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Original Research

Gemcitabine–erlotinib versus gemcitabine–erlotinib–capecitabine in the first-line treatment of patients with metastatic pancreatic cancer: Efficacy and safety results of a phase IIb randomised study from the Spanish TTD Collaborative Group

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KEYWORDS
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Abstract ***Background:*** Gemcitabine and erlotinib have shown a survival benefit in the first-line setting in metastatic pancreatic cancer (mPC). The aim of this study was to assess whether combining capecitabine (C) with gemcitabine + erlotinib (GE) was safe and effective versus GE in patients with mPC.
Patients and methods: Previously untreated mPC patients were randomised to receive G (1000 mg/m^2, days 1, 8, 15) + E (100 mg/day, days 1–28) + C (1660 mg/m^2, days 1–21) or GE, q4 weeks, until progression or unacceptable toxicity. Primary end-point: progression-free survival (PFS); secondary end-points: overall survival (OS), response rate, relationship of rash with PFS/OS and safety.
Results: 120 patients were randomised, median age 63 years, ECOG status 0/1/2 33%/58%/8%; median follow-up 16.5 months. Median PFS in the gemcitabine–erlotinib–capecitabine (GEC) and GE arms was 4.3 and 3.8 months, respectively (hazard ratio [HR]: 0.88, 95% confidence interval [CI]: 0.58–1.31; p = 0.52). Median OS in the GEC and GE arms was 6.8 and 7.7 months, respectively (HR: 1.09, 95% CI: 0.72–1.63; p = 0.69). Grade 3/4 neutropenia (GEC 43% versus GE 15%; p = 0.0008) and mucositis (GEC 9% versus GE 0%; p = 0.03) were the only statistically significant differences in grade 3/4 adverse events. PFS and OS were significantly longer in patients with rash (grade ≥1) versus no rash (grade = 0): PFS 5.5 versus 2.0 months (HR = 0.39, 95% CI: 0.26–0.6; p < 0.0001) and OS: 9.5 versus 4.0 months (HR = 0.51, 95% CI: 0.33–0.77; p = 0.0014).
Conclusion: PFS with GEC was not significantly different to that with GE in patients with mPC. Skin rash strongly predicted erlotinib efficacy.
The study was registered with ClinicalTrials.gov: NCT01303029.

1. Introduction

Pancreatic cancer is the eighth most common cancer in Europe, accounting for 3% of cancers in 2012 [1]. Survival is poor; 1-year survival has been estimated at 21% and less than 10% of pancreatic cancer patients survive for more than 5 years [2].

Since 1997, gemcitabine therapy has been the standard first-line treatment for patients with unresectable locally advanced or metastatic pancreatic cancer (mPC) [3]. Whereas many phase II studies evaluating combination chemotherapies in patients with advanced pancreatic cancer have shown promising results, most subsequent phase III studies have not shown significantly improved survival [for review see 4]. However, in 2007, the combination of gemcitabine plus erlotinib (GE) was shown to modestly, but statistically significantly, improve survival compared with gemcitabine alone, which was the primary objective of the study [5]. A phase III trial conducted by a French consortium study group in patients with metastatic pancreatic adenocarcinoma and an Eastern Cooperative Oncology Group (ECOG) score of 0–1 found that the combination of 5-FU, folinic acid, oxaliplatin and irinotecan (FOLFIRINOX) was associated with a median increase in overall survival (OS) of 4.3 months compared with gemcitabine [6]. The MPACT study randomised 842 patients with mPC and a Karnofsky Index above 70% to either gemcitabine or gemcitabine plus nab-paclitaxel and reported significantly increased OS (8.5 versus 6.7 months) and progression-free survival (PFS) (5.5 versus 3.7 months) with the combination [7].

In addition, the combination of gemcitabine and capecitabine has shown to be more effective than gemcitabine alone in patients with mPC and a good performance status [8], and a phase II study has shown the triplet combination of gemcitabine–erlotinib–capecitabine (GEC) to be effective and tolerable in this setting [9]. Hence, the aim of the present study was to compare the safety and effectiveness of the first-line treatment with the triple combination of GEC with GE doublet therapy in patients with mPC.

