FULL PAPER

BJC

British Journal of Cancer (2016) 115, 290–296 | doi: 10.1038/bjc.2016.209

Keywords: pancreas; PAXG; chemotherapy; *nab*-paclitaxel

Phase 1B trial of *Nab*-paclitaxel plus gemcitabine, capecitabine, and cisplatin (PAXG regimen) in patients with unresectable or borderline resectable pancreatic adenocarcinoma

Michele Reni*[,1], Gianpaolo Balzano[2], Silvia Zanon[1], Paolo Passoni[3], Roberto Nicoletti[4], Paolo Giorgio Arcidiacono[5], Gino Pepe[6], Claudio Doglioni[7], Clara Fugazza[1], Domenica Ceraulo[1], Massimo Falconi[2] and Luca Gianni[1]

[1]*Department of Medical Oncology, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy;* [2]*Department of Surgery, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy;* [3]*Department of Radiotherapy, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy;* [4]*Department of Radiology, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy;* [5]*Department of Gastroenterology, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy;* [6]*Nuclear Medicine Unit, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy and* [7]*Pathology Unit, San Raffaele Scientific Institute, via Olgettina 60, 20132 Milan, Italy*

Background: *Nab*-paclitaxel–gemcitabine combination significantly improved overall survival over gemcitabine in metastatic pancreatic adenocarcinoma. A phase 1b trial was performed (ClinicalTrials.gov number, NCT01730222) to determine the recommended phase 2 dose (RP2D) of *nab*-paclitaxel in combination with cisplatin, capecitabine, and gemcitabine at fixed dose (800, 30, and 1250 mg m^{-2} every 2 weeks, respectively; PAXG regimen).

Methods: *Nab*-paclitaxel doses were escalated from 100 (level one) to 125 (level two) and 150 mg m^{-2} (level three) every 2 weeks in cohorts of 3–6 patients with pathologically confirmed unresectable or borderline resectable pancreatic adenocarcinoma.

Results: Between Dec 2012 and Apr 2014, 24 patients were enroled (3 at level one, 5 at level two, 16 at level three) and received 117 cycles of PAXG. No dose-limiting toxicity occurred and level three was the RP2D. At this dose, *nab*-paclitaxel dose-intensity was 91%. Worse per patient grade 3/4 toxicity were neutropenia 25/31%; fatigue 19%; anaemia and hand-foot syndrome 12%, nausea 6%, and febrile neutropenia 6%. A partial response (PR) was observed in 16 (67%) and stable disease (SD) in 8 patients (33%). Among 21 patients with a baseline positive positron emission tomography (PET) scan, a complete metabolic response was observed in 9 (43%), PR in 10 (48%), SD in 2. CA19-9 decreased by $\geqslant$49% in all the 19 patients with elevated basal value. Six patients were resected after chemotherapy. Progression-free survival at 6 months (PFS-6) was 96%.

Conclusions: The RP2D of *nab*-paclitaxel in the PAXG regimen was 150 mg m^{-2} every 2 weeks. The preliminary results are promising and warrant further exploration.

*Correspondence: Dr M Reni; E-mail: reni.michele@hsr.it

Received 22 February 2016; revised 23 April 2016; accepted 13 June 2016; published online 12 July 2016

© 2016 Cancer Research UK. All rights reserved 0007 – 0920/16

Pancreatic adenocarcinoma is a rare disease, but is the seventh leading cause of cancer death (GLOBOCAN, 2015). Only 15–20% of patients present with resectable disease, whereas the majority of patients have metastatic disease at diagnosis, and nearly one-third have involvement of regional main vessels.

Randomised trials in locally advanced or borderline disease have been often prematurely interrupted for poor accrual (Chauffert *et al*, 2008; Loehrer *et al*, 2011); thus the results have limited statistical strength. Therefore, standard of care for this stage of disease is still controversial.

Currently, chemoradiation and chemotherapy alone, or followed by chemoradiation, are regarded both as acceptable treatment options. Prospective trials, including patients with both locally advanced and metastatic disease treated with combination regimens failed to show any OS improvement over gemcitabine (Cunningham *et al*, 2009; Poplin *et al*, 2009; Colucci *et al*, 2010), with the notable exception of the PEFG regimen (cisplatin, epirubicin, 5-fluorouracil (5-FU), gemcitabine) that showed a significant progression-free survival (PFS) and OS improvement compared to gemcitabine monotherapy (Reni *et al*, 2005). PEFG was modified by substituting oral capecitabine for 5-FU, originating the PEXG regimen (Reni *et al*, 2012). The subsequent inclusion of docetaxel instead of epirubicin (PDXG regimen) reduced grade 3 and 4 neutropenia and improved radiological and biochemical responses, particularly in locally advanced disease (Reni *et al*, 2012). These results might be explained by the well-known synergism of taxanes with fluoropyrimidines increasing intratumour conversion of capecitabine into 5-FU through the promotion of intra-cellular activity of thymidine phosphorylase (Sawada *et al*, 1998). Furthermore, taxanes reduce multi-drug resistance proteins favoring cisplatin cytotoxicity (Maeda *et al*, 2004). These data have been further enriched by the findings of a significantly better outcome of stage 4 patients treated with *nab*-paclitaxel and gemcitabine compared with those receiving gemcitabine alone in a phase 3 trial (Von Hoff *et al*, 2013).

