Cancer Chemother Pharmacol (2012) 69:115–123
DOI 10.1007/s00280-011-1680-2

ORIGINAL ARTICLE

A randomized phase II trial of two different 4-drug combinations in advanced pancreatic adenocarcinoma: cisplatin, capecitabine, gemcitabine plus either epirubicin or docetaxel (PEXG or PDXG regimen)

Michele Reni · Stefano Cereda · Alessia Rognone · Carmen Belli · Michele Ghidini · Simonetta Longoni · Clara Fugazza · Sara Rezzonico · Paolo Passoni · Najla Slim · Giampaolo Balzano · Roberto Nicoletti · Stefano Cappio · Claudio Doglioni · Eugenio Villa

Received: 9 February 2011 / Accepted: 11 May 2011 / Published online: 28 May 2011

Abstract
Purpose PEFG regimen (P:cisplatin, E:epirubicin, F:5-fluorouracil, G:gemcitabine) significantly prolonged progression-free (PFS) and overall survival (OS) of patients with advanced pancreatic adenocarcinoma (PA) with respect to standard gemcitabine. The current trial was aimed at assessing whether the replacement of E with docetaxel (D) may improve 6 months PFS (PFS6).
Methods Chemo-naive patients with stage III or metastatic PA received P (30 mg/m^2 day 1 and 15), G (800 mg/m^2 day 1 and 15), and capecitabine (1,250 mg/m^2/day days 1–28, without a break) and were randomized to receive either D at 25–30 mg/m^2 day 1 and 15 (arm A: PDXG regimen) or E at 30 mg/m^2 day 1 and 15 (arm B: PEXG regimen). Cycles were repeated every 28 days for a maximum of 6 months. The Fleming design was used to calculate the sample size on the probability of being PFS6. Assuming P0 = 40% and P1 = 60%, $\alpha = 0.05$ and $\beta = 0.10$; the study was to enroll 52 patients per arm.
Results Between July 2005 and September 2008, 105 patients were enrolled, stratified by stage and randomized. Patients' characteristics were (A/B) the following: median age 61/59, PS >70 92/88%, metastatic disease 66/65%. PFS6 was 58%, and median OS was 11 months in both arms. A partial response was observed in 60/37% of patients. Main per cycle G3-4 toxicity was the following: neutropenia 4/13%, thrombocytopenia 2/4%, anemia 4/4%, and fatigue 6/3%.
Conclusions The inclusion of D instead of E yielded more objective response and less G3-4 neutropenia but did not improve PFS and OS. The present trial confirms the relevant impact on outcome of advanced PA of 4-drug regimens.

Keywords Capecitabine · Chemotherapy · Cisplatin · Docetaxel · Gemcitabine · Pancreatic cancer

A summary of the data included in this manuscript was presented in abstract format at the 45th Annual Meeting of the American Society of Clinical Oncology, Orlando, FL, May 29–June 2, 2009.

M. Reni (✉) · S. Cereda · A. Rognone · C. Belli · M. Ghidini · S. Longoni · C. Fugazza · S. Rezzonico · E. Villa
Department of Oncology, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy
e-mail: reni.michele@hsr.it

P. Passoni · N. Slim
Department of Radiotherapy, San Raffaele Scientific Institute, Milan, Italy

G. Balzano
Department of Surgery, San Raffaele Scientific Institute, Milan, Italy

R. Nicoletti · S. Cappio
Department of Radiology, San Raffaele Scientific Institute, Milan, Italy

C. Doglioni
Department of Pathology, San Raffaele Scientific Institute, Milan, Italy

Introduction

About 80% of patients with pancreatic adenocarcinoma present with unresectable or metastatic disease. In these patients, gemcitabine is widely accepted as the standard first-line therapy [1]. Two surveys, mirroring the Italian clinical practice in the first-line treatment of pancreatic adenocarcinoma, showed that over 60% stage III and

over 70% of stage IV patients received gemcitabine [2, 3].

Most combination regimens failed to improve overall survival (OS) over gemcitabine [4–8]. Platinum- or capecitabine-based doublets reduced the hazard ratio (HR) for death to 0.85–0.91 and 0.83, respectively [8, 9] and a gemcitabine–erlotinib combination to 0.82 [10]. Whether such a modest impact on the outcome should be considered of clinical relevance is object of debate [11].

A PEFG regimen (cisplatin, epirubicin, 5-fluorouracil (5-FU), gemcitabine) showed promising activity in a phase II trial [12]. A randomized phase III trial showed that this regimen was significantly superior to gemcitabine in terms of progression-free survival (PFS; HR 0.51; range 0.33–0.78), overall survival (OS; HR 0.65; range 0.43–0.99), response rate, clinical benefit [13], without impairing quality of life [14]. This regimen has been subsequently modified and rendered more suitable for clinical use both in terms of toxicity and of the number of outpatient accesses, duplicating the outcome observed with the original schedule [15, 16].

