Nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in metastatic pancreatic adenocarcinoma (PACT-19): a randomised phase 2 trial

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Summary

Background Current treatment for metastatic pancreatic ductal adenocarcinoma includes combination chemotherapy, such as FOLFIRINOX or nab-paclitaxel plus gemcitabine. We investigated the activity of a novel four-drug regimen, consisting of cisplatin, nab-paclitaxel, capecitabine, and gemcitabine, compared with nab-paclitaxel plus gemcitabine, in the PACT-19 trial.

Methods This single-centre, randomised, open-label, phase 2 trial was done in San Raffaele Hospital in Italy. We enrolled patients aged 18–75 years with pathologically confirmed stage IV pancreatic ductal adenocarcinoma who had received no previous chemotherapy and had Karnofsky performance status of at least 70. Patients were randomly assigned (1:1) by computer-generated permutated block randomisation (block size of four) stratified by baseline concentration of carbohydrate antigen 19-9 to PAXG (cisplatin 30 mg/m², nab-paclitaxel 150 mg/m², and gemcitabine 800 mg/m² on days 1 and 15 and oral capecitabine 1250 mg/m² on days 1–28 every 4 weeks), or nab-paclitaxel and gemcitabine alone (nab-paclitaxel 125 mg/m² and gemcitabine 1000 mg/m² on days 1, 8, and 15 every 4 weeks). The primary endpoint was the proportion of patients who were progression-free at 6 months, analysed in the intention-to-treat population. Data cutoff was on March 31, 2018. The safety population included all patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT01730222, and is now closed.

Findings Between April 22, 2014, and May 30, 2016, we randomly assigned 83 patients to treatment: 42 patients to PAXG and 41 patients to nab-paclitaxel plus gemcitabine. At 6 months, 31 (74%, 95% CI 58–86) of 42 patients in the PAXG group were alive and free from disease progression compared with 19 (46%, 31–63) of 41 patients in the nab-paclitaxel plus gemcitabine group. The most frequent grade 3 adverse events were neutropenia (12 [29%] of 42 in the PAXG group *vs* 14 [34%] of 41 in the nab-paclitaxel plus gemcitabine group), anaemia (nine [21%] *vs* nine [22%]), and fatigue (seven [17%] *vs* seven [17%]). The most common grade 4 adverse event was neutropenia (five [12%] in the PAXG group *vs* two [5%] in the nab-paclitaxel plus gemcitabine group). Two (5%) treatment-related deaths occurred in the nab-paclitaxel plus gemcitabine group compared with none in the PAXG group.

Interpretation Despite the small sample size, our findings suggest that the PAXG regimen warrants further investigation in a phase 3 trial in patients with metastatic pancreatic ductal adenocarcinoma.

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Introduction

Most patients with pancreatic adenocarcinoma have metastatic disease at the time of diagnosis. Combination chemotherapy improves survival compared with single-agent treatment in this stage of the disease.[1–3] The multidrug regimen PEFG (cisplatin, epirubicin, fluorouracil, gemcitabine) was the first to show superiority over gemcitabine monotherapy in terms of progression-free survival (hazard ratio [HR] 0·51), overall survival (HR 0·65), the proportion of patients with a response to treatment, and clinical benefit in a phase 3 trial; however, restrictions of the study, including small sample size and the choice of progression-free survival as the primary endpoint, precluded acceptance of PEFG as a new standard for first-line treatment of advanced pancreatic cancer.[1] This regimen was then modified for easier administration by inclusion of oral capecitabine instead of fluorouracil, giving rise to the PEXG regimen.[4] The concept that combination chemotherapy might benefit patients with metastatic pancreatic adenocarcinoma was supported by results of the PRODIGE 4/ACCORD 11 trial, which showed a significant improvement in overall survival with the FOLFIRINOX regimen (fluorouracil, leucovorin, irinotecan, oxaliplatin) compared with gemcitabine alone.[2] However, the stringent eligibility criteria and the less favourable safety profile restricted the use of this regimen to well performing patients.

