Phase II Trial of Erlotinib plus Capecitabine as First-line Treatment for Metastatic Pancreatic Cancer (XELTA Study)

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Abstract. *Aim: To evaluate the efficacy and safety of erlotinib plus capecitabine for metastatic pancreatic cancer. Patients and Methods: This was a multicenter, uncontrolled, phase II trial. Patients with untreated metastatic pancreatic cancer received oral capecitabine at 1,000 mg/m^2 twice daily on days 1-14, of a 21-day treatment cycle; and oral erlotinib at 150 mg daily. Results: Thirty-two patients were enrolled. The overall response rate (ORR) was 6%, with a median time to treatment failure of 2.1 months. The median follow-up was 7.6 months. The median progression-free survival was 2.1 months and median overall survival was 4.3 months. The one-year survival rate was 22%. Major grade 1 and 2 non-hematological toxicities were skin rash (34%), asthenia (31%) and diarrhea (31%). Grade 3 hematological toxicity was <13%. No grade 4 toxicities were detected. None of the patients died due to treatment toxicity. Conclusion: The combination of capecitabine with erlotinib is an active regimen with a favorable safety profile for patients with metastatic pancreatic cancer.*

Pancreatic cancer represents a leading cause of cancer mortality, and is the eighth most common cause of cancer-related death worldwide (1). Prognosis of pancreatic cancer patients remains poor and the 5-year survival rate is approximately 6%, for all stages combined (1, 2). Gemcitabine has been regarded as the standard-of-care for untreated advanced/metastatic pancreatic cancer based on improved clinical benefit and prolongation of survival compared with bolus fluorouracil (3). However, the reported median overall survival (OS) was generally less than 6 months in randomized trials evaluating single-agent gemcitabine (4, 5). Subsequently, several cytotoxic agents have been investigated in combination with gemcitabine in randomized phase III clinical trials, but unfortunately most of these combinations have failed to demonstrate superiority in survival over gemcitabine-alone. or caused unacceptable toxicity (6-11). A likely survival benefit was seen with the use of gemcitabine doublets containing either platinum agents or the oral fluoropyrimidine capecitabine although toxicities associated with these combinations were also greater (12).

With the increasing knowledge over the molecular biology of pancreatic cancer, novel therapeutic targets have been identified. Epidermal growth factor receptor (EGFR) is known to be overexpressed in pancreatic cancer (13, 14), and this has been related to a more aggressive disease and worse prognosis (15). Modulation of EGFR-mediated signaling therefore provides a striking approach to the treatment of pancreatic cancer. Accordingly, erlotinib, an orally available small-molecule tyrosine kinase inhibitor with high activity against EGFR (16-18) has been evaluated in randomized trials. The phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) study PA.3, showed that patients with advanced pancreatic cancer receiving gemcitabine plus erlotinib experienced a significant, although modest, improvement in survival,

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compared with those treated with gemcitabine-alone (1-year survival: 23% *vs*. 17%, respectively) (17). However, patients in the erlotinib-containing arm experienced a slight increase of incidence of grade 3-4 rash and diarrhea.

To date, only the combination of gemcitabine plus erlotinib has shown a small, but significant improvement in survival, and a trend for better survival was also observed with a gemcitabine-capecitabine regimen (7). However, the relatively modest survival improvements, in addition to the increased toxicity associated with these combinations, has led to a change in paradigm in the investigation of new therapeutic strategies for use in the first-line setting. The activity of both capecitabine and erlotinib in advanced/metastatic pancreatic cancer prompted the design of the only phase III trial conducted to date, that has focused on comparison of the efficacy and safety of erlotinib plus capecitabine with erlotinib plus gemcitabine in advanced pancreatic cancer (19). The recently published results of that trial revealed that erlotinib can be safely combined with capecitabine, demonstrating comparable efficacy to erlotinib plus gemcitabine in terms of OS (19).

In the view of the limited available evidence regarding use of erlotinib plus capecitabine for pancreatic cancer, particularly in metastatic disease, we performed a phase II multicenter study to evaluate the safety and efficacy of this regimen in untreated patients with metastatic pancreatic cancer.