2. Patients and methods

2.1. Study design and patients

This was a phase IIb, open-label, randomised, two-arm, active comparator study. Patients with histologically or cytologically confirmed, measurable, metastatic pancreatic adenocarcinoma, aged ≥18 years and with an ECOG performance status 0–2 were eligible for inclusion in the study. Patients were required to have adequate bone marrow, liver and renal function and to be able to take oral medication.

Exclusion criteria included the history of another primary neoplasm in the 5 years before study entry, clinically significant cardiovascular disease or current infection grade ≥2. Patients with ampullary or pancreatic endocrine tumours, or previously treated with epidermal growth factor receptor inhibitors or capecitabine and those who had received any cancer treatment for metastatic disease were also excluded.

All patients provided written informed consent. The clinical trial protocol was approved by the institutional review board at each site. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2. Randomisation and treatment

Following recruitment, patients were randomised 1:1 to either GE arm or GEC arm. Patients were stratified according to ECOG performance status (0/1 versus 2).

Gemcitabine 1000 mg/m^2 was administered as an iv infusion on days 1, 8 and 15 of a 28-day cycle with erlotinib 100 mg/day continuous oral administration, with the addition of capecitabine 830 mg/m^2 orally twice daily on days 1–21 in the GEC arm. Treatment was administered until disease progression, unacceptable toxicity or withdrawal of consent.

If necessary, protocol-defined dose reductions were performed according to clinical and laboratory parameters; once reduced, the dose could not be increased again unless the dose reduction was in response to rash that subsequently resolved. To continue with treatment, patients were required to meet the following criteria: absolute neutrophil count ≥1.5 × 10^9/L and platelet count ≥100 × 10^9/L; any treatment-related non-haematological toxicity resolved to baseline level or grade <1; diarrhoea recovered to baseline level; rash grade ≤2; creatinine clearance ≥50 mL/min and bilirubin ≤1.5 × upper limit of normal. If the dose of one drug was delayed, all drugs in the combination were delayed. If one drug was discontinued as a result of toxicity, the patient could continue to receive the other components of their combination at the investigator's discretion. Patients whose treatment were withheld for >4 weeks were withdrawn from the study.

2.3. Assessments

Tumour assessment was performed at baseline using abdomen and pelvis computed tomography scan and chest radiography or computed tomography scan. Tumour assessment was repeated at week 8 and every 8 ± 2 weeks thereafter, using the same imaging methods. Medical history and ECOG performance status was assessed on days 1 and 15 of every 28-day cycle; haematology tests were also performed at these visits. Adverse events were also recorded at these visits and graded according to the National Cancer Institute Common Toxicity Criteria version 4.0.

2.4. Statistical analysis

The primary end-point of this study was PFS, defined as the time from inclusion in the study to the date of disease progression or death from any cause, whichever occurred first. Secondary end-points included OS, defined as the time from study entry until death from any cause, RR, duration of response, safety and occurrence of rash in patients treated with erlotinib and relationship of rash to PFS and OS. The intent to treat (ITT) population included all patients randomised to treatment. The per-protocol (PP) population included all subjects in the ITT population who had measurable disease and received any of the study treatments for at least 8 weeks with measurements made at baseline and after 8 weeks of treatment. The safety population comprised all patients who received at least one administration of the study drugs.

Assuming a median survival of 3.75 months in the GE arm and 6 months in the GEC arm (hazard ratio [HR] = 0.63), 112 events were required to achieve 80% power for the log-rank test with a significance level of 0.05. To achieve the required number of events, assuming a recruitment period of 12 months and a follow-up period of 24 months, 59 patients were recruited per group. In terms of OS, an estimated 101 events (112 patients in total) were needed to detect a statistically significant increase in median OS from 6.24 to 10.24 months (HR = 0.61). The log rank test was used for comparison of treatment arms.

All analyses were performed using SAS version 9.3.

3. Results

Between April 2011 and February 2013, 120 patients were recruited at 23 centres in Spain; 60 patients were randomised to the GE arm and 60 to the GEC arm. All patients were eligible for inclusion in the efficacy analyses. Two patients did not receive any treatment; therefore, the safety population comprised 118 patients (Fig. 1).

Patient characteristics for the ITT population are shown in Table 1. For both the ITT and PP populations, the two treatment groups were generally comparable although more patients in the GEC arm had had prior surgical interventions.