On the basis of this rational, a phase 1b trial was designed to determine the recommended phase 2 dose (RP2D) of *nab*-paclitaxel in combination with cisplatin, capecitabine, and gemcitabine (PAXG regimen).

MATERIALS AND METHODS

Chemo-naive patients with 18–75 years, pathologic diagnosis of unresectable or borderline resectable pancreatic adenocarcinoma, without distant metastases and a Karnofsky Performance Status (KPS) $\geqslant 70$ were eligible for the study. The study was conducted at a single institution with a high-volume pancreatic surgery unit (Balzano *et al*, 2008). Tumours were considered unresectable or borderline resectable on the basis of the National Comprehensive Cancer Network (NCCN) definition (Tempero *et al*, 2012). The assignment of tumours to the unresectable or borderline resectable category was jointly performed by a dedicated radiologist (RN) and an experienced pancreatic surgeon (GB). Patients were required to have adequate bone marrow (leucocytes $\geqslant 3500\,mm^{-3}$, absolute neutrophil count $\geqslant 1500\,mm^{-3}$; platelet count $\geqslant 100\,000\,mm^{-3}$; haemoglobin $\geqslant 10\,g\,dl^{-1}$), liver (total bilirubin $\leqslant 2\,mg\,dl^{-1}$; aspartate aminotransferase and alanine aminotransferase $\leqslant 3\times$ upper limit of normal) and kidney function (serum creatinine $\leqslant 1.5\,mg\,dl^{-1}$) and the ability to swallow and absorb oral medications. Prior therapy for their cancer diagnosis, lactation or a positive pregnancy test, clinically significant cardiac disease, concurrent treatment with other experimental drugs, previous or concurrent malignancies at other sites with the exception of surgically cured carcinoma *in situ* of the cervix and basal or squamous cell carcinoma of the skin, and of other neoplasms without evidence of disease at least from 5 years, history of interstitial lung disease, of connective tissue disorders, or of psychiatric disabilities were all exclusion criteria. Written informed consent was obtained from all patients, and the study was approved by the Health Superior Institute and by the institutional Ethics Committee.

The trial was a single-arm phase 1 study to design a new treatment regimen. The primary endpoint was to determine the RP2D of *nab*-paclitaxel when used in combination with cisplatin, capecitabine, and gemcitabine (PAXG regimen). Secondary endpoints were OS, PFS, PFS at 6 months (PFS-6), response rate as defined by RECIST (Response Evaluation Criteria in Solid Tumours), carcinoma antigen 19-9 (CA19-9) response, and resectability rate. A standard $3+3$ dose-escalation schema was used with preplanned cohort expansion at the maximum tolerated dose (MTD). Each treatment cycle consisted of a 28-day period with intravenous cisplatin administered at $30\,mg\,m^{-2}$ on days 1 and 15, intravenous *nab*-paclitaxel on days 1 and 15, oral capecitabine at $1250\,mg\,m^{-2}$ on days 1 through 28, intravenous gemcitabine at $800\,mg\,m^{-2}$ on days 1 and 15 at a fixed-rate infusion ($10\,mg\,m^{-2}\,min^{-1}$). The dose of cisplatin, capecitabine, and gemcitabine was maintained fixed at any dose level cohort, whereas *nab*-paclitaxel dose was escalated from the starting dose level (DL1: $100\,mg\,m^{-2}$) to DL2 ($125\,mg\,m^{-2}$), and DL3 ($150\,mg\,m^{-2}$). Dose-limiting toxicity (DLT) was defined as any of the following events attributable to the administered study drugs during the initial 4 weeks of treatment: grade $\geqslant 4$ neutropenia lasting 7 days or more; grade $\geqslant 3$ febrile neutropenia or fever of unknown origin $\geqslant 38.5\,^{\circ}C$; grade 4 thrombocytopenia; grade 3 thrombocytopenia which required transfusions; grade $\geqslant 3$ nausea or vomiting; grade $\geqslant 3$ diarrhoea; any grade $\geqslant 2$ neurological toxicity; any grade $\geqslant 3$ toxicities or representing a shift by two grades from baseline (in case of abnormal baseline); failure to recover to grade $\leqslant 1$ toxicity (except alopecia) or to baseline values after delaying the initiation of next cycle by >2 weeks. Treatment was continued until documented progressive disease, unacceptable toxicity, patient's refusal, medical decision or a maximum of six cycles whichever happened before. Surgery and/or chemoradiation after the end of chemotherapy were allowed but were not part of the phase Ib protocol and AE/activity reporting applies to chemotherapy alone.