Research in context

Evidence before this study

In 2013, at the time of study design, we searched PubMed for current combination chemotherapy regimens used for the treatment of stage IV pancreatic cancer. We used the terms "pancreatic cancer" and "advanced pancreatic cancer" and "metastatic pancreas cancer" and "trial" and "combination chemotherapy", and restricted our search to phase 2 and phase 3 clinical trials published between Jan 10, 2003, and Nov 22, 2013. We identified two published articles that investigated the use of two different multidrug regimens compared with the current standard treatment, which at the time was gemcitabine monotherapy. Both the studied regimens were superior to gemcitabine monotherapy. However, one combination regimen was eligible for well performing patients only, whereas the other was not chosen as a new standard first-line treatment because of study limitations. In the meantime, a phase 3 trial showed that the combination of gemcitabine with nab-paclitaxel resulted in increased overall survival in patients with metastatic pancreatic cancer. Moreover, an older study in human cancer xenografts had documented the synergism of taxanes with fluoropyrimidines and platinum agents. Thus, it seemed reasonable to investigate the addition of synergistic drugs to a previously investigated combination chemotherapy.

Added value of this study

Our randomised controlled trial investigated a four-drug regimen exploiting the characteristics of the individual drugs and their known synergism in the setting of metastatic pancreatic adenocarcinoma. Our results suggest that the use of PAXG (cisplatin, nab-paclitaxel, capecitabine, gemcitabine) is safe and effective, and that it may confer a therapeutic benefit. Moreover, the four-drug regimen seems to be associated with an acceptable tolerability and a toxicity profile that is similar to those of the current standards of treatment.

Implications of all the available evidence

Despite attempts to promote personalised medicine, no relevant outcome improvement has been seen in the setting of metastatic pancreatic cancer. The identification of a safe and effective combination of drugs could not only be of use in patients who are not eligible for targeted therapy to increase their progression-free survival and overall survival, but could also be used as a robust backbone on which to build personalised treatment. Our results suggest that the administration of the PAXG regimen is worth further investigation in a randomised controlled phase 3 clinical trial.

More recently, the combination of nanoparticle albumin-bound (nab)-paclitaxel and gemcitabine has shown a significantly better outcome for patients with metastatic disease than with gemcitabine alone.[3]

In view of the synergism of taxanes with fluoropyrimidines[5] and platinum agents,[6] a regimen of cisplatin, nab-paclitaxel, capecitabine, and gemcitabine (PAXG) was tested in a phase 1b trial to assess the recommended phase 2 dose.[7] This regimen subsequently showed promising results in a randomised phase 2 trial in patients with borderline resectable and unresectable disease.[8] Here, we present results of a phase 2 trial that assessed the antitumour activity of the PAXG regimen compared with nab-paclitaxel plus gemcitabine in patients with metastatic pancreatic adenocarcinoma.

Methods

Study design and participants

This single institution, open-label, randomised phase 2 trial was done in San Raffaele Hospital, Milan, Italy. The trial was approved by the local ethics committee and conformed to the Declaration of Helsinki. Each patient signed a written informed consent form after review of the protocol contents and after eligibility was confirmed by the attending physician who registered the case with the internal clinical research assistant team.

Patients were eligible if they were aged 18–75 years, had a Karnofsky performance status of at least 70, a pathological diagnosis of pancreatic ductal adenocarcinoma, measurable metastatic disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1,[9] and if they had not previously received chemotherapy. Other eligibility criteria included adequate bone marrow (white blood cell count ≥3500 cells per µL, neutrophils ≥1500 cells per µL; platelets ≥100 000 per µL; haemoglobin ≥10 g/dL), liver (total bilirubin ≤2 mg/dL; alanine aminotransferase and aspartate aminotransferase ≤3 upper limit of normal [ULN]), and kidney (serum creatinine ≤1·5 mg/dL) function. Criteria for exclusion were a personal history of 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 for at least 5 years; symptomatic brain metastases; history of interstitial lung disease; presence of serious diseases such as cardiac failure, myocardial infarction within the previous 6 months, cardiac arrhythmia, and history of psychiatric disabilities; pregnancy and lactation; and history of connective tissue disorders (eg, lupus, scleroderma, arteritis nodosa).