Patients and Methods

Patient population. Patients were eligible if they had cytologically- or histologically-confirmed metastatic pancreatic carcinoma (stage IV) or if they experienced recurrence after initial diagnosis of local (stage IA-IIB) or locally advanced (stage III) pancreatic cancer. Patients were further required to have measurable disease [by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (20)], Karnofsky performance status (KPS) ≥60%; life expectancy of at least 12 weeks and adequate renal, liver and bone marrow function. Prior neoadjuvant chemotherapy was allowed if administered ≥4 weeks prior to study inclusion and patients were fully-recovered from toxicities secondary to chemotherapy. Exclusion criteria included evidence of spinal cord compression, carcinomatous meningitis or brain metastases, uncontrolled hypertension or clinically significant cardiac disease. Pregnant or breast-feeding women were also excluded.

The study was approved by the Ethics Committee of Galicia, and written informed consent was obtained from all patients before they were included in the study. The study was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and their amendments. The trial is registered at www.clinicaltrials.gov with the identifier NCT00873353.

Study design and treatment. This was a multicenter, uncontrolled, non-randomized, phase II study conducted in nine Spanish centers. The primary study end-point was the objective response rate (ORR) according to RECIST criteria; secondary end-points were OS, 1-year OS, progression-free survival (PFS), time to treatment failure (TTF), clinical benefit response according to the criteria of Burris *et al*. (3) and toxicity.

The study regimen consisted of oral capecitabine (Xeloda®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) at 1,000 mg/m^2 twice daily (total daily dose of 2,000 mg/m^2) on days 1-14 of a 21-day treatment cycle; and oral erlotinib (Tarceva®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) at 150 mg given once daily. Patients were planned to receive six three-week courses of capecitabine (18 weeks) and an uninterrupted treatment of 18 weeks with erlotinib. Both treatments were given until 18 weeks, tumor progression, unacceptable toxicity, or premature withdrawal for any cause, whichever came first. Treatment was planned to be reduced in cases of grade >1 hematological toxicity. In the event of grade ≥2 non-hematological toxicity, capecitabine treatment had to be immediately interrupted until the resolution of toxicity or when the intensity grade was ≤1. Study treatment was permanently discontinued in patients experiencing a delay of treatment of more than three weeks. If a dose reduction of erlotinib was needed (to 100 mg), the related toxicity was required to be improved by at least one grade and needed to be grade ≤2 in the subsequent two weeks. If toxicities did not resolve, a further reduction (to 50 mg) or treatment discontinuation was performed. More than 2 reductions of erlotinib dose were not allowed. Patients experiencing an interruption for >14 days were withdrawn from the study.

Study assessments. Pre-treatment baseline evaluation included complete medical history, physical examination, blood analysis (hematology, biochemistry and CA19-9), electrocardiogram (ECG), and imaging studies including chest X-ray, brain magnetic resonance imaging (MRI) scans and computed tomography (CT) (if clinically indicated). Intensity of pain and analgesic consumption were also recorded prior to starting study treatment. Physical examination and blood analysis were repeated on day 1 of each cycle. Tumor response was evaluated every three cycles (every nine weeks), according to RECIST version 1.0 (20). Tumor marker CA19-9 was assessed at every cycle only if the baseline value was abnormal (<35 ng/ml). After completion or discontinuation of study treatment, patients were followed-up every two months for evaluation of survival until death or 18 months after the inclusion of the last patient, whichever was earlier. Patients were evaluated for toxicity before each treatment cycle and for 30 days after the last administration of study drug.

Statistical analysis. An optimal two-stage design described by Simon (21) was used to estimate the sample size. A 0.05 α error and a 0.10 β error were established. A response probability ≥20% was considered to be of interest to continue the accrual, while further testing would not be pursued if the response probability was ≤5%. In the first stage, a total of 10 patients were included and at least one response (complete response or partial response) was required in order to continue the study until 29 patients accrued in the second stage. Considering a 15% loss of patients to follow-up, 32 patients were required to be included.

PFS was estimated as the time elapsed from enrollment until documented disease progression or death. OS was measured from the enrollment to death. The probability of PFS and OS was estimated using the Kaplan Meier method. Patients were censored at the date of last follow-up or last study treatment administration if still alive. For the assessment of clinical benefit response, the criteria previously published by Burris *et al*. (3) were applied.