3.1. Treatment

The median duration of treatment was 16.5 weeks (range 8–29 weeks; four cycles). Patients in the GE arm received a median dose intensity of 80% (range 33–102%) of the planned gemcitabine dose and 97% (range 43–100%) of the erlotinib dose. Patients in the GEC arm received a median of 68% (range 33–100%) of the planned gemcitabine dose, 87% (range 43–100%) of the erlotinib dose and 72% (range 43–97%) of the planned capecitabine dose.

3.2. Efficacy

The final analysis was performed after 103 events, 52 in the GE arm and 51 in the GEC arm. The median follow-up time was 28.1 months in the GE arm and 23.5 months in the GEC arm. In the ITT population, median PFS was 3.8 months in the GE arm and 4.3 months in the GEC arm (HR 0.83; 95% confidence interval [CI] 0.56–1.23; p = 0.36), whereas median OS was 7.7 months in the GE arm and 6.8 months in the GEC arm (HR 1.03; 95% CI 0.71–1.50; p = 0.87) (Fig. 2). Similar results were observed in the PP population, median PFS was 4.4 months in the GE arm and 4.8 months in the GEC arm (HR 0.81; 95% CI 0.54–1.21; p = 0.29), whereas median OS was 8.1 months in the GE arm and 7.5 months in the GEC arm (HR 1.02; 95% CI 0.69–1.52; p = 0.92).

The response to treatment was similar in both arms in both the ITT and PP populations (Table 2). In the ITT population, partial responses were observed in 11 patients (18%) in the GE arm and in 13 patients (22%) in the GEC arm (p = 0.72). Confirmed partial responses were observed in 8 patients (13%) in the GE arm and 9 patients (15%) in the GEC arm (p = 0.73). The median duration of response was 6.0 months for the GE arm and 6.6 months in the GEC arm (HR 0.62; 95% CI 0.32–1.97; p = 0.62).

A total of 62 patients received subsequent anticancer treatments, 33 (55%) in the GE arm and 29 (50%) in the GEC arm. The most common second-line treatments in the GE arm were oxaliplatin-based chemotherapy (n = 16, 27%) and capecitabine (n = 7, 12%), whereas in the GEC arm this was oxaliplatin-based chemotherapy (n = 13, 22%). A total of 10 patients in the GE arm and three in the GEC arm received third-line treatment and two patients in the GE arm received further lines of treatment.

3.3. Efficacy analysis according to rash

Results for the subgroup analysis of survival according to the presence or absence of rash in the ITT population are shown in Fig. 3 and Table 3. The median OS for patients with rash grade ≥1 was 9.5 months compared with 5.2 months in those with no rash (HR 0.61; 95% CI 0.41–0.89; p = 0.011); median PFS for patients with rash grade ≥1 was 5.5 months compared with 2.1 months for those with no rash (HR 0.40; 95% CI 0.26–0.61; p < 0.0001). While the appearance of rash

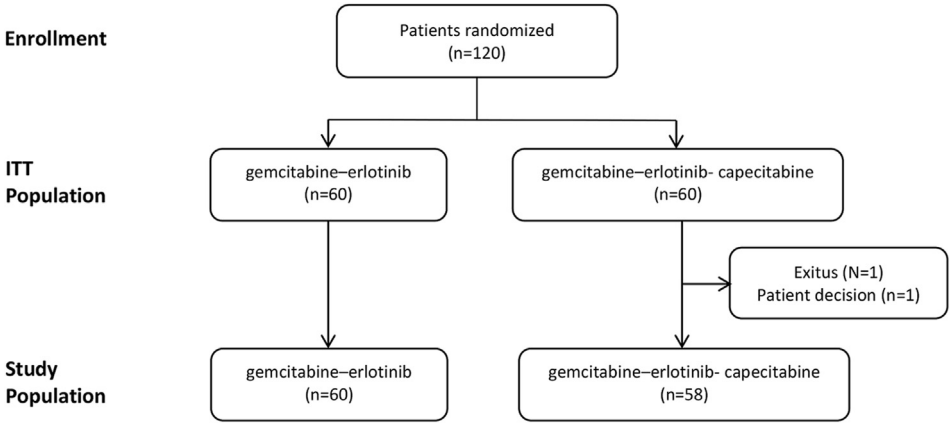

Fig. 1. Consort study flow diagram.

Table 1
Patient characteristics at baseline.