Pretreatment evaluation with review of inclusion/exclusion criteria, medical and medication history, physical examination, surgical assessment for recectability, KPS assessment, laboratory tests and CA19-9 was performed for all patients $\leqslant 14$ days before enrolment. Radiological imaging by computed tomography (CT) was performed within 3 weeks before treatment initiation by a three-phase, high-resolution thorax and abdomen contrast-enhanced CT scan. An 18-fluorodeoxyglucose positron emission tomography (FDG-PET) scan was also performed at baseline whenever possible. Clinical evaluation and haematology panel were repeated at every drugs administration or whenever needed. Haematological and chemistry panel (CA19-9) were repeated on day 1 of every cycle. Radiographic disease assessment was performed every 8 weeks until disease progression using the revised RECIST (version 1.1) guidelines. A FDG-PET scan was repeated after two cycles and at the end of treatment. Metabolic response was assessed according to Weber's criteria (Weber, 2005). Re-evaluation for surgical resectability was performed after four and six cycles. PFS was defined as the time from the day of treatment start to the disease progression or death (for any cause), whichever occurs first. OS was defined as the time interval between treatment start and the date of death, and censored at the date of the last study assessment. Best overall response was defined as the best response recorded from the start of treatment until disease progression.

Biochemical response was defined in relation to percentage of CA19-9 variation on nadir (minor value assessed while on

treatment) with respect to basal value only in patients with CA19-9 level elevated (namely over superior normal laboratory level), after normalisation of serum bilirubin levels. Patients were classified as non-responders if CA19-9 variation was $<50\%$; minor responders if CA19-9 variation was between 50 and 89%; major responders if CA 19-9 variation was $>89\%$ (Reni *et al*, 2009).

Safety was evaluated at the beginning of each treatment cycle based on patient-reported symptoms, physical examination findings, and clinical laboratory abnormalities. Toxicities were noted by grade and organ system using the National Cancer Institute Common Toxicity Criteria (CTC) (version 4.0), with the frequency and severity of all adverse events (grades 1–4) summarised descriptively. OS and PFS endpoints were measured according to the method of Kaplan and Meier.

Table 1. Characteristics of the patients at baseline

Age (year)	
Median	63
Range	50–75
Sex no. (%)	
Female	7 (29)
Male	17 (71)
Karnofsky Performance Status Score–no. (%)	
90–100	21 (88)
70–80	3 (12)
Pancreatic tumour location–no. (%)	
Head	17 (71)
Body/tail	7 (29)
Surgical assessment–no. (%)	
Borderline resectable	6 (25)
Unresectable	18 (75)
Biliary stent–no. (%)	
Yes	8 (33)
No	16 (67)
Level of carbohydrate 19-9 antigen–U ml^{-1}	
Median	295
Range	16–4591
>ULN no. (%)	19 (79)

Abbreviations: PS = performance status; ULN = upper limit of normal range.

RESULTS

Between December 2012 and April 2014, 24 patients with unresectable or borderline resectable pancreatic ductal adenocarcinoma, were enroled. Patients' characteristics are reported in Table 1. None of the patients enroled in the trial (three at DL1, five at DL2 and sixteen at DL3) experienced a DLT. Accordingly, DL3, which was expanded to obtain additional safety and efficacy information, was considered as RP2D. Both for the entire study cohort and for the RP2D, the median number of cycles was five (range: 3–6). One patient discontinued therapy due to disease progression at cycle five. One patient discontinued therapy due to poor subjective tolerance after 3.5 cycles; ten patients completed 6 months of therapy, whereas twelve patients discontinued treatment after 3–5 months due to medical decision, including four patients who were taken to surgery for resection and eight patients who were addressed to chemoradiation (Figure 1).

After eighty cycles at RP2D the dose-intensity was 90.5% for *nab*-paclitaxel (which was always administered at the planned dose but in two cycles in a single patient); 91% for cisplatin; 80.5% for gemcitabine with a dose reduction in 46% of cycles; and 75% for capecitabine. Chemoradiation, consisting of 44.25 Gy in fifteen fractions delivered with tomotherapy concomitant to capecitabine at 1250 mg m^{-2} daily was administered to all patients: at the end of chemotherapy to sixteen patients, after surgery to seven patients, and at time of recurrence in one patient. Sixteen patients (67%) experienced at least one grade 3–4 haematological and fifteen patients (60%) one grade 3–4 non-haematological adverse event at any point during therapy. Grade 3–4 neutropenia and grade 3 fatigue, neuropathy, anaemia, nausea, diarrhoea, hand-foot syndrome occurred in at least 5% of patients. Adverse events are summarised in Table 2. Granulocyte colony-stimulating factor was used in a single patient. No toxic death was observed.

