evaluated for toxicity and 36 for response. Baseline patient characteristics are summarized in Table 1. Most patients were male and median age was 63 (range 39–76) years. Most patients had an ECOG 1 (59 %), metastases at first diagnosis, and more than one site of metastatic disease.

- Drug exposure and toxicity

The median number of complete treatment cycles per patient was 4 (range 0 to 6). Mean dose-relative intensity was 90 % for Oxaliplatin and 92.7 % for Sorafenib (see Table 2).

Hematological toxicity consisted mainly of grade 1–2 events always below 40 % (Table 3). Grade 3 neutropenia occurred in 4 (9.8 %) patients and grade 3 thrombocytopenia in 2 (4.9) patients. There were two cases of grade 4

Table 1 Baseline characteristics

	Patients	
	N	%
Age, years Median(range)	63(39–76)	Age, years Median(range)
Female	14	34.2
ECOG		
0	14	35
1	23	57.5
2	2	5
Time to progression to first line chemotherapy		
<6 months	15	40
≥6 m	23	57.5
Grade of differentiation		
Well	1	2.5
Moderately	12	30
Poorly	14	35
Location		
Gastric	22	55
Gastro-esophageal junction	11	27.5
Prior gastrectomy	10	25
Site of disease at study entry		
- liver	26	65
- lymph nodes	18	45
- primary tumor	14	35
- peritoneal carcinomatosis	6	15
- lung	3	7.5
- ovary	3	7.5
Nº of sites involved		
- 1	11	27.5
- ≥2	29	72.5
Prior chemotherapy regimen		
- Cisplatin- FU/Capecitabine	19	47.5
- Docetaxel-Cisplatin-FU/Capecitabine	13	32.5
- Epirrubicin-Cisplatin-FU/Capecitabine	5	12.5
- Cisplatin-FU-Trastuzumab	1	2.5

Table 2 Drug delivery and treatment response

		p-value
Drug delivery		
Complete chemotherapy cycles received (%)[a]		
0	2 (5.1)	
1–2	4 (10.3)	
3–4	21 (53.9)	
5–6	12 (30.8)	
Relative dose intensity		
Oxaliplatin	90 %	
Sorafenib	92,7 %	
Tumor response[b] (%)		
CR	1 (2.8)	
PR	0 (0)	
SD	17 (47.2)	
PD	18 (50)	
Median PFS (95 % CI), months	3.0 (2.3–4.1)	
Median OS (95 % CI), months	6.5 (5.2–9.7)	
Median PFS (95 % CI) among patients with time to first progression ≤6 months	2.8 (2.0–3.8)	0.1987
Median PFS (95 % CI) among patients with time to first progression >6 months	4.1 (2.2–4.9)	
Median OS (95 % CI) among patients with time to first progression ≤6 months	5.6 (4.0–7.0)	0.0410
Median OS (95 % CI) among patients with time to first progression >6 months	9.7 (5.2–15.5)	

[a] This variable has two missing values

[b] Response was not assessable in 5 patients

Table 3 Number of patients with toxicity

	Grade 1–2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic toxicity			
Leukopenia	13 (31.7)	0	0
Neutropenia	12 (29.3)	4 (9.8)	0
Anemia	15 (36.6)	0	1 (2.4)
Thrombocytopenia	9 (22.0)	2 (4.9)	1 (2.4)
Non hematological toxicity			
AST/ALT elevation	6 (14.6)	0	0
Asthenia	5 (12.5)	6 (15 %)	1 (2.5 %)
Neurotoxicity	13 (31.7)	2 (4.9)	0
Diarrhea	7 (17.1)	2 (4.9)	0
Vomiting	3 (7.3)	1 (2.4)	0
Rash	3 (7.3)	0	0
Hand-foot syndrome	3 (7.3)	0	0
Dysesthesia	2 (4.9)	1 (2.4)	0
Paresthesia	2 (4.9)	0	0
Abdominal pain	0	2 (4.9)	0
Toxic syndrome	0	2 (4.9)	0

hematological toxicity in the form of anemia and thrombocytopenia. Non-hematological grade 3 toxicity happened in 11 patients (27.5 %) in the form of asthenia (15 %), neurotoxicity (4.9 %), diarrhea (4.9 %), abdominal pain (4.9 %), toxic syndrome (4.9 %) dysesthesia (2.4 %) and vomiting (2.4 %). There was one case of grade 4 non-hematological toxicity (asthenia). There were no treatment-related deaths.