Randomisation and masking

Eligible patients were randomly assigned (1:1) to each treatment group by a permuted block randomisation (block size of four) list that had been previously computer-generated by our institution clinical trial office and was conserved by the internal clinical research assistant team, which was also responsible for electronic data

collection, and for monitoring accuracy, completeness, and reliability of the acquired data. The attending physician did not have access to the randomisation list. Randomisation was stratified by baseline concentration of carbohydrate antigen 19-9 (CA19-9 <10×ULN *vs* ≥10×ULN). Neither patients nor investigators were masked to treatment allocation.

Procedures

Patients randomly allocated to PAXG received an intravenous infusion of nab-paclitaxel 150 mg/m², followed by gemcitabine 800 mg/m², followed by cisplatin 30 mg/m² on days 1 and 15, and oral capecitabine 1250 mg/m² on days 1–28. Patients randomly allocated to nab-paclitaxel plus gemcitabine received an intravenous infusion of nab-paclitaxel 125 mg/m² followed by gemcitabine 1000 mg/m² on days 1, 8, and 15. Nab-paclitaxel was provided for free by Celgene (Boudry, Switzerland) for both groups.

One cycle of chemotherapy consisted of 28 days of treatment for both groups. All treatment was given until disease progression, intolerable toxicity, patient refusal, or medical decision. In all other cases, six cycles of chemotherapy were administered. Afterwards, continuation of treatment was allowed only in case of clinical benefit, defined as continuous decrease of CA19-9 concentration or radiological response.

Tumour measurement was done at baseline by CT or MRI scan of the chest, abdomen, and pelvis, performed within 3 weeks before the date of the randomisation. RECIST (version 1.1) response[9] was assessed by a radiologist, masked to treatment group, every 8 weeks until disease progression or in the case of any symptom suggestive of disease progression. Tumour markers (ie, carcinoembryonic antigen [CEA] and CA19-9) were repeated every 4 weeks only if elevated at baseline. Haematological tests were done at baseline and at every chemotherapy administration (ie, every 2 weeks for PAXG and on days 1, 8, and 15 for nab-paclitaxel plus gemcitabine), whereas chemistry tests were done at baseline and every 4 weeks, or more often if clinically necessary. Side-effects of treatment were monitored separately for each cycle. The worst toxicity observed for each patient was recorded.

Outcomes

The primary endpoint of the study was the proportion of patients progression-free at 6 months from randomisation. The secondary endpoints were overall survival, defined as the time between randomisation and the date of death or last follow-up visit; progression-free survival, defined as the time from the day of randomisation to disease progression or death from any cause, whichever occurred first; the proportion of patients who achieved radiological response according to RECIST criteria; tumour marker response, defined as a percentage of CA19-9 variation at nadir with respect to baseline in patients with basal concentrations higher than normal laboratory concentrations, after normalisation of serum bilirubin concentrations. Response was classified as major (CA19-9 reduction >89%), minor (CA19-9 reduction between 50% and 89%), or absent (CA19-9 reduction <50% or increase).[10] Adverse events were registered and classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4. The database lock for the present analysis was March 31, 2018, when all living patients had completed at least 22 months of follow-up.

Statistical analysis

We designed the study as a calibrated phase 2 clinical trial with an A'Hern single-stage phase 2 design.[11] This design includes a calibration group that is used to contextualise the trial population and better estimate whether the sample of patients who receive the investigational regimen has the capability of showing a promising response. Because this design does not have power for a head-to-head comparison, no formal efficacy comparison between the two groups was planned. The analyses were performed separately for each group. Patients with metastatic disease who were assigned to the standard treatment group (nab-paclitaxel plus gemcitabine regimen) formed the calibration group, in which 6-month progression-free survival was expected to be 45%.[3] This null hypothesis was verified against the alternative hypothesis that the true percentage of success with the PAXG regimen is 65% with a two-tailed test. The total number of patients to consider for each group was 42. If at least 25 of 42 patients were progression-free