All patients who had received at least one dose of study treatment were included in the safety analysis. In order to assess toxicity per patient, the maximum grade for each toxicity recorded during the

Table I. *Patient demographic and clinical characteristics (n=32).*

Characteristic	No.	(%)
Median age (range), years	64 (56-70)	
Gender		
Male	16	(50)
Female	16	(50)
Performance status,		
KPS 70-80%	18	(56)
KPS 90-100%	14	(44)
Primary tumor site		
Head	14	(44)
Body	7	(22)
Tail	4	(13)
Head, body	1	(3)
Body, tail	5	(16)
Missing data	1	(3)
Histological degree of tumor differentiation		
Well-differentiated	3	(9)
Moderately-differentiated	15	(47)
Poorly-differentiated	3	(9)
Unknown	10	(31)
Missing data	1	(3)
Distant metastasis[a]		
Liver	20	(63)
Lung	3	(9)
Peritoneum	6	(19)
Other[b]	9	(28)
Median CA 19-9 (range), ng/dl	648.3 (40.3-6,570.3)	
Previous treatment		
Surgery[c]	11	(34)
Chemotheraphy[d]	3	(9)
Radiotherapy	2	(6)

KPS: Karnosfsky performance status. [a]Patients could have more than one metastasic site. [b]Retroperitoneal node metastases, other metastatic sites. [c]Biliary derivation and distal pancreatectomy were the most common procedures (36% and 27.3%, respectively). [d]Each patient was given single-agent gemcitabine, 5-fluorouracil/leucovorin, and gemcitabine/oxaliplatin, respectively.

Table II. *Treatment toxicity (maximum grade of toxicity per patient) (n=32).*

	NCI-CTC grade			
	Grade 1/2[a]		Grade 3[b]	
Toxicity	No.	(%)	No.	(%)
Hematological				
Thrombocytopenia	1	(3)	--	--
Neutropenia	1	(3)	--	--
Non-hematological				
Rash	11	(34)	--	--
Asthenia	10	(31)	--	--
Diarrhea	10	(31)	--	--
Stomatitis	7	(22)	--	--
Vomiting	7	(22)	--	--
Nausea	5	(16)	--	--
Abdominal pain	3	(9)	--	--
Paronychia	3	(9)	--	--
Anorexia	2	(6)	--	--
Fever	2	(6)	--	--
Hand-foot syndrome	1	(3)	3	(9)

NCI-CTC: National Cancer Institute Common Terminology Criteria for Adverse Events. [a]Most common grade 1 or 2 toxicities detected in >5% of patients. [b]All grade 3 toxicities are recorded. No grade 4 toxicities were detected.

treatment was considered for evaluation. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 3.0) (22).

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. From March, 2008 to November, 2009, a total of 32 patients from nine Spanish centers were enrolled in the study. The demographic and clinical characteristics of the patients are shown in Table I. The median age of the patients was 64 (range 56-70) years and all patients had a KPS ≥70%. All patients had metastatic disease and presented with more than one metastatic site, involving two or three lesions (71% and 26%, respectively). Liver metastases were found in 63% of patients. Eleven (34%) patients underwent surgery and three (9%) patients had received prior adjuvant chemotherapy.

Safety. All patients enrolled in the study were considered evaluable for safety analyses (n=32). Twenty-two patients (69%) experienced at least one toxicity during the study. Non-hematological and hematological treatment-related adverse events are summarized in Table II. No grade 4 hematological or non-hematological toxicities were detected. No grade 3 hematologic toxicities were found and the only grade 3 non-hematological toxicities reported were hand-foot syndrome in three patients and infection of biliary prosthesis in one patient. The hematological toxicities were infrequent and mild with only two patients experiencing grade 1 or 2 thrombocytopenia and neutropenia, in one case each, respectively. The most common grade 1 or 2 non-hematological toxicities were skin rash (34%), asthenia (31%), diarrhea (31%), stomatitis (22%) and vomiting (22%).

Treatment duration and dosage modifications. A total of six (19%) patients completed the planned six cycles of study treatment. Patients received a median of three cycles (range 2-4). The mean treatment duration was 65±41 weeks. Twenty-six (81%) patients did not require any treatment delay. Dose reduction of capecitabine was necessary in only

Table III. *Treatment delay and dose reductions (n=32).*

	Capecitabine		Erlotinib	
Modification	No.	(%)	No.	(%)
Treatment delay				
Delayed cycles/doses				
1	4	(13)[a]	5	(16)[a]
Reasons for treatment delay				
Hematological toxicity	2	(50)	--	--
Non-hematological toxicity	1	(25)	2	(40)
Not related to treatment Adverse events	--	--	1	(20)
Not related to treatment	1	(25)	2	(40)
Dose reduction				
1	3	(9)	7	(22)
2	--		1	(3)
Reason for dose reduction				
Nonhematological toxicity	2	(67)	5	(56)
Not related to treatment Averse events	1	(33)	1	(11)
Not related to treatment	--	--	3	(33)

[a]Three patients delayed capecitabine and erlotinib treatment at the same time.