The delivery of 5-fluorouracil by continuous infusion has the inconvenience of portable pumps use that hampers patients' compliance. Further, indwelling catheter infections, rupture, or thrombotic complications are often observed. The availability of oral fluoropyrimidines could overcome these problems and improve patients' quality of life. Oral capecitabine 1,250 mg/m^2/day continuously was shown to be equally effective as 5-FU 200 mg/m^2/day in esophago-gastric cancer [17]. Accordingly, oral capecitabine was included in the PEFG regimen instead of 5-FU, originating the PEXG regimen.

Docetaxel showed promising anti-tumor activity in a variety of solid tumors, including pancreatic cancer [18, 19], and synergism with capecitabine [20], gemcitabine [21], and cisplatin [22]. Docetaxel increases intra-cellular activity of thymidine phosphorylase, a key enzyme for the conversion of the oral prodrug capecitabine into 5-FU [23]. An increased cellular integration of gemcitabine–triphosphate, of its interaction with target mRNA, and of apoptotic index has been observed in cell lines of numerous tumor types [24]. Finally, docetaxel enhances the cytotoxicity of cisplatin by down-regulation of multi-drug resistance proteins [25].

Accordingly, the combination of docetaxel with gemcitabine, cisplatin, and capecitabine deserves to be investigated. A randomized phase II trial was designed aiming to explore activity of the PDXG (cisplatin, docetaxel, capecitabine, gemcitabine; Arm A) and of the PEXG (Arm B) regimens in patients with stage III or IV metastatic pancreatic adenocarcinoma [26].

Methods

Patient population

PACT-9 (Pancreatic AdenoCarcinoma Trials-9; ClinicalTrials.gov ID: NCT00966706) is an open, single institution, randomized phase II trial, which was approved by the local ethics committee and was conducted in accordance with the principles of good clinical practice, the ethical principles stated in the current revision of the Declaration of Helsinki, and local legal and regulatory requirements. Written informed consent was obtained from all patients.

Chemotherapy-naive patients aged 18–70 years and Karnofsky Performance Status (KPS) >60 or 71–75 years and KPS >80 with pathologically proven stage III–IV pancreatic adenocarcinoma [26], and at least one measurable lesion according to RECIST [27] criteria were eligible. All stage III patients underwent a three-phase, high-resolution total body computed tomography (CT) scan and endoscopic ultrasound and were assessed by experienced pancreas-dedicated radiologist, surgeon, and gastroenterologist. Tumors were considered unresectable in the presence of thrombosis or encasement >180° or longitudinal involvement >2 cm of one of the major peripancreatic vessels, with the exception of splenic vessels. Patients with prior adjuvant chemotherapy or prior malignancy were ineligible for the study, with the exception of those having had basal cell carcinoma of the skin, carcinoma in situ of the cervix, or other cancers for which the patient had been disease free for at least 5 years. Patients had to have adequate bone marrow (absolute neutrophil count (ANC) ≥1,500 cells/mm^3; platelet count ≥100,000 cells/mm^3; and hemoglobin ≥10 g/dl); kidney (serum creatinine ≤1.5 mg/dl); and liver function (serum total bilirubin ≤1.5 mg/dl and serum transaminases ≤3 times the upper limit of laboratory normal).

Randomization

Patients fulfilling all inclusion criteria were registered by the attending physician at an independent Contract Research Organization (CRO) that performed randomization on a 1:1 basis to either arm A or B. Patients were stratified according to stage of disease (III vs. IV).

Treatment plan

Cycles were repeated every 28 days for a maximum of 6 cycles or until there was evidence of either unacceptable side effects or progression of disease (PD). Cisplatin, capecitabine, and gemcitabine were administered with the same schedule in both arms. Oral capecitabine was

administered at 1,250 mg/m^2/day days 1–28 without a break. Cisplatin was infused at 30 mg/m^2 and gemcitabine at 800 mg/m^2 on days 1 and 15. Patients were randomized to receive either docetaxel at 25 mg/m^2 on days 1 and 15 (arm A: PDXG regimen) or epirubicin at 30 mg/m^2 on days 1 and 15 (arm B: PEXG regimen). After the enrollment of the first 64 patients (32 per arm), based on the favorable toxicity profile and on the intriguing results observed in the PDXG arm, the study was emended to increase docetaxel dose to 30 mg/m^2.

Guidelines for dose reduction and treatment delay were the same in both arms and were made according to the greatest degree of toxicity. Gemcitabine dose was reduced by 25% in case of grade 2 neutropenia and/or grade 1 thrombocytopenia. Treatment was delayed for a maximum of 2 weeks in case of grade $\geq$3 neutropenia, anemia or non-hematological toxicity, or of grade >1 thrombocytopenia. If recovery was not evident within 2 weeks, the patient was discontinued from the study. If the patient had grade 4 neutropenia or thrombocytopenia, capecitabine administration was withheld until recovery to grade 3 level. In case of grade 4 neutropenia or grade $\geq$3 thrombocytopenia, gemcitabine dose was reduced by 25% in the subsequent cycles. If the patient had $\geq$grade 3 non-hematologic toxicity, the treatment was withheld until recovery to grade 1 level and the dose of the drug responsible for toxicity was subsequently reduced by 25%.