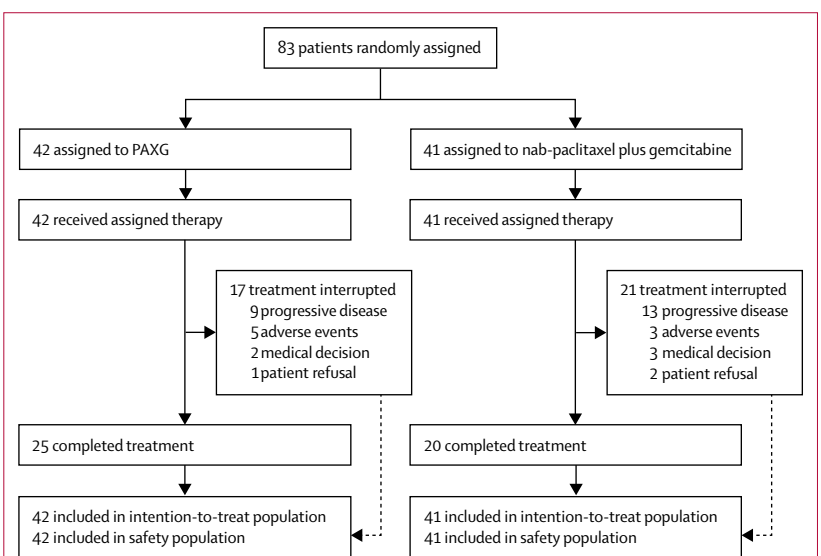

Figure 1: **Trial profile**
The intention-to-treat population included all randomly assigned patients. The safety population included all patients who received at least one dose of study treatment. PAXG=cisplatin, nab-paclitaxel, capecitabine, gemcitabine.

	PAXG (n=42)	Nab-paclitaxel plus gemcitabine (n=41)
Sex		
Male	19 (45%)	24 (59%)
Female	23 (55%)	17 (41%)
Age (years)	66 (44–75)	64 (29–75)
Karnofsky performance status		
100	11 (26%)	16 (39%)
90	22 (52%)	8 (20%)
80	7 (17%)	14 (34%)
70	2 (5%)	3 (7%)
Metastatic site		
Liver	27 (64%)	32 (78%)
Peritoneum	8 (19%)	6 (15%)
Lung	4 (10%)	6 (15%)
Other	13 (31%)	15 (37%)
Tumour site		
Pancreatic head	24 (57%)	21 (51%)
Pancreatic body	14 (33%)	15 (37%)
Pancreatic tail	4 (9%)	5 (12%)
Biliary stent	12 (29%)	5 (12%)
Surgical biliary bypass	3 (7%)	4 (10%)
Previous surgery	7 (17%)	6 (15%)
Baseline CA19-9 (IU/mL)	2180 (37–36 645)	1373 (46–739 108)
>ULN	32 (76%)	31 (76%)
>10 × ULN	11 (34%)	12 (35%)
Neutrophil lymphocyte ratio	2·9 (0·7–23·0)	2·6 (1·3–12·6)

Data are n (%) or median (range). CA19-9=carbohydrate antigen 19-9. PAXG=cisplatin, nab-paclitaxel, capecitabine, gemcitabine. ULN=upper limit of normal.

Table 1: **Baseline characteristics**

at 6 months, the null hypothesis was to be rejected and the PAXG treatment considered active. This design has an α error of 5% and a power of 80%.

Primary analyses were done in the intention-to-treat population, which included all randomly assigned patients. The safety population included all patients who received at least one dose of study treatment. Progression-free survival and overall survival were described using Kaplan-Meier curves for each treatment group and differences in the curves were tested using the log-rank test in an exploratory analysis. Binomial exact 95% CIs were calculated for proportions.[12] All analyses were done with Statistica (version 12.0; statistical package for Windows). This trial is registered with ClinicalTrials.gov, number NCT01730222.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between April 22, 2014, and May 30, 2016, 83 patients were randomly assigned to receive PAXG (n=42) or nab-paclitaxel plus gemcitabine (n=41; figure 1). Several baseline characteristics were balanced between groups; however, the PAXG group had a higher median CA19-9 concentration, a higher proportion of female patients, and a higher proportion of patients with biliary stent placement than did the nab-paclitaxel plus gemcitabine group (table 1). Additionally, Karnofsky performance scale of 100 and liver metastases were more common in the nab-paclitaxel plus gemcitabine group than in the PAXG group. All patients received the assigned treatment.