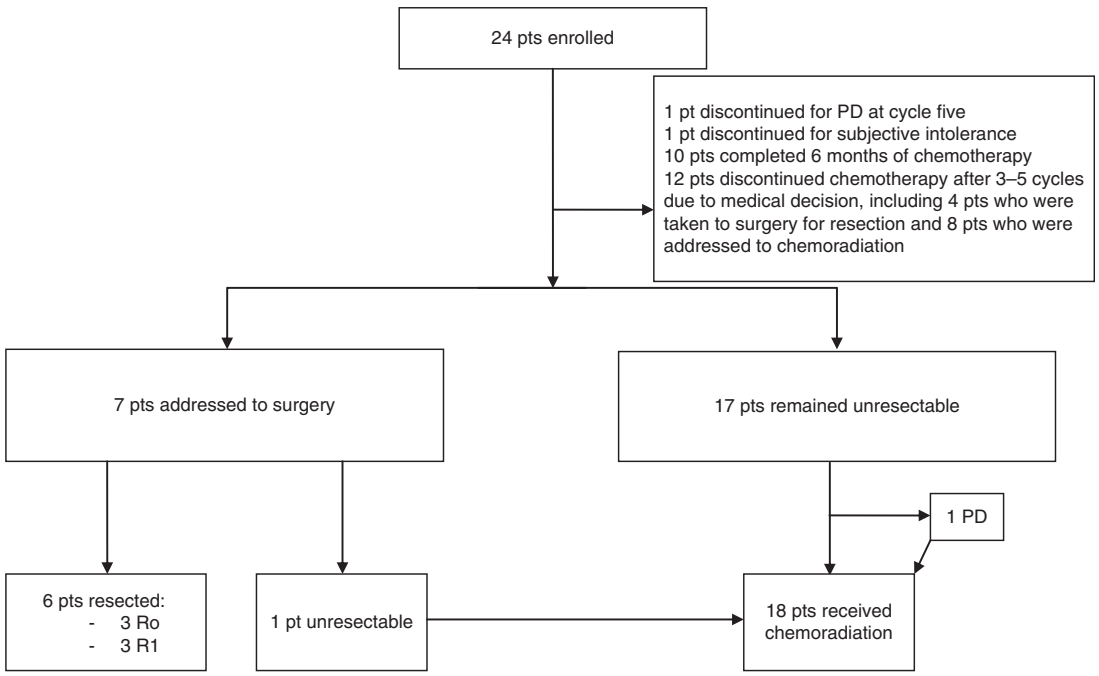

Figure 1. CONSORT flow diagram. PD = progressive disease; Pts = patients.

All patients were assessable for efficacy analyses and had a radiographically measurable disease. Sixteen patients (67%) had partial response according to RECIST criteria, whereas eight (33%) had stable disease. Among nineteen patients with elevated basal CA19-9 value, one was a CA19-9 non-responder (CA19-9 reduction = 49%), ten (53%) had a CA19-9 minor response, and eight (42%) had a CA19-9 major response. Among five patients with normal basal CA19-9 value, one had elevated basal CA125 and one elevated basal CEA. Both patients had a nadir marker reduction >50%. A basal FDG-PET scan was performed in twenty-two patients. All but one was FDG avid. A complete metabolic response was observed in nine (43%), partial metabolic response in ten (48%), and a stable disease in two patients (9%). After chemotherapy, 17 patients remained unresectable by radiological criteria, whereas 7 patients were taken to surgery. In six cases (three borderline, three unresectable) resection was successfully performed, whereas one patient was found unresectable at surgical exploration: three had microscopically free surgical margins (R0) and three microscopically infiltrated margins (R1); four had negative nodes (N0) and two had positive nodes (N1).

At time of report, all patients had disease progression; all patients but one were progression free at 6 months (PFS-6, 96%) and twelve (50%) were progression free at 1-year; median PFS was 12 months. Site of progression was local only in 3 patients; systemic only in 14 patients; both local and systemic in 6 patients and unknown in 1 patient. Noteworthy, the main site of recurrence was peritoneum ($N = 10$), whereas liver metastases were observed only in 7 patients. Nineteen patients died of disease progression and five were alive at a median follow-up of 25 months (range: 22.2–28.9); mOS was 18.1 months; 1yOS and 2yOS were 83.3 and 29.2%, respectively. Efficacy results are summarised in Table 3.