The reasons for discontinuing the study protocol were progressive disease in 29 patients (72.5 %), toxicity in 6 patients (15 %), other comorbidities in 3 patients (7.5 %), and patient decision in 1 case (2.5 %). At the time of administrative censoring, two patients remained under treatment.

- Efficacy

Thirty-six of the 40 enrolled patients were assessed for response. We were unable to evaluate the response in four patients who discontinued treatment before the third cycle: two due to grade 3 toxicity (neurotoxicity in one and thrombocytopenia in the other), one due to refusal to continue treatment, and one due to impairment of previous comorbidity.

No partial response was observed, but a complete response was reached in one patient (2.7 %). This patient had been submitted to salvage surgery because he presented a local relapse, but peritoneal carcinomatosis was observed and the intervention was interrupted. The patient was then enrolled in the study. After the first three cycles, the radiologic image completely disappeared. This response was maintained at the following evaluation, after the sixth cycle. Progressive disease was observed 2.5 months later.

Seventeen patients (47.2 %) showed stable disease as the best response.

Median follow-up time was 5.5 (range 1.1 to 20.5) months. Median PFS was 3 months (95 % confidential interval (Cl) 2.3–4.1 months). At 4 months, 44.3 % of the patients were alive and progression free. At the last follow-up, 33 patients had deceased due to disease progression. Median OS was 6.5 months (95 %, CI 5.2–9.6 months) (Table 3 and Figs. 1and 2).

No differences were detected in PFS or OS according to sex, ECOG, tumor localization, prior gastrectomy, or number of metastatic sites. Interestingly, time to progression under the first line of therapy received (TTPFL) arose as a significant prognostic factor. Patients with a TTPFL ≤6 months showed a median OS of 5.6 (95 % CI 4.0–7.0) months, whereas those with a PFS >6 months had a median OS of 9.7 (95 % CI 5.2–15.5, p-value=0.04) months (Table 2 and Fig. 3). After adjusting for age, sex and performance status, the multivariate model assessing OS of patients with a TTPFL≤6 months yielded an HR of 2.5 (95 % CI 1.1 to 5.9, p-value=0.0289) compared to those with a TTFPL >6 months. Patients with a TTPFL≤6 months and patients with a TTPFL >6 months had a median PFS of 2.8 (95 % CI 2.0–3.8) months and 4.1 (95 % CI 2.2–4.9) months, respectively. This difference was not statistically significant.