The median number of chemotherapy cycles was six (range 1–8) in the PAXG group and six (range 1–9) in the nab-paclitaxel plus gemcitabine group. 25 (60%) patients in the PAXG group and 19 (46%) patients in the nab-paclitaxel plus gemcitabine group received treatment for at least 6 months. The number of administered cycles and reasons for interruption are reported in figure 1. In the PAXG group, median relative dose intensity was 80% for cisplatin, 77% for nab-paclitaxel, 75% for capecitabine, and 72% for gemcitabine. In the nab-paclitaxel plus gemcitabine group, the relative dose intensity was 80% for nab-paclitaxel and 78% for gemcitabine.

At 6 months, 31 (74%, 95% CI 58–86) of 42 patients in the PAXG group were alive and free from disease progression compared with 19 (46%, 31–63) of 41 patients in the nab-paclitaxel plus gemcitabine group. At database lock, on March 31, 2018, all patients had had a progression-free survival event. Median progression-free survival was 8·3 months (95% CI 1·5–36·3) in the PAXG group and 6·1 months (1·1–18·7) in the nab-paclitaxel plus gemcitabine group (HR for progression 0·56, 95% CI 0·36–0·87; p=0·01; figure 2).

The survival analysis was based on 39 (93%) deaths in the PAXG group and 39 (95%) in the nab-paclitaxel plus gemcitabine group. One patient in the nab-paclitaxel plus gemcitabine group was lost to follow-up after progression of disease at 1·7 months. After a median follow-up of 30·9 months (range 22·1–34·9), median overall survival was 14·4 months (95% CI 2·7–37·4) in the PAXG group and 10·7 months (1·7–31·9) in the nab-paclitaxel plus gemcitabine group; 1-year overall survival was 62% (95% CI 46–76) in the PAXG group and 44% (28–60) in the nab-paclitaxel plus gemcitabine group; 2-year overall survival was 24% (12–39) in the PAXG group and 12% (2–26) in the nab-paclitaxel plus gemcitabine group (HR for death 0·60, 95% CI 0·39–0·95; p=0·03; figure 2).

In the PAXG group, one (2%) patient had a complete response and 20 (48%) patients had partial responses, with an overall response of 50% (95% CI 32–64). 14 (33%) patients had stable disease, and seven (17%) had disease progression. In the nab-paclitaxel plus gemcitabine group, two (5%) patients had complete responses and ten (24%) had partial responses, with an overall response

of 29% (95% CI 12–40). 18 (44%) patients had stable disease, and eight (20%) had disease progression. 32 (76%) patients in the PAXG group and 31 (76%) in the nab-paclitaxel plus gemcitabine group had a baseline CA19-9 concentration higher than the upper limit of laboratory normal. Among these patients, a decrease from baseline of 50% or more was recorded in 24 (75%; 13 major and 11 minor) patients in the PAXG group and 18 (58%; 13 major and five minor) in the nab-paclitaxel plus gemcitabine group. In a post-hoc analysis, patients obtaining a CA19-9 reduction of 50% or more survived significantly longer compared with those without response (median overall survival 16·0 months [95% CI 12·1–21·9] in patients with CA19-9 reduction of ≥50% *vs* 6·5 months [3·2–11·7] in patients with CA19-9 reduction of <50% or increase; p=0·016).

In an exploratory multivariable analysis stratified by the factors with an imbalance between groups at baseline (ie, Karnofsky performance status, sex, biliary stent placement, median CA19-9 concentration, metastatic site), the HR for progression was 0·55 (95% CI 0·34–0·89; p=0·01) and HR for death was 0·58 (0·36–0·96; p=0·03).