Characteristic	ITT population	
	Gemcitabine–erlotinib (n = 60)	Gemcitabine–erlotinib–capecitabine (n = 60)
Sex, n (%)		
Male	34 (57)	34 (57)
Female	26 (43)	26 (43)
Median age, years (range)	64 (29–78)	62 (31–77)
Median time since diagnosis (range), months	0.6 (0–28)	0.6 (0.7–70.1)
Median no. of metastatic sites at study entry (range)	2.5 (1–9)	3 (1–5)
Sites of metastases, n (%)		
Pancreas	50 (83)	50 (83)
Local lymph	23 (38)	31 (52)
Distant lymph	10 (17)	8 (13)
Liver	43 (72)	50 (83)
Lung	14 (23)	10 (17)
Others	26 (43)	23 (38)
ECOG performance status, n (%)		
0	22 (37)	18 (30)
1	35 (58)	35 (58)
2	3 (5)	6 (10)
Unknown	0	1 (2)
Prior radiotherapy, n (%)	4 (7)	0
Prior surgical procedure, n (%)	17 (28)	30 (50)
Diagnostic	16 (27)	26 (43)
Radical	3 (5)	14 (23)
Palliative	3 (5)	3 (5)
Prior adjuvant systemic chemotherapy, n (%)	3 (5)	0

ECOG, Eastern Cooperative Oncology Group.

was predictive of efficacy (Table 3), the severity of rash as a predictive factor of efficacy was not demonstrated in either treatment arm (Table 3, Fig. 4).

Among patients with rash in the ITT population, median PFS was 5.4 months for GE and 5.9 months for GEC ($p = 0.27$) and median OS was 9.5 months for GE and 10.1 months for GEC ($p = 0.93$). There was no statistically significant difference in median duration of response between the two arms (6.0 months for GE versus 9.1 months for GEC; $p = 0.72$).

Multivariate analysis showed no effect of treatment on efficacy regardless of the presence or severity of rash.

3.4. Safety

Adverse events related to treatment occurring in ≥10% of patients are shown in Table 4. A total of 34 patients (57%) in the GE arm and 42 patients (72%) in the GEC arm had grade ≥3 adverse events related to treatment ($p = 0.07$). Treatment discontinuation due to treatment-related adverse events occurred in eight patients in both the GE arm (13%) and the GEC arm (14%), and one patient in the GE arm died of sepsis that was documented as 'possibly' related to treatment by the investigator. This was the only adverse event related to treatment resulting in death reported.

Haematological toxicities were generally more frequent in the GEC arm. Grade 3–4 neutropenia was more common in the GEC arm (43% versus 17%; $p = 0.001$), although the incidence of febrile neutropenia was similar in both arms (GEC 3% versus GE 3%). Mucositis was also more frequent in the GEC arm (9% versus 0%; $p = 0.03$).

4. Discussion

The results of this phase IIb study by the Spanish TTD Group have shown that triplet chemotherapy with GEC was no more effective than doublet GE in patients with advanced pancreatic cancer. This is the first randomised study to examine the efficacy of triplet therapy containing erlotinib with an erlotinib-based doublet regimen.

Treatment with GEC was less effective than expected based on the results of the previous phase II study by Oh et al [9], who reported a PFS of 6.5 months and an OS of 12.0 months. In our study, the efficacy of GEC appeared to be comparable with that of GE. One possible explanation for this might be a result of the delivered dose intensity of both gemcitabine and erlotinib being lower in the GEC arm, primarily as a result of haematological toxicities. Indeed, in the Korean study by Oh et al [9],