At the end of chemotherapy, stage III patients whose disease became resectable were recommended for surgery and were allowed to receive post-operative concomitant chemoradiation, which was also indicated for stage III patients whose disease remained unresectable.

Outcome measures

Toxicity was graded according to the NCI-CTC [28]. CT of the abdomen and chest was made at baseline, every 8 weeks during chemotherapy and then every 3 months or when PD was clinically suspected. All scans were reviewed by one expert radiologist who was blinded to arm assignment. Complete blood, platelet, and differential counts were carried out every 2 weeks, while biochemistry profile and CA 19.9 measure were done on a monthly basis. Biochemical response was assessed according to the previously reported definition [29]. Briefly, non-responders were patients with an increase or a decrease in CA 19.9 <50%, minor responders were patients with a decrease in CA 19.9 between 50 and 89%, and major responders were patients with a decrease in CA 19.9 >89%.

PFS was calculated as the interval between the initiation of treatment and the occurrence of PD or death, and OS was measured from initiation of treatment to date of death or to the last follow-up assessment.

Clinical benefit was not analyzed in the current study because it is not a validated endpoint, has numerous questionable aspects [12], and in our previous experience was assessable in only 43–65% of patients [12, 13].

Sample size and statistical analysis

The primary outcome measure was the probability of being progression free at 6 months (PF6) from treatment start. The maximum PF6 considered of low interest was 40% (P0), and the minimum PF6 considered of interest was 60% (P1). According to the Fleming design, the target enrollment ($\alpha = 0.05$; $\beta = 0.10$) was estimated to be 52 patients per treatment arm. Each treatment arm had to be separately considered to warrant further testing if >26 patients were PF6.

Secondary endpoints were OS, toxicity, radiological, and biochemical response rate.

Final analysis was performed on December 2010, when all living patients had completed at least 26 months of follow-up. The survivor function curves were estimated according to the Kaplan–Meier method. No formal comparison of survival curves between the two arms was planned. Clinical characteristics and toxicities were compared using the χ^2 test or Fisher's exact test for categorical variables, as appropriate. All the probability values were from two-sided tests. Analyses were carried out using the Statistica 4.0 statistical package for Windows (1993 Statsoft; Tulsa; OK).

Funding source

This work was supported in part by a grant from the non-profit organization 'Per la Vita' ('For Life'). Capecitabine and docetaxel were supplied by F. Hoffman-La Roche, Italy and Sanofi-Aventis, Italy, respectively.

Results

Patient population

Between July 2005 and September 2008, 105 patients were enrolled and assigned to either arm A ($N = 53$) or arm B ($N = 52$). All patients received the assigned treatment and are included in the final analysis. Participant flow is summarized in Fig. 1. No patient was lost to follow-up. Main patient characteristics are reported in Table 1. No significant imbalances were observed between the two arms.

Treatment summary

In arm A, 144 cycles (median 6; range 1–6) of PDXG were administered in 32 patients treated before dose amendment