Table IV. *Response to treatment (n=32).*

Confirmed response	No.	(%)
Overall response rate	2	(6)
95% Confidence interval	1.1-22.3	
Complete response	0	(0)
Partial response	2	(6)
Stable disease	7	(22)
Disease control rate	9	(28)
95% Confidence interval	14.4-47.0	
Progressive disease	23	(72)
Median time to treatment failure, months	2.1	
95% Confidence interval	1.8-2.3	

Overall response rate: rate of complete response + partial response. Disease control rate: rate of complete response + partial response + stable disease.

three (9%) patients. None of the patients needed a dose reduction in more than one cycle. Eight (25%) patients experienced a dose reduction for erlotinib, and among them only one patient required a further dose reduction. The causes for treatment delay and dose reductions are shown in Table III. The median relative dose intensity (ratio of doses received to doses planned) was 1.0 (range 0.9-1.1) mg/day for capecitabine and 0.9 (range 0.9-1.0) mg/day for erlotinib.

The majority of patients (69%) discontinued treatment due to progressive disease, whereas four (9%) patients discontinued therapy because of adverse events (acute cholecystitis, cholestasis, acute hepatitis and biliary infection in each patient respectively).

Efficacy. Efficacy analyses were conducted on all patients enrolled in the study (n=32). Treatment responses are summarized in Table IV. The ORR was 6%. Disease stabilization was achieved in seven (22%) patients and 23 (72%) showed progression during treatment. The median TTF was 2.1 months (95% Confidence interval=1.8-2.3 months). Three patients achieved a positive clinical benefit response and 18 (70%) patients were classified as stable regarding clinical benefit response, according to the criteria of Burris *et al*. (3). Among 13 evaluable patients, two (15%) experienced an early decrease in CA 19-9 of ≥20% after two cycles of treatment. Five (25%) out of the 26 evaluable patients showed a reduction in CA 19-9 of ≥20% between baseline and the tumor marker nadir concentrations.

The median duration of follow-up was 7.6 (range 1.7-10.6) months. At the time of the analysis, disease in all patients had progressed. The median PFS was 2.1 (95% CI=1.9-2.3) months (Figure 1A) and median OS was 4.3 (95% CI: 1.6-7.0) months (Figure 1B). The one-year survival rate was 22% and 6-month survival was 44%. Thirty-one (97%) patients had died by the time of this analysis. The majority of patients died because of disease progression (97%), one patient died due to concomitant disease. None of the deaths were attributable to treatment toxicity.

Post-study treatment. Overall, half of all patients received second-line chemotherapy after study treatment. Twelve (75%) patients received single-agent gemcitabine as second-line treatment. Other second-line regimens administered to patients included a combination of fluorouracil, leucovorin and oxaliplatin (FOLFOX) (12%), paclitaxel (6%) and pemetrexed (6%). One patient that was withdrawn from the study because of a serious adverse event unrelated to study treatment (acute cholangitis) continued to receive treatment with erlotinib plus capecitabine after having fully-recovered and given that a partial response was achieved with this therapy. Two patients received third line treatment. None of the patients underwent surgery for metastatic disease and only one patient received radiotherapy.

Discussion

This phase II study suggests that the combination of capecitabine plus erlotinib is an active regimen with a favorable safety profile for patients with metastatic pancreatic cancer. The objective tumor response associated with this regimen was 6% and the 1-year survival rate was 22%. Toxicities associated with erlotinib plus capecitabine regimen were mild-to-moderate and no treatment-related death was observed.