Table 2. Selected non-haematologic and haematologic events treatment-related adverse events

	Dose level 1 ($n = 3$)		Dose level 2 ($n = 5$)		Dose level 3 ($n = 16$)	
Adverse event	**No.**	**%**	**No.**	**%**	**No.**	**%**
Nausea						
Grade 1	1	33	3	60	8	50
Grade 2	0		0		0	
Grade 3	0		0		1	6
Grade 4	0		0		0	
Vomiting						
Grade 1	1	33	1	20	6	38
Grade 2	0		0		2	12
Grade 3	0		0		0	
Grade 4	0		0		0	
Fatigue						
Grade 1	0		3	60	6	38
Grade 2	2	67	1	20	5	31
Grade 3	1	33	1	20	3	19
Grade 4	0		0		0	
Diarrhoea						
Grade 1	1	33	1	20	2	12
Grade 2	1	33	1	20	3	19
Grade 3	0		1	20	0	
Grade 4	0		0		0	
Sensory neuropathy						
Grade 1	1	33	1	20	8	50
Grade 2	1	33	1	20	2	12
Grade 3	0		0		0	
Grade 4	0		0		0	
Hand-foot syndrome						
Grade 1	0		0		2	12
Grade 2	1	33	1	20	3	19
Grade 3	0		0		2	12
Grade 4	0		0		0	
Neutropenia						
Grade 1	0		2	40	4	25
Grade 2	0		0		1	6
Grade 3	2	67	1	20	4	25
Grade 4	1	33	0		5	31
Anaemia						
Grade 1	1	33	2	40	7	44
Grade 2	2	67	2	40	6	38
Grade 3	0		1	20	2	12
Grade 4	0		0		0	
Thrombocytopenia						
Grade 1	2	67	2	40	6	38
Grade 2	1	33	1	20	4	25
Grade 3	0		0		0	
Grade 4	0		0		0	
Febrile neutropenia						
Grade 1	0		0		0	
Grade 2	0		0		0	
Grade 3	0		0		1	6
Grade 4	0		0		0	

DISCUSSION

This phase 1 trial was designed to define the RP2D of *nab*-paclitaxel in combination with cisplatin, gemcitabine, and capecitabine as first-line treatment for patients with chemo-naive, borderline or unresectable pancreatic cancer. Overall, the four-drug combination was safely administered. None of the dose levels of *nab*-paclitaxel, which included the recommended dose of 150 mg m^{-2} in many other indications, was associated with toxicity consistent with MTD, and albeit the rate of grade 3–4 neutropenia (56%) and febrile neutropenia (6%) at the RP2D seems higher as compared to nab-paclitaxel–gemcitabine trial (38% and 3%) (Von Hoff *et al*, 2013), this may be related to small sample size of our series and appears acceptable in the neoadjuvant setting. Furthermore, despite the number of patients with a biliary stent

Table 3. Response rates, progression-free and overall survival for all patients, in the RP2D cohort, borderline resectable and unresectable patients

	All patients		RP2D		Borderline resectable		Unresectable	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
RECIST response ($N = 24$; 16; 6; 18)								
Partial	16	67	10	63	5	83	11	61
Stable	8	33	6	37	1	17	7	39
CA19-9 response ($N = 19$; 13; 5; 14)								
Major	8	42	6	46	2	40	6	43
Minor	10	53	7	54	2	40	8	57
FDG-PET response ($N = 21$; 16; 5; 16)								
Complete	9	43	7	44	3	60	6	38
Partial	10	48	7	44	2	40	8	50
Stable	2	9	2	13	0	0	2	12
Progression-free survival								
Median (mo.)	12.0		11.1		12.5		9.8	
6-month (%)	96		100		83		100	
12-month (%)	50		50		83		44	
Overall survival								
Median (month)	18.1		18.1		14.5		19.9	
1 year (%)	83.3		81.3		67		89	

Abbreviations: CA19-9 = carcinoma antigen 19-9; FDG-PET = 18-fluorodeoxyglucose positron emission tomography; RECIST = Response Evaluation Criteria in Solid Tumours.

Table 4. Prospective clinical trials about locally advanced pancreatic ductal adenocarcinoma

							Resection (%)				
Ref.	Treatment	Study design	*N*	DCR (%)	CR + PR (%)	SD (%)	BL[a]	UNR[a]	mPFS (mo)	mOS (mo)	1yOS (%)
Chauffert *et al*, 2008	CRT → maintenance gemcitabine/gemcitabine	Phase III	59/60	NA	NA	NA	NA	3.4/5	NA	8.6/13	32/53
Loehrer *et al*, 2011	gemcitabine/gemcitabine + RT	Phase III	37/34	40/74	5/6	35/68	NA	0	6.7/6	9.2/11.1	NA
Mukherjee *et al*, 2013	Capecitabine/gemcitabine-based CRT	Phase II RCT	38/36	86/86	23/19	63/67	NA	5.6/7.9	12/10.4	15.2/13.4	79.2/64.2
Marthey *et al*, 2015	FOLFIRINOX	Observational	77	84	28	56	NA	36	13	22	77
Sherman *et al*, 2015	GTX ± GX + RT	Non-randomised phase II	45	95	51	44	100	85.3	NA	32.5	NA
Current	PAXG ± CRT	Phase IB	24	100	67	33	50	16.7	12	18.1	83.3

Abbreviations: BL = borderline resectable disease; CR + PR-SD = complete response + partial response-stable disease; CRT = chemoradiotherapy; CT = chemotherapy; DCR = disease control rate; FOLFIRINOX = oxaliplatin, irinotecan, leucovorin, and fluorouracil; GTX = gemcitabine, docetaxel, and capecitabine; GX = gemcitabine and capecitabine; mOS = median overall survival; mPFS = median progression-free survival; *N* = number; NA = not available; PAXG = cisplatin, *nab*-paclitaxel, capecitabine, gemcitabine; RCT = randomised clinical trial; Ref. = reference; RT = radiotherapy; UNR = unresectable disease; 1yOS = one year overall survival.
[a]The definition of borderline resectable and unresectable locally advanced pancreatic cancer changes between different trials.