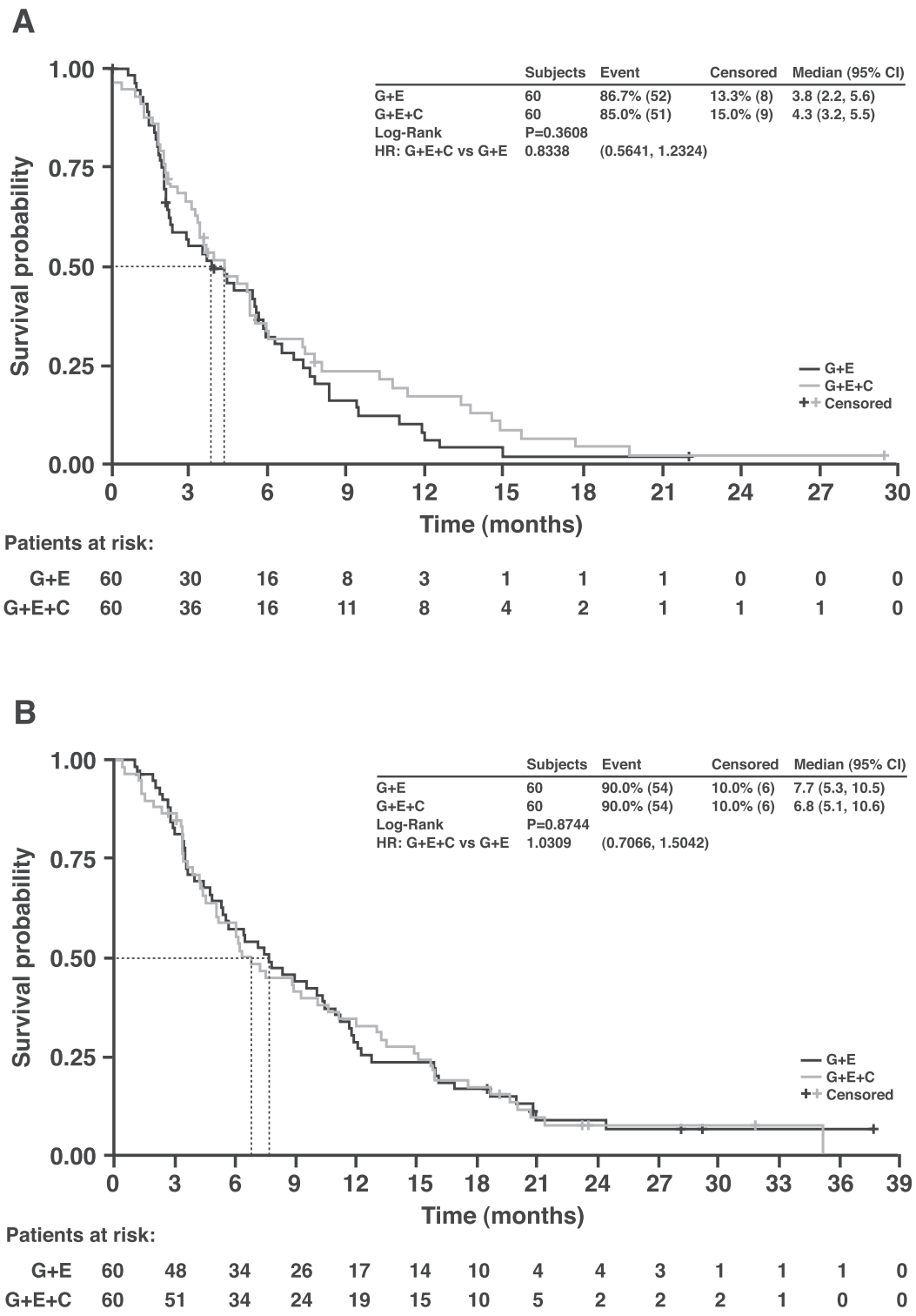

Fig. 2. Progression-free survival (A) and overall survival (B) in the ITT population.

patients appeared able to tolerate a higher dose intensity than in the present study, with patients receiving 89–100% of the planned dose compared with 68–87% of the planned dose in our study. Other studies evaluating the efficacy of the GE doublet in locally advanced cancer/mPC reported PFS values in the range of 3.5–4.5 months and OS values in the range 6.2–9.9 months [5,10–12], which are in line with those found in this study. This would suggest that the patient population being evaluated here is at least similar to that reported in other studies. Indeed, over the past 10–15 years, gemcitabine monotherapy has been compared with numerous combinational chemotherapy arms containing gemcitabine plus platinum derivatives, taxanes and

Table 2
Response to treatment.