Given the activity of both capecitabine and erlotinib in clinical trials and based on the synergistic pre-clinical data (23) and the promising efficacy and safety data in gemcitabine-

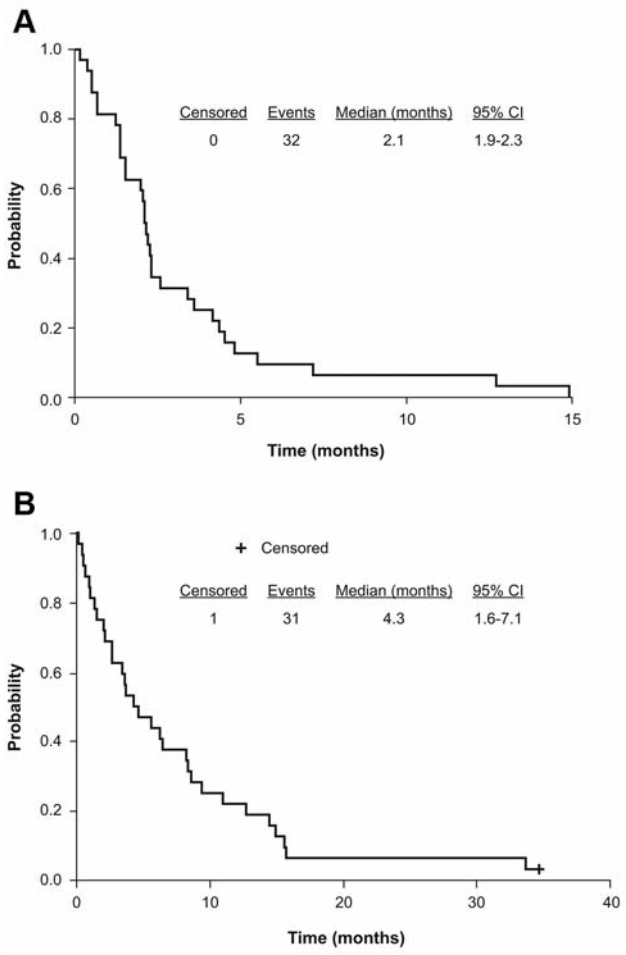

Figure 1. *Kaplan-Meier curves for progression-free (A) and overall survival (B). 95% CI: 95% Confidence interval.*

refractory pancreatic cancer (24), the erlotinib-capecitabine regimen has been regarded as a feasible treatment for patients with advanced or metastatic pancreatic cancer. However, currently available data on the combined use of erlotinib and capecitabine as first-line therapy is limited. The phase III trial of the Arbeitsgemeinschaft Internistische Onkologie (AIO) group is so far the only study that has been conducted to compare the efficacy and safety of erlotinib (150 mg/day) plus capecitabine (2,000 mg/m^2/day for 14 days, once every three weeks) with erlotinib (150 mg/day) plus gemcitabine (1,000 mg/m^2 as a 30-min infusion) for advanced pancreatic cancer (19). The recently updated efficacy results of this trial have shown an ORR of 5% and a median TTF of 2.2 months for the erlotinib-capecitabine combination as first-line treatment (19). The results obtained in our study, with an ORR of 6% and a median TTF of 2.1 months, confirm the efficacy findings of the AIO trial. Conversely, the median OS achieved in our study (4.3 months) was lower than that recorded in the AIO study (6.9 months), which was similar to the OS reached in the gemcitabine plus erlotinib arm (6.2 months) and the OS benefit obtained with gemcitabine-erlotinib regimen in the pivotal study of Moore *et al*. (17) (6.4 months). Indeed, efficacy results of the German group revealed that both gemcitabine-erlotinib and capecitabine-erlotinib treatment strategies are feasible and demonstrate comparable efficacy (19). A possible explanation for our trial failing to reach a longer OS may be the smaller sample size. However, it should be noted that the 1-year survival rate found in our study (22%) is consistent with that obtained for the gemcitabine-erlotinib regimen from Moore *et al*. (17) (23%) and to that previously found with gemcitabine plus capecitabine combination (24%) (7).