(47% of those with tumour located in the pancreatic head) appears higher in our series as compared to the *nab*-paciltaxel–gemcitabine (40%) phase III trial (Von Hoff *et al*, 2013), only one patient experienced a febrile neutropenia. In addition, secondary end-points analysis showed encouraging preliminary anti-tumour activity. In particular, results are numerically superior to those of our previous experience in a comparable patients population that was selected by the same team of surgeons, radiologists, and medical oncologists, and treated with other four-drug regimens, namely cisplatin, epirubicin, 5-fluorouracil, gemcitabine (PEFG), cisplatin, capecitabine, gemcitabine plus either epirubicin (PEXG) or docetaxel (PDXG) (Reni *et al*, 2005, 2009, 2012). Data should be considered with caution in view of the small cohort of patients enroled in this phase 1 trial at the RP2D. However, the PAXG regimen reported here obtained numerically superior results in terms of measurable response, disease control rate, mPFS and PFS at 6 months (*vs* 62.5–82.1%). The relevance of the observations should also be weighted in light of the high resectability rate of 25% obtained in spite of the fact that borderline resectability was present in only six patients at diagnosis. Albeit all patients recurred, OS at 1-year and 2-year (83.3 and 29.2%, respectively) are unusual in other prospective trials in this patients' population (Table 4).

The relevance of the present data relies also on the homogeneous definition of resectability, which was performed in a single high-volume institution by the blinded assessment of experienced surgical and radiological teams, and the brief timeframe study period.

Overall, collection of pharmacodynamic information in pancreatic adenocarcinoma is very challenging. Tumour tissue is rarely available in pancreatic adenocarcinoma, and the collection of serial biopsies to study the effects of therapy during and after treatment is often limited by the risk linked to the anatomical site to biopsy. A functional characterisation of the response was therefore based on the prospective evaluation with FDG-PET (Chirindel *et al*, 2015) that can be viewed as a surrogate pharmacodynamic endpoint. A complete or partial FDG-PET response was observed in over 90% of patients, suggesting that the PAXG regimen could achieve a remarkable reduction of tumour metabolism consistent with the high rate of objective responses.

Recently, a few series of patients treated with original or modified FOLFIRINOX regimen (5-FU/leucovorin, irinotecan, and oxaliplatin) reported relevant results as well (Hosein *et al*, 2012; Blazer *et al*, 2015; Marthey *et al*, 2015). Although these data are in some cases preliminary, with short follow-up, and retrospective or observational, they support the concept that further prospective randomised studies of combination chemotherapy should be conducted in this setting.

Currently, the combination of *nab*-paclitaxel and gemcitabine is considered a standard therapy of metastatic pancreatic adenocarcinoma based on the significant survival improvement over single agent gemcitabine that was demonstrated in a large randomised phase III trial (Von Hoff *et al*, 2013). The 2-drug regimen has a manageable safety profile, and represents a suitable backbone for building more effective chemotherapy. Another phase 1 trial has tested the addition of capecitabine to *nab*-paclitaxel and gemcitabine in the AGX regimen in patients with metastatic pancreatic adenocarcinoma, but results were disappointing (Ko *et al*, 2012). The AGX regimen has several differences in respect to PAXG regimen reported here. The first is the presence of platinum in the PAXG. Platinum compounds are among the most active drugs for pancreatic cancer, and are used in first and second-line setting in the clinical practice. In addition, platinum compounds are synergistic with the other drugs in PAXG (Sawada *et al*, 1998; Maeda *et al*, 2004). Another relevant difference is the planned dose-intensity of *nab*-paclitaxel (75 *vs* 50 mg m^{-2} week^{-1} in AGX) and capecitabine (8750 *vs* 5250 mg m^{-2} week^{-1}) that is substantially greater in PAXG, whereas that of gemcitabine is 20% lower (400 *vs* 500 mg m^{-2} week^{-1}). Finally, the order of drug administration was different. In the PAXG regimen *nab*-paclitaxel is given before gemcitabine, as in the original phase 3 trial (Von Hoff *et al*, 2013), whereas in AGX the inverse sequence is used (Ko *et al*, 2012). Of note, pre-clinical studies showed that *nab*-paclitaxel decreases cytidine-deaminase levels (Freese *et al*, 2012), and increases the integration and interaction of gemcitabine-triphosphate with mRNA and favoring gemcitabine activity (Ricotti *et al*, 2003; Von Hoff *et al*, 2011).