Response n (%)	ITT population		PP population	
	Gemcitabine–erlotinib (n = 60)	Gemcitabine–erlotinib–capecitabine (n = 60)	Gemcitabine–erlotinib (n = 54)	Gemcitabine–erlotinib–capecitabine (n = 54)
Partial response	11 (18)	13 (22)	11 (20)	13 (24)
Stable disease	22 (37)	25 (42)	22 (41)	25 (46)
Progressive disease	23 (38)	17 (28)	20 (37)	15 (28)
Not evaluable	4 (7)	5 (8)	1 (2)	1 (2)
Objective response rate (95% CI)	18.3 (9.5–30.4)	21.7 (12.1–34.2)	20.4 (10.6–33.5)	24.1 (13.5–37.6)
Clinical benefit rate (95% CI)	55.0 (41.6–67.9)	65.0 (51.6–76.9)	61.1 (46.9–74.1)	70.4 (56.4–82.0)

Not all responses were confirmed.
PP, per-protocol population; ITT, intent to treat population.

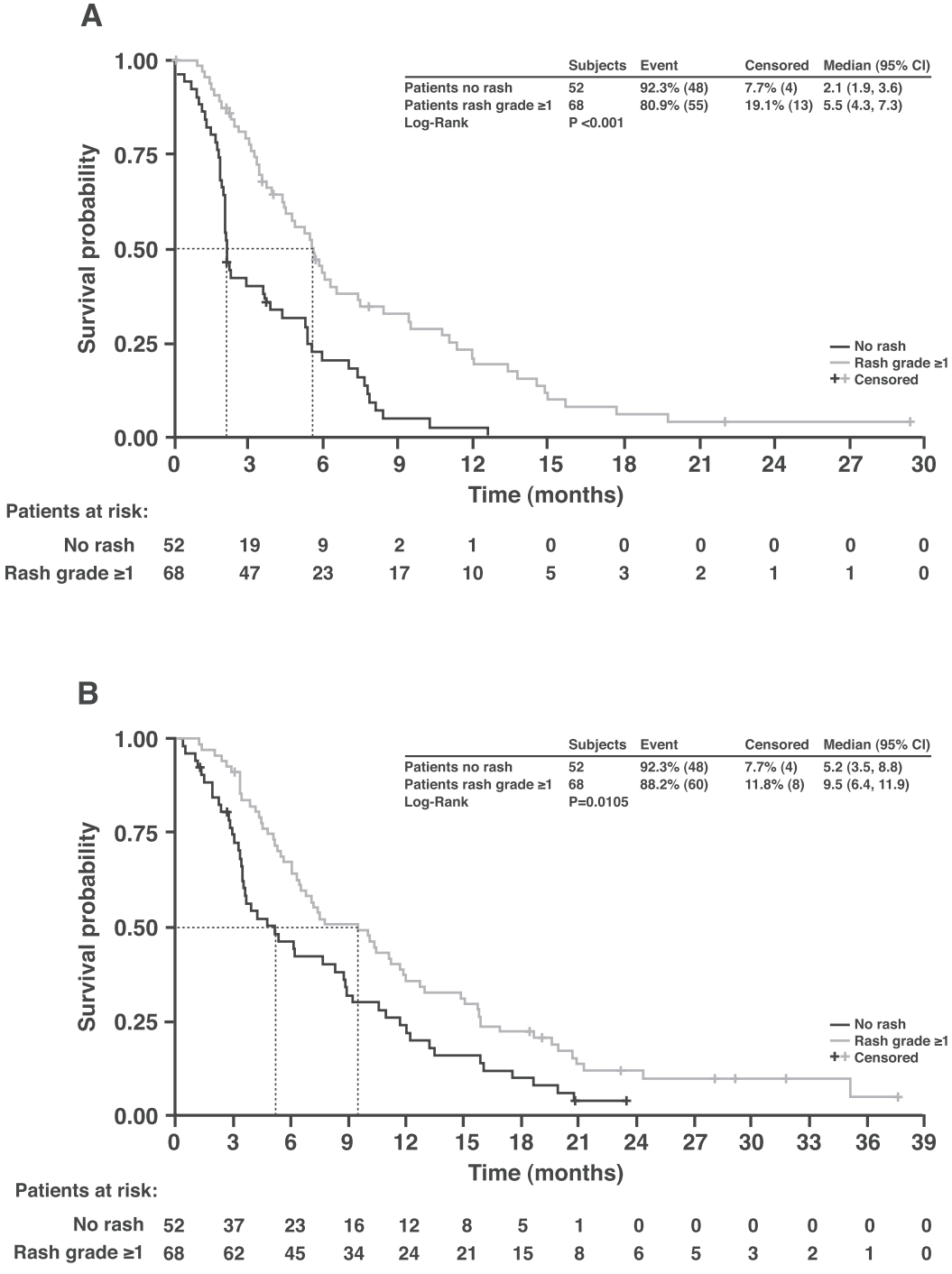

Fig. 3. Survival according to skin rash in the ITT population: A) Progression-free survival; B) overall survival.