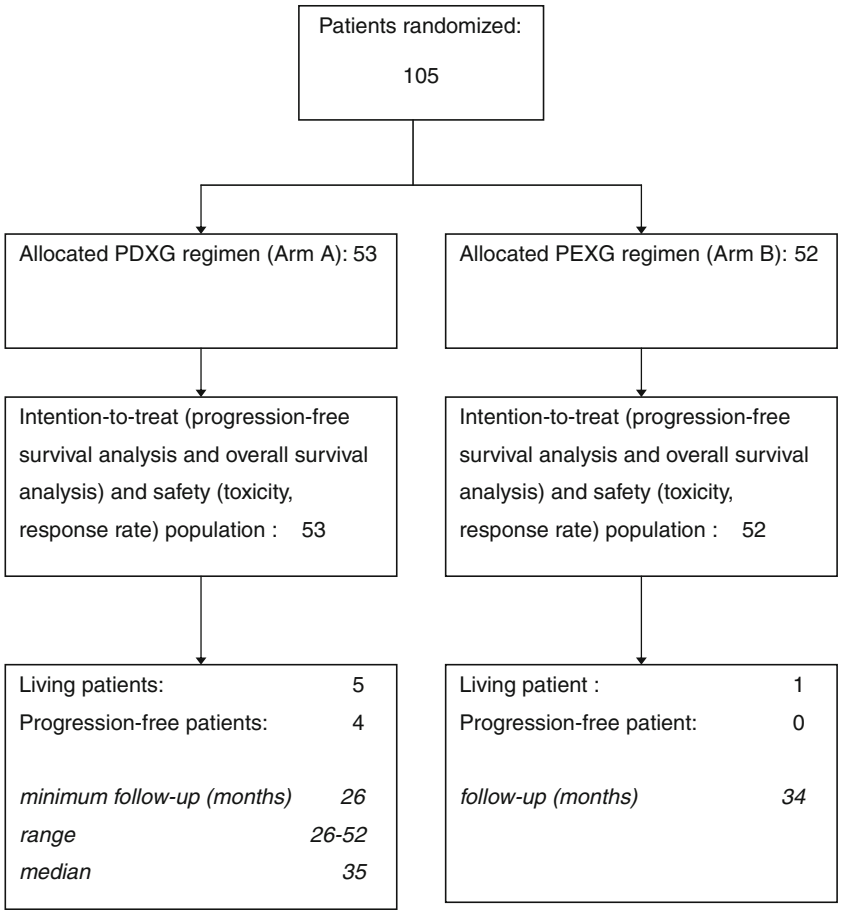

Fig. 1 Flow of study participants

(A1) and 104 cycles (median 6; range 1–6) in 21 patients treated after dose amendment (A2). The median interval between randomization and treatment initiation was 1 day (range 0–7 days). In A1 patients, dose intensity was 91% of the intended dose for cisplatin; 86% for capecitabine; 88% for gemcitabine; and 90% for docetaxel. In A2 patients, dose intensity was 89% of the intended dose for cisplatin; 89% for capecitabine; 85% for gemcitabine; and 85% for docetaxel.

Therapy was discontinued prior to completion in 20 arm A patients (38%; 7 A2): 16 patients (6 A2) had PD; 2 patients refused to continue chemotherapy; one patient discontinued treatment due to toxicity; and one A2 patient due to medical advice for surgery. Total number of cycles received is reported in Table 2.

In arm B, 260 cycles of PEXG regimen were administered (median 6; range 1–6). The median interval between randomization and treatment initiation was 1 day (range 0–11 days). Dose intensity was 85% of the intended dose for cisplatin, 84% for epirubicin, 81% for capecitabine, and 81% for gemcitabine.

Therapy was discontinued before the completion in 18 arm B patients (35%): 14 patients had PD and 4 patients discontinued treatment due to toxicity. Total number of cycles received is reported in Table 2.

Three (17%) arm A patients and one (6%) arm B patient became amenable to resection after the end of chemotherapy and were submitted to surgery with radical intent. Neither margin involvement (R0) nor nodal involvement was observed in 3 arm A patients, while arm B patient had both microscopic involvement (R1) and nodal involvement. ypT0, ypT1, and ypT2 were reported in arm A patients with a survival of 31+, 35 and 51+ months, while ypT3 was observed in arm B patient with a survival of 9.2 months.

Radiotherapy with a biological effective dose equivalent to 54–56 Gy, 2 Gy/day (median 54 Gy) was delivered in 15 fractions with tomotherapy to 12 of 18 (67%) stage III patients in arm A and to 13 of 18 (72%) stage III patients in arm B.

Safety and toxicity

Table 3 summarizes the main side effects observed. One treatment-related death due to grade 5 diarrhea was observed in arm B. Grade 3–4 neutropenia and thrombocytopenia were more common in arm B than in arm A ($P = 0.0005$). Febrile neutropenia was observed in 6 patients in each arm. Growth factors were utilized for

Table 1 Patient characteristics at baseline

Characteristics	Arm A *n* (%)	Arm B *n* (%)
Patients enrolled	53	52
Age (years)		
Median	61	59
Range	38–72	32–74
Gender		
Male	27 (51)	36 (69)
Female	26 (49)	16 (31)
Karnofsky PS		
>70	49 (92)	46 (88)
≤70	4 (8)	6 (12)
Stage		
III	18 (34)	18 (35)
IV	35 (66)	34 (65)
Site of metastases		
Liver	33 (94)	25 (74)
Lymph nodes	19 (54)	13 (38)
Lung	12 (34)	10 (29)
Peritoneum	9 (26)	8 (24)
Median basal CA19.9 (UI/ml)	820	755
Range	1–368,450	7–120,368
>ULN	46 (87)	47 (90)
<ULN	7 (13)	5 (10)
Prior pancreatic surgery	5 (9)	3 (6)

PS performance status, *n* number, *ULN* upper limit of laboratory normal

Table 2 Total number of cycles received

Number of cycles	Arm A $n = 32$ (%)	Arm A1 $n = 21$ (%)	Arm B $n = 52$ (%)
1	3 (10)	0 (0)	4 (8)
2	7 (22)	3 (14)	5 (10)
3	1 (3)	2 (10)	0 (0)
4	2 (6)	2 (10)	5 (10)
5	0 (0)	0 (0)	4 (8)
6	19 (59)	14 (67)	34 (65)

n number of patients, *A1* patients treated after dose amendment

3 days in 1 PDXG cycle and in 8 PEXG cycles. Three and two patients in arm A and B, respectively, developed non-neutropenic infections, while 2 patients in arm B developed a neutropenic infection. Hospitalization was necessary in 9 arm A patients and in 10 arm B patients. In two arm A patients and in four arm B patients, the serious adverse event was attributed to treatment-related infective complications in 5 cases and to grade 5 diarrhea in one case. Disease progression was the cause of hospitalization in four patients per arm. In two arm A and in three arm B patients, hospitalization was due to cardiovascular events (angina pectoris, transient ischemic attack, cerebral vascular accident, and two cases of pulmonary embolus) and was attributed to a combination of cancer and protocol treatment complications.