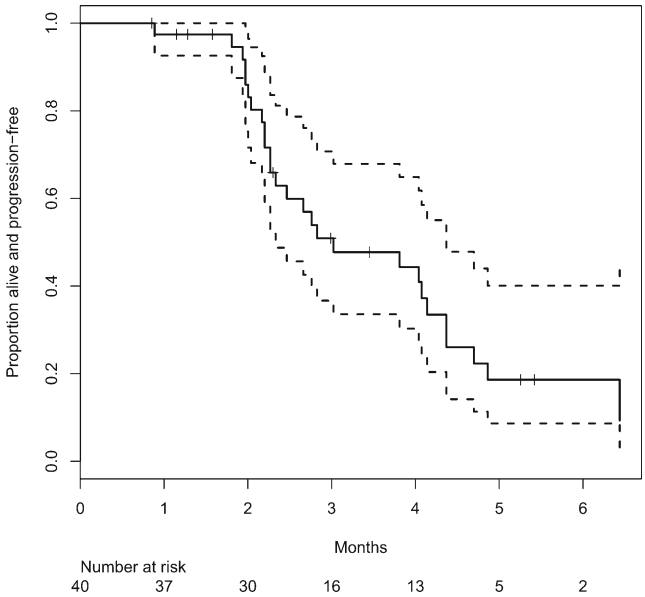

Fig. 1 Kaplan- Meier estimates for progression free survival

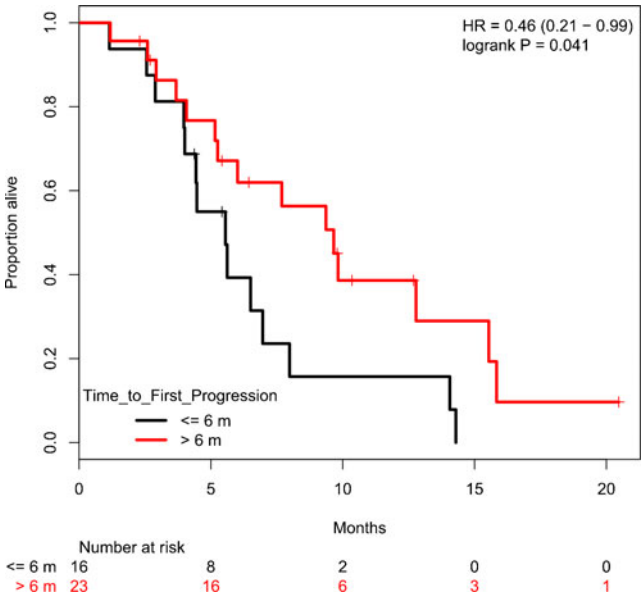

Fig. 3 Kaplan- Meier estimates for overall survival according to Time to First- Line Progression (TTFLP)

Discussion

This study did not meet its primary endpoint of efficacy. However, the results showed that the combination of Oxaliplatin and Sorafenib in patients with advanced gastric cancer is safe and well tolerated. The most frequent grade 3–4 toxicity was asthenia. However, It is hard to elucidate whether this was caused by the drug or was due to underlying disease, because about half of the patients presented this symptom when disease progression was detected. Other severe toxicities were sensory neurotoxicity and diarrhea, both observed in fewer than 8 % of the patients. These percentages are in accordance with other studies administering the same dose of Oxaliplatin [17, 23, 24].

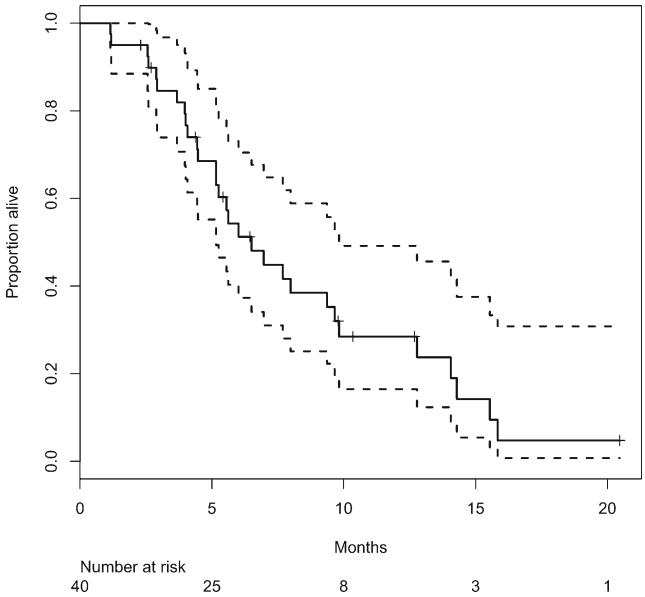

Fig. 2 Kaplan- Meier estimates for overall survival

The PFS in our study was lower than that used as the null hypothesis. This can be explained either by a real lack of benefit of the treatment (or even a detrimental effect) or by wrong assumptions taken at the time of study design. When the study was conceived, data about second-line chemotherapy efficacy in GC were limited. We therefore based our assumptions for sample size calculation on the only phase II study available at that time with Oxaliplatin treatment in patients with GC after a Cisplatin- fluorouracil first-line treatment [22]. The authors of the study found a PFS of 4.3 months. The 7. 2 months chosen in our study may therefore be deemed over-optimistic.

Later studies have shown results similar to ours. A single-arm phase II trial by Jeong et al. assessing the efficacy of the regimen FLOX (Oxaliplatin 75 mg/m2 as a 2-h infusion on day 1, followed by a bolus injection of leucovorin 20 mg/m2 on days 1–3 and continuous i.v. infusion of 5-FU 1,000 mg/m2 on days 1–3, repeated every 3 weeks) reported a response rate of 5 %. Median PFS and OS were 3.0 and 6.4 months respectively (25). Nevertheless, the population of this study differed from ours because only 50 % of patients had progressed after first-line treatment and first-line chemotherapy was Cisplatin-based in only 32 % of cases [25].

Of note, our study population may be considered as having worse prognosis than the study by Jeong et al. since all patients had progressed to Cisplatin plus fluoropyrimidine-based chemotherapy. This suggests a beneficial effect of Oxaliplatin plus Sorafenib.