No toxicity-related deaths were reported in the PAXG group. Two (5%) patients in the nab-paclitaxel plus gemcitabine group died within 30 days of chemotherapy administration from myocardial infarction and sepsis, respectively. The most frequent grade 3 adverse events were neutropenia, anaemia, and fatigue, and the most common grade 4 adverse event was neutropenia (table 2). Sepsis (all grades) was reported in two (5%) of 41 patients in the nab-paclitaxel plus gemcitabine group compared with none of 42 in the PAXG group. Severe adverse events were reported in 12 (29%) patients in the PAXG group and 12 (29%) patients in the nab-paclitaxel plus gemcitabine group. Subsequent therapy at time of progression was given to 28 (67%) patients in the PAXG group and 24 (59%) patients in the nab-paclitaxel plus gemcitabine group, and it consisted of combination chemotherapy in 16 and 11 patients, respectively.

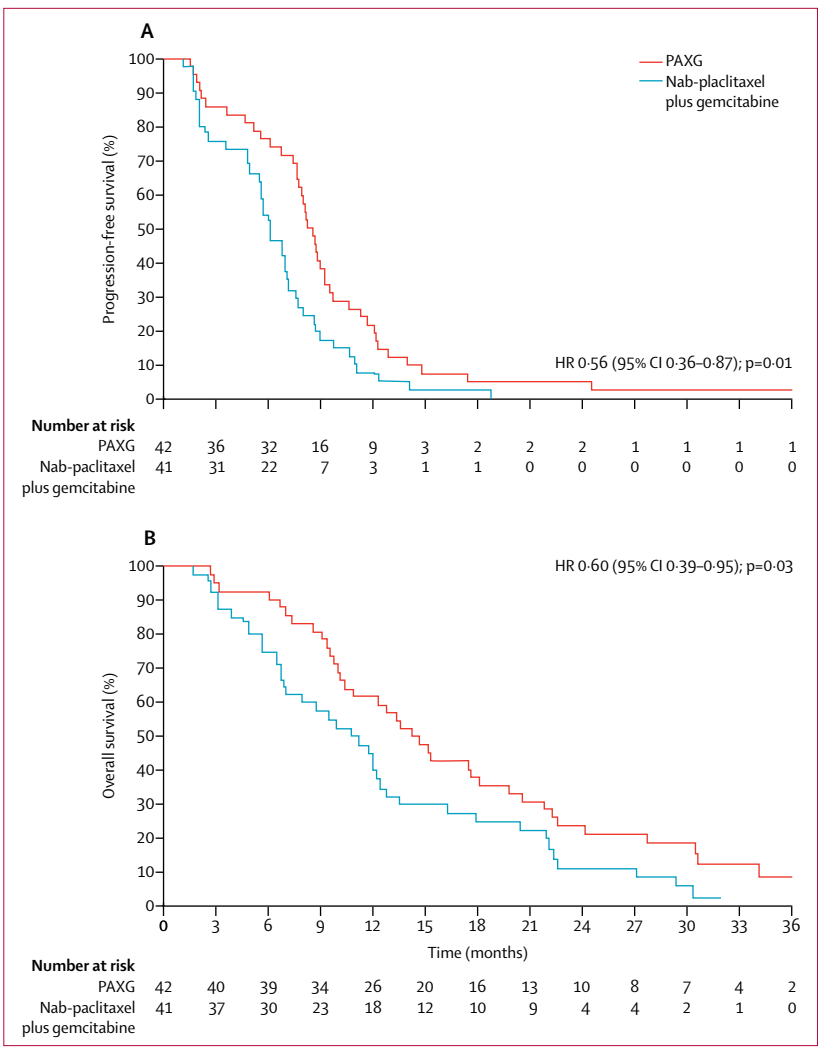

Figure 2: **Progression-free survival (A) and overall survival (B)**
HR=hazard ratio. PAXG=cisplatin, nab-paclitaxel, capecitabine, gemcitabine.