Red cell transfusion was used in 16 arm A cycles and in 7 arm B cycles. Erythropoietin was administered to 8 arm A patients and to 13 arm B patients. Platelet transfusion was used in 1 arm A patient. There was no significant difference in terms of toxicity between A1 and A2 patients (data not shown).

Efficacy and activity analyses

A summary of activity analyses is reported in Table 4. One hundred and one patients had PD. Four arm A patients were progression free at 27–50 months. Thirty-one patients in arm A and 30 patients in arm B were progression free at 6 months from enrollment (PFS-6 58% in both arms; 95% confidence interval: 45–71%; Fig. 2). A summary of survival analyses is reported in Table 5. The median PFS was 7.4 months (interquartile range: 3.5–11.7 months) in arm A and 7.6 months (interquartile range: 4.2–10.0 months) in arm B.

Ninety-nine patients died of disease progression or of treatment-related complications. Five arm A patients were alive at a median of 35 months (range 26–51 months). One arm B patient was alive at 34 months (Fig. 3).

There was no significant difference in terms of activity and efficacy between A1 and A2 patients treated (data not shown).

Salvage therapy

The median interval between progression and death was 4.0 months in arm A and 3.5 months in arm B. Twenty-three (47%) arm A patients and 30 (58%) arm B patients received a second-line therapy based on investigator choice at time of progression. In this subset of patients submitted to salvage treatment, the median interval between progression and death was 7.2 months in arm A and 5.8 months in arm B.

Discussion

This single-center, randomized phase II trial showed that both the PDXG and the PEXG regimen fulfilled the study hypothesis, yielding a PFS6 of 58%. The choice of PFS as the primary endpoint is appropriate for activity assessment in the context of a phase II study. As pancreatic cancer progression is inevitably followed by morbidity and, due to the absence of active salvage treatments, by death,

Table 3 Treatment-related toxicity per cycle

Toxicity	Arm A			Arm B		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Granulocytes	60 (24%)	9 (4%)	1 (<1%)	85 (33%)	29 (11%)	4 (2%)
Platelets	53 (21%)	1 (<1%)	5 (2%)	85 (33%)	8 (3%)	2 (1%)
Hemoglobin	114 (46%)	10 (4%)	0	140 (54%)	9 (4%)	0
Stomatitis	19 (8%)	0	0	14 (5%)	3 (1%)	0
Nausea	70 (28%)	1 (<1%)	0	63 (25%)	6 (2%)	0
Vomiting	19 (8%)	0	2 (1%)	42 (16%)	2 (1%)	0
Diarrhea	33 (13%)	3 (1%)	1 (<1%)	29 (11%)	3 (1%)	0
Fatigue	60 (24%)	15 (6%)	0	61 (24%)	8 (3%)	0
Hand–foot syndrome	40 (16%)	4 (2%)	0	51 (20%)	11 (4%)	0
Fever	23 (9%)	1 (<1%)	0	14 (15%)	1 (<1%)	0
Febrile neutropenia	5 (2%)	1 (<1%)	0	6 (2%)	0	0
Non-neutropenic infection	0	3 (1%)	0	0	1 (<1%)	0

Data of toxicity for 2 cycles in arm A and for 3 cycles in arm B are lacking

One arm B patients died due to grade 5 diarrhea

Table 4 Activity analyses summary

	Arm A			Arm B		
	All $n = 53$	Stage III $n = 18$	Stage IV $n = 35$	All $n = 52$	Stage III $n = 18$	Stage IV $n = 34$
Radiological response						
Complete response	1 (2%)	1 (6%)	0	2 (4%)	0	2 (6%)
Partial response	31 (58%)	11 (61%)	20 (57%)	17 (33%)	6 (33%)	11 (32%)
Stable disease	10 (19%)	4 (22%)	6 (17%)	24 (46%)	10 (56%)	14 (41%)
Progressive disease	11 (21%)	2 (11%)	9 (26%)	8 (15%)	2 (11%)	6 (18%)
Not assessable	0	0	0	1 (2%)	0	1 (3%)
	$n = 46$	$n = 16$	$n = 30$	$n = 47$	$n = 16$	$n = 31$
Biochemical response						
Major response	19 (41%)	8 (50%)	11 (37%)	15 (32%)	4 (25%)	11 (35%)
Minor response	18 (39%)	5 (31%)	13 (43%)	15 (32%)	6 (38%)	9 (29%)
Non-responders	6 (13%)	2 (13%)	4 (13%)	15 (32%)	6 (38%)	9 (29%)
Not assessable	3 (7%)	1 (6%)	2 (7%)	2 (4%)	0	2 (6%)

prolonging PFS should be considered of benefit. In the current trial, the timing of tumor assessment was identical in the two arms and a radiologist blinded to treatment arm reviewed CT scans, thus avoiding the potential impact on PFS of investigator-related biases. PFS-6 figures of this trial were consistent with four prior series treated with 4-drug regimens, in which PFS was 42–69% [12, 13, 15, 16].