Table 3
Survival according to rash in the ITT population.

	All patients				GEC				GE			
	N	Median	HR (95% CI)[a]	P-value	N	Median	HR (95% CI)[a]	P-value	N	Median	HR (95% CI)[a]	P-value
PFS												
No rash	52	2.1			25	2.1			27	2.1		
Rash	68	5.5	0.40 (0.26–0.61)	**<0.0001**	35	5.9	0.34 (0.18–0.62)	**0.0006**	33	5.4	0.52 (0.30–0.90)	**0.0208**
No rash	52	2.1			25	2.1			27	2.1		
Rash grade 1	43	5.4	0.38 (0.24–0.61)[a]	**<0.0001**	25	6.0	0.31 (0.16–0.61)[a]	**0.0006**	18	4.0	0.58 (0.30–1.12)[a]	0.1035
Rash grade ≥2	25	5.6	0.43 (0.25–0.75)[a]	**0.0027**	10	3.9	0.42 (0.17–1.04)[a]	**0.0601**	15	5.8	0.45 (0.23–0.92)[a]	**0.0277**
Rash grade <2	95	3.5			50	4.3			45	2.9		
Rash grade ≥2	25	5.6	0.74 (0.45–1.21)	0.2281	10	3.9	0.88 (0.39–1.97)	0.7504	15	5.8	0.58 (0.30–1.12)	0.1027
OS												
No rash	52	5.2			25	5.3			27	5.3		
Rash	68	9.5	0.61 (0.41–0.89)	**0.0114**	35	10.1	0.57 (0.33–0.99)	**0.0455**	33	9.5	0.65 (0.37–1.12)	0.1173
No rash	52	5.2			25	5.2			27	5.3		
Rash grade 1	43	10.4	0.57 (0.37–0.88)[a]	**0.0119**	25	13.0	0.51 (0.28–0.93)[a]	**0.0280**	18	7.6	0.68 (0.36–1.31)[a]	0.2482
Rash grade ≥2	25	7.1	0.68 (0.41–1.11)[a]	0.1245	10	6.1	0.78 (0.36–1.69)[a]	0.5249	15	10.5	0.61 (0.31–1.20)[a]	0.1498
Rash grade <2	95	7.4			50	8.8			45	7.4		
Rash grade ≥2	25	7.1	0.90 (0.56–1.42)	0.6405	10	6.1	1.12 (0.55–2.31)	0.7528	15	10.5	0.72 (0.38–1.34)	0.2982

PFS, progression-free survival; OS, overall survival; GE, gemcitabine–erlotinib; GEC, gemcitabine–erlotinib–capecitabine.
[a] HR versus No rash; p-values <0.05 highlighted in bold.

molecular targeted agents, with the outcomes of these studies generally being no more positive than gemcitabine monotherapy [for review see 13]. There have been some positive exceptions, GE [5], FOLFIRINOX [6] and gemcitabine + nab-paclitaxel [7].

Another possible explanation for the efficacy, or rather reduced efficacy, observed with the combination of gemcitabine and erlotinib comes from pharmacokinetic studies that have demonstrated that erlotinib inhibits nucleoside transporters in the cell membrane, which affects the entry of gemcitabine into the cells and consequently its efficacy [14–16]. It should be noted, however, that this would be expected to affect both arms similarly.

Perhaps unsurprisingly, with the lower dose intensity reported in this study compared with that of Oh et al [9], the addition of capecitabine to GE was considerably less well tolerated than the GE doublet; more patients receiving triplet therapy experienced neutropenia, thrombocytopenia, anaemia, hand–foot syndrome and diarrhoea. The incidence of grade 3/4 neutropenia was notably higher in GEC patients compared with those receiving GE. Again, the toxicities reported here were more frequent compared with the Korean study [9] but were similar to other published studies [5,17].