Discussion

This randomised phase 2 trial was designed to assess the proportion of patients who were progression-free at 6 months with the PAXG regimen in patients with metastatic pancreatic adenocarcinoma. More than 70% of patients assigned to PAXG were event-free at 6 months. The proportion of patients who were progression-free at 6 months in the calibration group (nab-paclitaxel plus gemcitabine; 46%) was in line with the null hypothesis and with the outcome previously reported in the phase 3 MPACT trial (44%).[3] One should note that the proportion of patients who are progression-free at 6 months as a primary study endpoint is not a fully validated, consensual surrogate of progression-free survival or overall survival in pancreatic adenocarcinoma. Nonetheless, no universally accepted primary endpoint for phase 2 trials in pancreatic cancer exists. However, the proportion of patients who are progression-free at 6 months seems to be more reliable than any other measure of activity (eg, RECIST and CA19-9 response, or clinical benefit) for selecting promising treatments to be tested in phase 3 trials and could be considered of clinical relevance in metastatic pancreatic adenocarcinoma, because nearly all chemotherapy regimens have not overcome the 6 month progression-free survival threshold of 50%.

The overall outcome of the calibration group was similar to that reported for the nab-paclitaxel plus gemcitabine group of the pivotal MPACT trial;[3] the proportion of patients achieving investigator-assessed RECIST response was 29% in both trials and median progression-free survival was 6·1 months in the present study and 5·5 months in MPACT. Overall survival in the nab-paclitaxel plus gemcitabine group in our study was

	PAXG (n=42)			Nab-paclitaxel plus gemcitabine (n=41)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	8 (19%)	12 (29%)	5 (12%)	7 (17%)	14 (34%)	2 (5%)
Anaemia	32 (76%)	9 (21%)	0	28 (68%)	9 (22%)	0
Thrombocytopenia	23 (55%)	3 (7%)	0	21 (51%)	2 (5%)	1 (2%)
Nausea	17 (40%)	3 (7%)	0	17 (41%)	0	1 (2%)
Vomiting	15 (36%)	2 (5%)	0	6 (15%)	1 (2%)	1 (2%)
Diarrhoea	11 (26%)	3 (7%)	0	11 (27%)	3 (7%)	0
Constipation	8 (19%)	0	0	12 (29%)	0	0
Mucositis	4 (10%)	0	0	6 (15%)	0	0
Fatigue	19 (45%)	7 (17%)	0	24 (59%)	7 (17%)	0
Increased AST or ALT	13 (31%)	0 (0)	0	23 (56%)	0	0
Hand-foot syndrome	14 (33%)	3 (7%)	0	5 (12%)	0	0
Fever	19 (45%)	2 (5%)	0	17 (41%)	1 (2%)	1 (2%)
Venous thromboembolism	3 (7%)	1 (2%)	0	1 (2%)	1 (2%)	0
Infections (other than cholangitis)	8 (19%)	1 (2%)	0	9 (22%)	1 (2%)	0
Peripheral neuropathy	27 (64%)	3 (7%)	0	22 (54%)	4 (10%)	0
Cholangitis	10 (24%)	4 (10%)	0	7 (17%)	1 (2%)	0
Oedema	7 (17%)	0	0	20 (49%)	0	0
Rash	2 (5%)	0	0	4 (10%)	0	0

ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 2: **Treatment-related adverse events**

also similar to that of the western European cohort of the MPACT trial (median overall survival 10·7 months *vs* 10·7 months; 1-year overall survival 44% *vs* 39%; 2-year overall survival 12% *vs* 10%, respectively),[13] suggesting that the results of the experimental group in our study could be interpreted as promising, also in view of the mature follow-up. Furthermore, although our study was done in a single centre and might not reflect a real-world situation, the baseline characteristics of the trial population and the outcome of the calibration group do not suggest major bias in patient selection. Notably, the results in this cohort of patients with metastatic pancreatic adenocarcinoma are paralleled by those seen with the same regimen in the recently reported cohort of patients with non-metastatic disease.[8] The absence of any overt detrimental effect on tolerability associated with PAXG compared with nab-paclitaxel plus gemcitabine is also reassuring. From this perspective and taking into account the calibration group results, the median overall survival (longer than 14 months), 1-year overall survival (62%), and, more importantly, 2-year overall survival (24%) seen in the PAXG group are unusual in the context of metastatic pancreatic adenocarcinoma.