Overall, baseline characteristics of the two arms appear to be well balanced, and no significant difference with regard to consolidation radiotherapy use in stage III disease or impact of salvage therapy on the outcome was observed.

OS, with over 40% of patients alive at 1 year and 16–24% at 2 years, reproduced previously reported figures as well [12, 13, 15, 16].

Altogether, the outcome of the present trial is remarkable and unusual in stage III–IV pancreatic cancer when treated with single agent or doublets, including prior experience with docetaxel/gemcitabine [30–32]. Comparisons across different trials are always troublesome to perform and remain speculative, due to differences and imbalances in selection criteria and prognostic factors. In other phase II or III trials in pancreatic adenocarcinoma [4–8, 10, 30–37], the percentage of patients with KPS >70

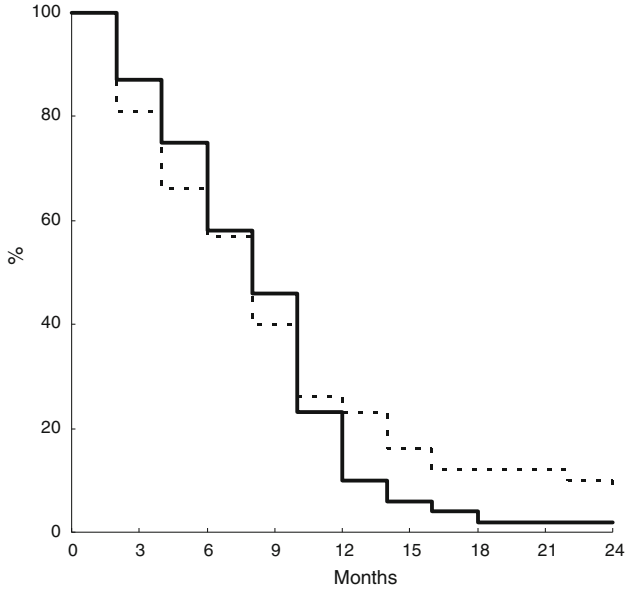

Fig. 2 Progression-free survival curves. *Dotted line* PDXG arm (cisplatin, docetaxel, capecitabine, gemcitabine) and *Solid line* PEXG arm (cisplatin, epirubicin, capecitabine, gemcitabine)

(74–100%) or with metastatic disease (68–100%) were comparable to our series. Conversely, the inclusion in some of these trials of patients with stage I–II disease [4, 8, 10] may have positively influenced the outcome. Overall, similarities among main known prognostic variables do suggest that the population enrolled in our trial was not better selected than in other trials.

Noteworthy, two surveys mirroring the Italian clinical practice in the therapeutic management of advanced pancreatic adenocarcinoma suggested that 4-drug combinations may yield a better outcome when compared with other regimens [2, 3]. In 650 stage III patients, median survival was 9.5 months with gemcitabine, 13.3 months with gemcitabine/platinum compound doublets, and 16.2 months with 4-drug combinations [2]. In 943 stage IV patients, median survival was 5.1 months with gemcitabine, 7.4 months with gemcitabine/platinum compound doublets, and 9.1 months with 4-drug combinations [2]. Interestingly, other phase III trials showed that drug combination including more than two agents may improve OS when compared with gemcitabine [36, 37]. In particular, the combination of 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin improved PFS (6.4 months vs. 3.3 months; $P < 0.0001$) and OS (11.1 months vs. 6.8 months; 1-y OS 48.4% versus 20.6% $P < 0.0001$), compared with gemcitabine, in metastatic patients with normal bilirubin and good PS [36]. The figures of this phase III trial are difficult to interpret, and results generalization should be made with caution due to the selection of enrolled patients, which is evident on the basis of the better than expected standard arm outcome, and due to the remarkable grade 3–4 toxicity, which is barely acceptable in the context of a palliative therapy (neutropenia 46%; thrombocytopenia 9%; anemia 8%; fatigue 23%; vomiting 15%; diarrhea 13%; peripheral neuropathy 9%;). Altogether, these findings endorse the rational for further exploring the use of more than 2 drugs as upfront treatment in pancreatic adenocarcinoma.

An exploratory analysis of patients with stage III disease showed that patients treated by PDXG had double chance to achieve a radiological (67% vs. 33%) or a major biochemical response (50% vs. 25%) when compared with patients receiving PEXG. Furthermore, 2-year OS was 43% in arm A patients and 16% in arm B patients. Due to the small sample size of this subpopulation, whether this difference suggests a different role of docetaxel in stage III or occurs by chance may be object of speculation.

In conclusion, the present trial confirms the relevant impact of 4-drug regimens on the outcome of advanced pancreatic adenocarcinoma. The use of capecitabine instead of 5-fluorouracil did not modify the results. The inclusion of docetaxel instead of epirubicin yielded less G3-4 neutropenia and more objective and biochemical responses, particularly in stage III disease, but did not improve PFS or OS.