Previous studies have shown that the development of skin rash is a predictor of improved survival with erlotinib treatment in patients with non-small cell lung cancer [18] and, more recently, similar observations with erlotinib-based chemotherapy has been seen in patients with pancreatic cancer [5,17,19–21]. These findings are supported by the present study, where the presence of rash was associated with better outcomes for both PFS and OS, compared with no rash, in both treatment groups (and in both the ITT and PP populations). More severe rash, however, did not appear to be associated

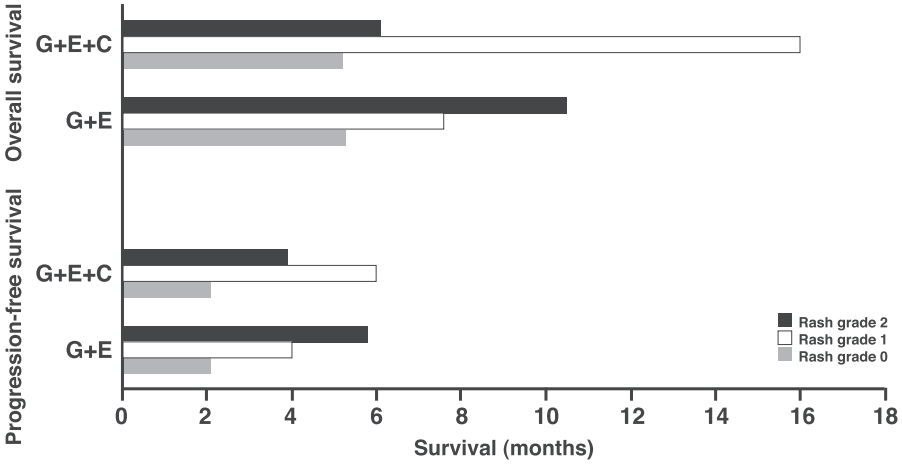

Fig. 4. Survival according to treatment arm and skin toxicity.

Table 4
Adverse events related to treatment occurring in ≥10% of patients (n = 118).

Adverse event, n (%)	Gemcitabine–erlotinib (n = 60)		Gemcitabine–erlotinib–capecitabine (n = 58)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any	56 (93)	34 (57)	56 (97)	42 (72)
Asthenia	32 (53)	6 (10)	37 (64)	6 (10)
Diarrhoea	24 (40)	3 (5)	33 (57)	4 (7)
Neutropenia	20 (33)	10 (17)	36 (62)	25 (43)
Reduced appetite	20 (33)	2 (3)	22 (38)	0
Thrombocytopenia	18 (30)	4 (7)	29 (50)	6 (10)
Nausea	24 (40)	0	23 (40)	0
Anaemia	19 (32)	5 (8)	21 (36)	4 (7)
Rash	29 (48)	3 (5)	27 (47)	2 (3)
Constipation	7 (12)	0	12 (21)	0
Mucositis	11 (8)	0	22 (38)	5 (9)
Vomiting	23 (38)	2 (3)	19 (33)	1 (2)
Pyrexia	10 (17)	0	10 (17)	1 (2)
Elevated GGT	6 (10)	5 (8)	1 (2)	1 (2)
Hand–foot syndrome	2 (3)	0	13 (22)	3 (5)
Peripheral oedema	3 (5)	0	6 (10)	0

ALT, alanine aminotransferase; GGT, gamma glutamyltransferase.

with greater efficacy, although when analysing these sub-populations the number of patients in each group became relatively small.

In conclusion, the present study is the first randomised study to compare a gemcitabine-based triplet regimen with that of a doublet in patients with advanced pancreatic cancer. This study did not show any benefit for the addition of capecitabine to the GE doublet in this population. As seen in previous studies, the appearance of rash was predictive of efficacy, which could be a useful clinical tool to further improve clinical outcome, although the severity of rash as a predictive factor was not demonstrated. Defining the optimal treatment regimen for patients with pancreatic cancer remains a challenge, the solution to which appears to be some way off.

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Conflict of interest statement

F. Rivera has an advisory relationship and has received honoraria and research funding from Roche and Celgene; T. García has received honoraria and travel expenses to medical meetings from Roche; E. Aranda has received honoraria for an advisory role from Amgen, Bayer, Celgene, Merck, Roche and Sanofi; M. Benavides and E. Aranda have received honoraria for advisory roles from Amgen, Bayer, Celgene, Merck, Roche and Sanofi. The other authors have no conflicts of interest.

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