The treatment regimen used in the current study was well-tolerated and relatively easy to administer, as demonstrated by the low incidence of dose reductions and the consequent high relative dose intensity for both capecitabine and erlotinib. Capecitabine dose reductions were only required for three (9%) patients, and eight (25%) required a dose reduction for erlotinib. The toxicity profile of the current study regimen is comparable to that previously known to be associated with both agents. The toxicity data of our study support the notion that erlotinib can be safely combined with capecitabine in agreement with Heinemann *et al*. (19, 25). The interim toxicity evaluation of the AIO group showed that a daily dose of 150 mg of erlotinib does not result in an increased toxicity rate compared with the recommended erlotinib dose of 100 mg per day from the pivotal trial by Moore *et al*. (17). Moreover, the safety analysis of the AIO showed that gastrointestinal toxicity was similar in both combination regimens (erlotinib in combination with either capecitabine or gemcitabine), providing further evidence for the statement that the addition of erlotinib does not increase gastrointestinal toxicity of capecitabine, and thus confirming the data of Kulke *et al*. (24) in the second line setting. In our study, major adverse events were non-hematological, in line with the AIO trial (19, 25), with skin rash (34%), asthenia (31%) and diarrhea (31%) being the most frequent grade 1 or 2 toxicities. It should be noted that no grade 3 or 4 hematological toxicities were detected. Hand-foot syndrome was the only grade 3 or 4 non-hematological toxicity reported (9%), showing a similar incidence to that previously reported in the AIO study (19). Interestingly, no grade 4 toxicities were found and none of the patients died due to treatment toxicity. Therefore, the manageable toxicity profile of the erlotinib and capecitabine combination warrants further clinical investigation of these agents.

Based on the evidence provided, the combination of erlotinib and capecitabine seems to be a suitable treatment option for patients with metastatic pancreatic cancer, although the data reported in our study are limited to a relatively small cohort size. However, although modest, our findings are especially interesting given that the present study comprises a small proportion or a lack of patients with characteristics

which have been associated with better outcomes, including locally-advanced disease (8, 10, 11) and a good performance status (26, 27). Previous clinical trials addressing gemcitabine-erlotinib and gemcitabine-capecitabine regimens (7, 9, 17), and the capecitabine plus erlotinib arm of the AIO trial (19), included patients with both locally-advanced and metastatic pancreatic cancer. This is the first clinical trial evaluating capecitabine and erlotinib combination in a homogeneous population of very poor prognosis. The proportion of locally-advanced disease in previous clinical trials could have led to a better prognosis of the overall population given that metastatic pancreatic cancer usually has a worse outcome than locally-advanced disease (8, 10, 11). Moreover, it should be noted that patients with either poor (KPS 70-80%: 56%) or good performance status (KPS 90-100%: 44%) were enrolled in our study, whereas 80% of patients had a performance status of 0 or 1 in previous randomized clinical trials (7, 17). It has been shown that patients with poor performance status do not appear to benefit from combination chemotherapy or, if they do, they benefit to a lesser extent than those with a good performance status (26, 27). Therefore, the question that arises is whether the combination of capecitabine and erlotinib would achieve a better outcome in patients with metastatic disease selected for a good performance status. On the basis of a more precise selection than in previous studies, particularly with regard to tumor stage and performance status, a large phase III study has been recently conducted to compare the FOLFIRINOX regimen (oxaliplatin, irinotecan, fluorouracil, and leucovorin) with gemcitabine-alone in a selected population with metastatic pancreatic disease and good performance status [Eastern Cooperative Oncology Group (ECOG) 0-1] (28). A significant increased response rate (19% *vs*. 12%) and a prolonged median survival (11 *vs*. 7 months) was found with the FOLFIRINOX regimen compared to gemcitabine-alone, adding further evidence to that gemcitabine-free regimens may be of particular clinical benefit. However, the FOLFIRINOX regimen showed an increased toxicity when compared with single-agent gemcitabine, furthermore, patients were required to have a good performance status, a subgroup that has usually been associated with a better prognosis.

Considering the limited available data on gemcitabine-free treatment options, and particularly concerning the erlotinib-capecitabine regimen, our findings, although modest, offer a basis for further clinical investigation of this combination in metastatic disease. Moreover, further trials would be required to better-define which patient populations might derive a greater benefit from the capecitabine and erlotinib combination. In addition, this well-tolerated regimen could represent a suitable platform for combination with other drugs in patients with metastatic pancreatic cancer. Hence, the combination of erlotinib, capecitabine and gemcitabine has recently shown promising efficacy and good tolerability for metastatic pancreatic cancer (29). Accordingly, the combination of erlotinib plus capecitabine might become the basis on which novel biological therapies could be developed.

In conclusion, the results of this phase II study suggest that the combination of capecitabine and erlotinib is a reasonable and well-tolerated treatment option for patients with metastatic pancreatic cancer, representing a promising new approach in this setting. Further randomized clinical trials are needed to validate the clinical benefit of this regimen for metastatic pancreatic cancer.

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