The efficacy of Sorafenib in GC should be confirmed in randomized studies using Sorafenib as monotherapy. Unfortunately, such studies are lacking and the only data

available to date come from two studies in first line therapy in combination with chemotherapy. The first was a phase I dose-finding study, which evaluated the combination of Cisplatin-Capecitabine plus Sorafenib in non-resectable or metastatic GC, not previously treated [26]. The recommended dose was Sorafenib 400 mg bid daily, Capecitabine 800 mg/m2 bid (days 1–14), and Cisplatin 60 mg/m2 (day 1) . Sixteen of the 21 patients had measurable disease and objective response was 62.5 %, median PFS was 10 months, and median OS was 14.7 months. The second was a phase II study that evaluated the combination of Cisplatin 75 mg/m2- Docetaxel 75 mg/m2 on day +1 with Sorafenib 400 mg b.i.d every 3 weeks [27]. Forty-four patients were included, and 20 % had locally advanced disease. The response rate was 41 %, median PFS was 5.8 months, and median OS was 13.6 months. In both studies the results were better than could be expected with chemotherapy alone and the investigators concluded that Sorafenib had an additive effect. Supporting the relevance of inhibiting the VEGF pathway in GC, Bevacizumab has shown efficacy in GC. A phase III trial in first-line therapy compared the addition of Bevacizumab to CF vs. placebo. The results evidenced an improvement of clinical response and PFS in favor of the Bevacizumab arm, although the increase in OS did not reach statistical significance [28]. More recently, a phase III study with Ramucirumab, an antibody targeting VEGFR2 demonstrate in patients with progressive gastric cancer after platine-fluoropyrimidine first line a statistically significant improvement in PFS and overall survival in comparison with placebo. The median overall survival of patients treated with the drug was 5.2 m in front of 3.8 m in the placebo arm (HR 0.77 Ci 0.603–0.998 p 0.04) reflecting the convenience of the inhibition of the VEGF pathway in gastric cancer[29].

Nowadays, the benefit of second line-chemotherapy is clear. Two randomized trials compared chemotherapy to best supportive care (BSC) after progression to platinum and fluoropyrimidine. In the first trial, a phase II German study, Irinotecan at a dosis of 250-350 mg/m2 every 3 weeks was compared to BSC [30]. Although it was prematurely closed due to a poor inclusion rate after the enrollment of 40 patients and although no objective response was detected, a benefit in terms of median OS was found in the experimental arm (4 vs. 2.4 months, $p=0.02$). The second trial, a phase III Korean study, compared chemotherapy (either Irinotecan 150 mg/m2 every 2 weeks or Docetaxel 60 mg/m2 every 3 weeks) vs. BSC in 201 patients who progressed after one or two lines of platinum- and fluoropyrimidine-containing chemotherapy. A statistically significant improvement in overall survival in the chemotherapy arm was found (5.3 vs. 3.8 months, $p=0.007$). [31]. As measurable disease was not mandatory in either study, PFS was not reported. In view of the results from these two trials, overall survival in our study is not discouraging.

Although all patients had been treated with platinum-fluoropyrimidine in the three above-mentioned studies, direct comparison is questionable, particularly considering the lack of prognostic factors in patients receiving a second-line treatment. The few studies carried out to date in this target population were performed in small samples only, and are therefore especially prone to harbor heterogeneous populations. In our study the TTPFL determined two subpopulations with markedly different prognosis, thus supporting Kang et al.'s findings [31].

To allow comparison between studies, efforts should be made to define a subgroup of patients who show with a higher sensitivity to cisplatin-FU as first line treatment and present a better prognosis. The Korean study defined sensitivity as the interval from last therapy to progression, and this definition could be influenced by personal preferences in the duration of first-line treatment. In agreement with others authors, our definition seems to be more objective and therefore more appropriate [32]. Furthermore, in our study the TTPFL maintain its prognostic value after adjusting for other factors, such as ECOG and age, which have shown a prognostic value in the first -line setting.

In conclusion, our study shows that although the combination of Oxaliplatin and Sorafenib was safe, median PFS after Cisplatin-fluoropyrimidine-based first-line chemotherapy in patients with progressive disease was only 3 months. As this result did not reach our primary objective we cannot recommend the implementation of a phase III study. The powerful prognostic value of previous sensitivity to first line-treatment found in this study should be taken in account when designing futures studies exploring second-line therapies.

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Ethical standards This study comply with the current laws of Spain.

Conflict of interest The authors declare that they have no conflict of interest

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