Table 5 Survival analyses summary

	Arm A			Arm B		
	All $n = 53$	Stage III $n = 18$	Stage IV $n = 35$	All $n = 52$	Stage III $n = 18$	Stage IV $n = 34$
Progression-free survival						
Median (months)	7.4	9.9	5.8	7.6	9.5	6.5
6 month (%)	58	83	46	58	72	59
12 month (%)	23	33	17	13	22	9
Overall survival						
Median (months)	10.7	19.0	9.0	11.0	12.6	10.6
1 year (%)	43	78	26	46	56	41
2 year (%)	24	43	13	16	13	17

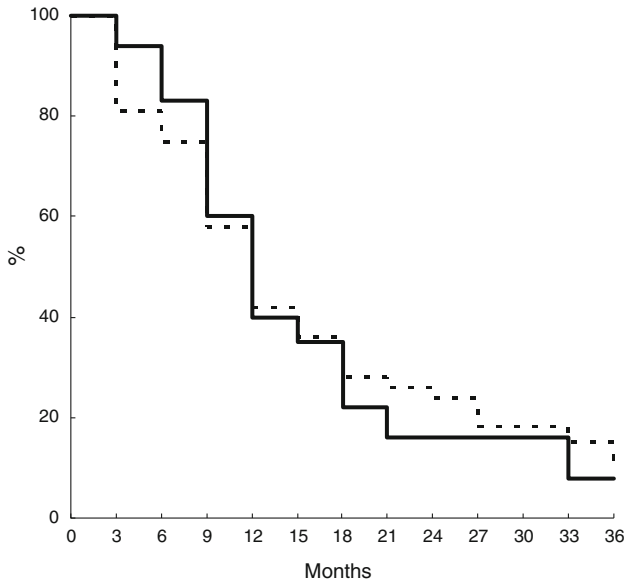

Fig. 3 Overall survival curves. *Dotted line* PDXG arm (cisplatin, docetaxel, capecitabine, gemcitabine) and *Solid line* PEXG arm (cisplatin, epirubicin, capecitabine, gemcitabine)

Both regimens were manageable on an outpatient basis with a mild toxicity profile and warrant further investigation. We are further investigating the PEXG regimen in resectable pancreatic cancer randomizing patients to receive either 6 months of adjuvant gemcitabine or 6 months of adjuvant 4-drug regimens or a perioperative treatment with the 4-drug regimens for 3 months before and 3 months after surgery (NCT01150630). We are also assessing the therapeutic activity of PEXG in combination with metformin in patients with metastatic pancreatic adenocarcinoma (NCT01167738). Finally, we plan to explore the role of the PDXG regimen in stage III pancreatic cancer.

Acknowledgments This work was supported in part by a grant from the non-profit organization 'Per la Vita' ('For Life'). Capecitabine and docetaxel were supplied gratuitously by F. Hoffman-La Roche, Italy and Sanofi-Aventis, Italy, respectively.

Conflict of interest No author has conflict of interest.

References

1. Cascinu S, Falconi M, Valentini V et al (2010) Pancreatic cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 21:55–58
2. Reni M, Sartori N, Mambrini A et al (2010) An Italian study on treatment trends and outcomes of patients with stage III pancreatic adenocarcinoma in the gemcitabine era: is it time to change? Anticancer Drug 21:459–464
3. Reni M, Pasetto LM, Passardi A et al (2011) Treatment trends in metastatic pancreatic cancer patients: is it time to change? Dig Liv Dis 43:225–230
4. Berlin JD, Catalano P, Thomas JP et al (2002) Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: eastern cooperative oncology group trial E2297. J Clin Oncol 20:3270–3275
5. Herrmann R, Bodoky G, Ruhstaller T et al (2007) Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss group for clinical cancer research and the Central European cooperative oncology group. J Clin Oncol 25:2212–2217
6. Cunningham D, Chau I, Stocken C et al (2009) Phase III randomised comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27:5513–5518
7. Poplin E, Feng Y, Berlin J et al (2009) Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30 min infusion) in patients with pancreatic carcinoma E6201: a trial of the eastern cooperative oncology group. J Clin Oncol 27:3778–3785
8. Colucci G, Labianca R, Di Costanzo F et al (2010) Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. J Clin Oncol 28:1645–1651
9. Sultana A, Tudur Smith C, Cunningham D et al (2008) Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer. J Clin Oncol 25:2607–2615
10. Moore MJ, Goldstein D, Hamm J et al (2007) Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the national cancer institute of Canada clinical trials group. J Clin Oncol 25:1960–1966
11. Sobrero A, Bruzzi P (2009) Incremental advance or seismic shift? The need to raise the bar of efficacy for drug approval. J Clin Oncol 27:5868–5873
12. Reni M, Passoni P, Panucci MG et al (2001) Definitive results of phase II trial of cisplatin, epirubicin, continuous-infusion fluorouracil, and gemcitabine in stage IV pancreatic adenocarcinoma. J Clin Oncol 19:2679–2686
13. Reni M, Cordio S, Milandri C et al (2005) Gemcitabine versus cisplatin, epirubicin, 5-fluorouracil, gemcitabine in advanced pancreatic cancer: a phase III trial. Lancet Oncol 6:369–376
14. Reni M, Bonetto E, Cordio S et al (2006) Quality of life assessment in advanced pancreatic adenocarcinoma: results from a phase III randomized trial. Pancreatology 6:454–463
15. Reni M, Cereda S, Bonetto E et al (2007) Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma: a dose-finding study. Cancer Invest 25:594–598
16. Reni M, Cereda S, Bonetto E et al (2007) Dose-intense PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) in advanced pancreatic adenocarcinoma. Cancer Chemother Pharmacol 59:361–367
17. Cunningham D, Starling N, Rao S et al (2008) Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 358:36–46
18. Lenzi R, Yalcin S, Evans DB et al (2002) Phase II study of docetaxel in patients with pancreatic cancer previously untreated with cytotoxic chemotherapy. Cancer Invest 20:464–472
19. Androulakis N, Kourosis C, Dimopoulos MA et al (1999) Treatment of pancreatic cancer with docetaxel and granulocyte colony-stimulating factor: a multicenter phase II study. J Clin Oncol 17:1779–1785
20. Venturini M, Durando A, Garrone O et al (2003) Capecitabine in combination with docetaxel and epirubicin in patients with