In conclusion, the study proved the possibility of including *nab*-paclitaxel in the regimen and allowed to define the RP2D. An ongoing phase 2 trial is randomizing patients with unresectable, borderline resectable or metastatic pancreatic adenocarcinoma to receive the PAXG regimen or the standard *nab*-paclitaxel–gemcitabine combination.

ACKNOWLEDGEMENTS

Celgene provided funding for the study with an unrestricted grant and the supply of the drug. We thank all the patients who participated in this study.

CONFLICT OF INTEREST

This work was supported by Celgene, which provided funding for the study with an unrestricted grant and the supply of the drug. MR discloses: advisory role for Celgene, Boehringer Ingelheim, Genetech, Lilly, Merck Serono, Baxalta; research funding to his institution from Celgene, PharmaMar, and Novartis; expenses reimbursement from Celgene. GB discloses: advisory role for Celgene. MF discloses: research funding to his institution from Novartis. LG discloses: consulting or advisory role for Roche, Pfizer, GlaxoSmithKline, Synthon, Taiho Pharmaceutical, AstraZeneca, Genomic Health, Merck Sharp & Dohme, Boehringer Ingelheim, Tiziana Pharma, Synaffix, and Celgene; patents/royalties/other intellectual property with Roche. All other authors disclose no conflict of interest.

REFERENCES

Balzano G, Zerbi A, Capretti G, Rocchetti S, Capitanio V, Di Carlo V (2008) Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. *Br J Surg* **95**: 357–362.

Blazer M, Wu C, Goldberg RM, Phillips G, Schmidt C, Muscarella P, Wuthrick E, Williams TM, Reardon J, Ellison EC, Bloomston M, Bekaii-Saab T (2015) Neoadjuvant modified (m) FOLFIRINOX for locally advanced unresectable (LAPC) and borderline resectable (BRPC) adenocarcinoma of the pancreas. *Ann Surg Oncol* **22**: 1153–1159.

Chauffert B, Mornex F, Bonnetain F, Rougier P, Mariette C, Bouché O, Bosset JF, Aparicio T, Mineur L, Azzedine A, Hammel P, Butel J, Stremsdoerfer N, Maingon P, Bedenne L (2008) Phase III trial comparing intensive induction chemoradiotherapy (60 Gy, infusional 5-FU and intermittent cisplatin) followed by maintenance gemcitabine with gemcitabine alone for locally advanced unresectable pancreatic cancer. Definitive results of the 2000-01 FFCD/SFRO study. *Ann Oncol* **19**: 1592–1599.

Chirindel A, Alluri KC, Chaudhry MA, Wahl RL, Pawlik TM, Herman JM, Subramaniam RM (2015) Prognostic Value of FDG PET/CT-derived parameters in pancreatic adenocarcinoma at initial PET/CT staging. *AJR Am J Roentgenol* **204**: 1093–1099.

Colucci G, Labianca R, Di Costanzo F, Gebbia V, Cartenì G, Massidda B, Dapretto E, Manzione L, Piazza E, Sannicolò M, Ciaparrone M, Cavanna L, Giuliani F, Maiello E, Testa A, Pederzoli P, Falconi M, Gallo C, Di Maio M, Perrone F. Gruppo Oncologico Italia Meridionale (GOIM), Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD), Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC) (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.

Cunningham D, Chau I, Stocken DD, Valle JW, Smith D, Steward W, Harper PG, Dunn J, Tudur-Smith C, West J, Falk S, Crellin A, Adab F, Thompson J, Leonard P, Ostrowski J, Eatock M, Scheithauer W, Herrmann R, Neoptolemos JP (2009) Phase III randomised comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol* **27**: 5513–5518.

Frese KK, Neesse A, Cook N, Bapiro TE, Lolkema MP, Jodrell DI, Tuveson DA (2012) nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. *Cancer Discov* **2**: 260–269.

GLOBOCAN. (IARC). Section of Cancer Surveillance (2012) http://globocan.iarc.fr/Pages/fact_sheets_population.aspx (accessed on 26 September 2015).

Hosein PJ, Macintyre J, Kawamura C, Maldonado JC, Ernani V, Loaiza-Bonilla A, Narayanan G, Ribeiro A, Portelance L, Merchan JR, Levi JU, Rocha-Lima CM (2012) A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline resectable locally advanced pancreatic adenocarcinoma. *BMC Cancer* **12**: 1–7.

Ko AH, Truong TG, Kantoff E, Jones KA, Dito E, Ong A, Tempero MA (2012) A phase I trial of nab-paclitaxel, gemcitabine, and capecitabine for metastatic pancreatic cancer. *Cancer Chemother Pharmacol* **70**: 875–881.