One limitation of the present trial is that an imbalance in several patient baseline characteristics (Karnofsky performance status, sex, biliary stent placement, median CA19-9 concentration, metastatic site) between groups occurred by chance. However, in an exploratory multivariable analysis stratified by these factors, HRs for progression and death remained unmodified.

During the past two decades, little progress has been made in advancing the treatment of patients with metastatic pancreatic adenocarcinoma, despite extensive investigation of novel therapies.[14] Only two combination chemotherapy regimens, FOLFIRINOX and nab-paclitaxel plus gemcitabine, are recommended in this setting.[2,3] Studies of several targeted agents combined with nab-paclitaxel plus gemcitabine[15–17] or FOLFIRINOX[18] have not shown a survival benefit. Accordingly, therapeutic options remain limited. FOLFIRINOX yielded a median overall survival of 9·5–11·2 months and 1-year overall survival of between 43% (including patients with non-metastatic disease) and 48% in phase 2 and 3 trials.[2,19] Febrile neutropenia (4–5% of patients) and grade 3–4 extra-haematological toxicity (neuropathy 9–15%, fatigue 22–24%, vomiting 14–17%, diarrhoea 13–17%, thromboembolism 7%, transaminitis 7%) were reported with remarkable frequency with the FOLFIRINOX regimen and raised concerns about the risk–benefit ratio in the context of palliative treatment for metastatic pancreatic adenocarcinoma.[2,14] The nab-paclitaxel plus gemcitabine regimen yielded a similar median overall survival of 8·5–12·2 months and 1-year overall survival of 35–48% in phase 2 and 3 trials.[3,20] The toxicity profile was similar to that of FOLFIRINOX with regards to febrile neutropenia (2–3%), neuropathy (17–20%), and fatigue (17–27%), but lower frequencies of vomiting (7%), diarrhoea (1–6%), thromboembolism (none), and

transaminitis (none) were reported with nab-paclitaxel plus gemcitabine than with FOLFIRINOX.[3,15] However, nab-paclitaxel plus gemcitabine was associated with toxicity-related death in 4% of patients,[3] consistent with the 5% reported in the nab-paclitaxel plus gemcitabine group in the present study. Despite this study's limitation of a small sample size, the safety profile of PAXG seems consistent with those previously reported with this regimen,[7,8] and compares favourably with other available combination chemotherapies.

To date, new drugs and personalised medicine have not resulted in an improvement in the required relevant outcomes for the treatment of metastatic ductal pancreatic adenocarcinoma. The investigation of methods to better exploit the available therapeutic resources could represent an opportunity to create a more robust treatment backbone on which to build.

Contributors

MR, SZ, UP, MC, DB, CP, MM, SR, and EM contributed to the acquisition of data. MR, SZ, UP, MC, DB, CP, GB, MM, SR, EG, EM, RN, CD, MF, and LG contributed to the literature search, study design, data analysis and interpretation, and writing and approval of the final version of the manuscript. MR guarantees the integrity, accuracy, completeness of data analyses, and adherence to the protocol. The chairperson (MR) wrote the manuscript; he has not been paid to write the report.

Declaration of interests

MR reports grants, personal fees, and non-financial support from Celgene; grants and personal fees from Baxalta; grants and personal fees from Merck Serono; grants from Helsinn; and personal fees from Lilly, Pfizer, AstraZeneca, NovoCure, Halozyme, Novartis, and Shire. LG reports personal fees from Roche, Pfizer, Boehringer Ingelheim, Celgene, Taiho Pharmaceutical, Synthon, AstraZeneca, Genomic Health, Merck Sharp & Dohme, Synaffix, Eli Lilly, Odonate Therapeutics, Sandoz, Onkaido, Oncolytics Biotech, ADC Therapeutics, and Seattle Genetics. All other authors declare no competing interests.

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