previously untreated, advanced breast carcinoma. Cancer 97:1174–1180
21. Alexopoulos A, Karamouzis MV, Rigatos G et al (2004) In vivo synergism between docetaxel and gemcitabine in patients with metastatic breast cancer: general concepts and future perspectives. Semin Oncol 2:25–30
22. Rigas JR (2004) Taxane-platinum combinations in advanced non-small cell lung cancer: a review. Oncologist 9:16–23
23. Sawada N, Ishikawa T, Fukase Y et al (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by Taxol/Taxotere in human cancer xenografts. Clin Cancer Res 4:1013–1019
24. Ricotti L, Tesei A, De Paola F et al (2003) In vitro schedule-dependent interaction between docetaxel and gemcitabine in human gastric cancer cell lines. Clin Cancer Res 9:900–905
25. Maeda S, Sugiura T, Saikawa Y et al (2004) Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. Cancer Sci 95:679–684
26. Greene FL, Page D, Fleming ID et al (eds) (2002) Exocrine pancreas. In: AJCC cancer staging manual, 6th edn. Springer, New York, pp 157–164
27. Eisenhauer EA, Therasse P, Bogaerts J et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247
28. Ajani JA, Welch SR, Raber MN et al (1990) Comprehensive criteria for assessing therapy-induced toxicity. Cancer Invest 8:147–159
29. Reni M, Cereda S, Balzano G et al (2009) Carbohydrate antigen (CA)19–9 change during chemotherapy for advanced pancreatic adenocarcinoma. Cancer 115:2630–2639
30. Kulke MH, Tempero MA, Niedzwiecki D et al (2009) Randomized phase II study of gemcitabine administered at a fixed dose rate or in combination with Cisplatin, Docetaxel, or Irinotecan in patients with metastatic pancreatic cancer: CALGB 89904. J Clin Oncol 27:5506–5512
31. Lutz MP, Van Cutsem E, Wagener T et al (2005) Docetaxel Plus Gemcitabine or Docetaxel Plus Cisplatin in advanced pancreatic carcinoma: randomized phase II study 40984 of the European organisation for research and treatment of cancer gastrointestinal group. J Clin Oncol 23:9250–9256
32. Cascinu S, Gasparini G, Catalano V et al (1999) A phase I–II study of gemcitabine and docetaxel in advanced pancreatic cancer: a report from the Italian group for the study of digestive tract cancer (GISCAD). Ann Oncol 10:1377–1379
33. Fine RL, Fogelman DR, Schreibman SM et al (2008) The gemcitabine, docetaxel, and capecitabine (GTX) regimen for metastatic pancreatic cancer: a retrospective analysis. Cancer Chemother Pharmacol 61:167–175
34. Hess V, Pratsch S, Potthast S et al (2010) Combining gemcitabine, oxaliplatin and capecitabine (GEMOXEL) for patients with advanced pancreatic carcinoma (APC): a phase I/II trial. Ann Oncol 21:2390–2395
35. Boeck S, Hoehler T, Seipelt G et al (2008) Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. Ann Oncol 19:340–347
36. Conroy T, Desseigne F, Ychou M et al (2010) Randomized phase III trial comparing FOLFIRINOX (F: 5FU/leucovorin [LV], irinotecan [I], and oxaliplatin [O]) versus gemcitabine (G) as first-line treatment for metastatic pancreatic adenocarcinoma (MPA): Preplanned interim analysis results of the PRODIGE 4/ACCORD 11 trial. Proc Am Soc Clin Oncol 28:abstr 4010
37. Cantore M, Fiorentini G, Luppi G et al (2004) Gemcitabine versus FLEC regimen given intra-arterially to patients with unresectable pancreatic cancer: a prospective randomized phase III trial of the Italian society for integrated locoregional therapy in oncology. J Chemother 16:34–39