Loehrer Sr PJ, Feng Y, Cardenes H, Wagner L, Brell JM, Cella D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, Benson 3rd AB (2011) Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* **29**: 4105–4112.

Maeda S, Sugiura T, Saikawa Y, Kubota T, Otani Y, Kumai K, Kitajima M (2004) Docetaxel enhances the cytotoxicity of cisplatin to gastric cancer cells by modification of intracellular platinum metabolism. *Cancer Sci* **95**: 679–684.

Marthey L, Sa-Cunha A, Blanc JF, Gauthier M, Cueff A, Francois E, Trouilloud I, Malka D, Bachet JB, Coriat R, Terrebonne E, De La Fouchardière C, Manfredi S, Solub D, Lécaille C, Thirot Bidault A, Carbonnel F, Taieb J (2015) FOLFIRINOX for locally advanced pancreatic adenocarcinoma: results of an AGEO multicentre prospective observational cohort. *Ann Surg Oncol* **22**: 295–301.

Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, McDonald A, Ray R, Joseph G, Staffurth J, Abrams RA, Griffiths G, Maughan T (2013) Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol* **14**(4): 317–326.

Poplin E, Feng Y, Berlin J, Rothenberg ML, Hochster H, Mitchell E, Alberts S, O'Dwyer P, Haller D, Catalano P, Cella D, Benson 3rd AB (2009) Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* **27**: 3778–3785.

Reni M, Cordio S, Milandri C, Passoni P, Bonetto E, Oliani C, Luppi G, Nicoletti R, Galli L, Bordonaro R, Passardi A, Zerbi A, Balzano G, Aldrighetti L, Staudacher C, Villa E, Di Carlo V (2005) Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol* **6**: 369–376.

Reni M, Cereda S, Balzano G, Passoni P, Rognone A, Fugazza C, Mazza E, Zerbi A, Di Carlo V, Villa E (2009) Carbohydrate antigen 19-9 change during chemotherapy for advanced pancreatic adenocarcinoma. *Cancer* **115**: 2630–2639.

Reni M, Cereda S, Balzano G, Passoni P, Rognone A, Zerbi A, Nicoletti R, Mazza E, Arcidiacono PG, Di Carlo V, Villa E (2009) Outcome of upfront combination chemotherapy followed by chemoradiation for locally advanced pancreatic adenocarcinoma. *Cancer Chemother Pharmacol* **64**: 1253–1259.

Reni M, Cereda S, Rognone A, Belli C, Ghidini M, Longoni S, Fugazza C, Rezzonico S, Passoni P, Slim N, Balzano G, Nicoletti R, Cappio S, Doglioni C, Villa E (2012) 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). *Cancer Chemother Pharmacol* **69**: 115–123.

Ricotti L, Tesei A, De Paola F, Ulivi P, Frassineti GL, Milandri C, Amadori D, Zoli W (2003) *In vitro* schedule-dependent interaction between docetaxel and gemcitabine in human gastric cancer cell lines. *Clin Cancer Res* **9**: 900–905.

Sawada N, Ishikawa T, Fukase Y, Nishida M, Yoshikubo T, Ishitsuka H (1998) Induction of thymidine phosphorylase activity and enhancement of capecitabine efficacy by taxol/taxotere in human cancer xenografts. *Clin Cancer Res* **4**: 1013–1019.

Sherman WH, Chu K, Chabot J, Allendorf J, Schrope BA, Hecht E, Jin B, Leung D, Remotti H, Addeo G, Postolov I, Tsai W, Fine RL (2015) Neoadjuvant gemcitabine, docetaxel, and capecitabine followed by gemcitabine and capecitabine/radiation therapy and surgery in locally advanced, unresectable pancreatic adenocarcinoma. *Cancer* **121**(5): 673–680.

Tempero MA, Arnoletti JP, Behrman SW, Ben-Josef E, Benson 3rd AB, Casper ES, Cohen SJ, Czito B, Ellenhorn JDI, Hawkins WG, Herman J, Hoffman JP, Ko A, Komanduri S, Koong A, Ma WW, Malafa MP, Merchant NB, Mulvihill SJ, Muscarella 2nd P, Nakakura EK, Obando J, Pitman MB, Sasson AR, Tally A, Thayer SP, Whiting S, Wolff RA, Wolpin BM, Freedman-Cass DA, Shead DA (2012) Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* **10**: 703–713.

Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T,

Rajeshkumar NV, Maitra A, Hidalgo M (2011) Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol* **29**: 4548–4554.

Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjulandin SA, Ma WW, Saleh MN, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan RK, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, Renschler MF (2013) Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med* **369**: 1691–1703.

Weber WA (2005) Use of PET for monitoring cancer therapy and for predicting outcome. *J Nucl Med* **46**: 983–995.

This work is published under the standard license to publish agreement. After 12 months the work will become freely available and the license terms will switch to a Creative Commons Attribution-NonCommercial-Share Alike 4.0 Unported License.