Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2–3 trial

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Summary

Background Pancreatic ductal adenocarcinoma are known to metastasise early and a rationale exists for the investigation of preoperative chemotherapy in patients with resectable disease. We aimed to assess the role of combination chemotherapy in this setting in the PACT-15 trial.

Methods We did this randomised, open-label, phase 2–3 trial in ten hospitals in Italy. We report the phase 2 part here. Patients aged 18–75 years who were previously untreated for pancreatic ductal adenocarcinoma, with Karnofsky performance status of more than 60, and pathologically confirmed stage I–II resectable disease were enrolled. Patients were randomly assigned (1:1:1), with a minimisation algorithm that stratified treatment allocation by centre and concentrations of carbohydrate antigen 19-9 (CA19-9 ≤5 × upper limit of normal [ULN] *vs* >5 × ULN), to receive surgery followed by adjuvant gemcitabine 1000 mg/m² on days 1, 8, 15 every 4 weeks for six cycles (arm A), surgery followed by six cycles of adjuvant PEXG (cisplatin 30 mg/m², epirubicin 30 mg/m², and gemcitabine 800 mg/m² on days 1 and 15 every 4 weeks and capecitabine 1250 mg/m² on days 1–28; arm B), or three cycles of PEXG before and three cycles after surgery (arm C). Patients and investigators who gave treatments or assessed outcomes were not masked to treatment allocation. The primary endpoint was the proportion of patients who were event-free at 1 year. The primary endpoint was analysed in the per-protocol population. Safety analysis was done for all patients receiving at least one dose of study treatment. The trial is registered with ClinicalTrials.gov, number NCT01150630.

Findings Between Oct 5, 2010, and May 30, 2015, 93 patients were randomly allocated to treatment. One centre was found to be non-compliant with the protocol, and all five patients at this centre were excluded from the study. Thus, 88 patients were included in the final study population: 26 in group A, 30 in group B, and 32 in group C. In the per-protocol population, six (23%, 95% CI 7–39) of 30 patients in group A were event-free at 1 year, as were 15 (50%, 32–68) of 30 in group B and 19 (66%, 49–83) of 29 in group C. The main grade 3 toxicities were neutropenia (five [28%] of 18 in group A, eight [38%] of 21 in group B, eight [28%] of 29 in group C before surgery, and ten [48%] of 21 in group C after surgery), anaemia (one [6%] in group A, four [19%] in group B, eight [28%] in group C before surgery, and five [24%] in group C after surgery), and fatigue (one [6%] in group A, three [14%] in group B, two [7%] in group C before surgery, and one [5%] in group C after surgery). The main grade 4 toxicity reported was neutropenia (two [11%] in group A, four [19%] in group B, none in group C). Febrile neutropenia was observed in one patient (3%) before surgery in group C. No treatment-related deaths were observed.

Interpretation Our results provide evidence of the efficacy of neoadjuvant chemotherapy in resectable pancreatic ductal adenocarcinoma. Since the trial began, the standard of care for adjuvant therapy has altered, and other chemotherapy regimens developed. Thus, we decided to not continue with the phase 3 part of the PACT-15. We are planning a phase 3 trial of this approach with different chemotherapy regimens.

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Introduction

Most patients with pancreatic adenocarcinoma receive a diagnosis at an advanced stage; this late diagnosis largely explains why more than 97% of patients die from pancreatic ductal adenocarcinoma within 5 years[1] and only 10–20% can undergo surgical resection,[2] which is viewed as the only therapy with curative potential. Surgery alone yields a median survival of 15–20 months and a 2-year survival of 30–42% due to the high frequency of distant or local relapses.[3,4] The standard of care for resectable pancreatic ductal adenocarcinoma consists of upfront surgical resection followed by 6 months of adjuvant chemotherapy. Compared with patients treated with surgery alone, patients receiving postoperative chemotherapy have a modest improvement in median survival (20–22 months) and 2-year survival (40–48%).[3,4]

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Research in context

Evidence before this study

In 2010, at the time of study design, we searched PubMed for studies done in the neoadjuvant setting for patients affected with resectable pancreatic cancer, published between Jan 1, 2000, and Feb 13, 2010, without language restrictions. We found no relevant article when searching with the terms "pancreatic cancer" or "adenocarcinoma" and "pancreatic" and "neoadjuvant" or "preoperative" and "resectable", and "trial", and excluding studies that were dated (ie, before Jan 1, 2000) or had small sample sizes (ie, ≤50 patients). During the following years, we identified three trials in this setting; however, one was not randomised and the other two did not complete the accrual and implied the use of chemoradiotherapy that offered suboptimal control for systemic disease. Moreover, three pooled analyses were taken into account, but these also had preoperative treatment that consisted of chemoradiotherapy in most patients. Overall, given the few relevant trials exploring the role of the neoadjuvant chemotherapy, this approach seemed worthy of investigation.

Added value of this study

To our knowledge, this is the first randomised controlled trial to investigate combination chemotherapy in the preoperative setting. Our results suggest that the use of neoadjuvant combination chemotherapy is safe and effective, and that it seems to confer a therapeutic benefit. Moreover, the risk of surgical complications is not increased when chemotherapy is used before surgery and we observed fewer intraoperative or postoperative metastases compared with patients undergoing upfront surgical resection. This approach could also help to identify those patients who could benefit the most from the surgical intervention.

Implications of all the available evidence

Although in the past decade new combinations of chemotherapy have slightly increased the survival of patients affected by pancreatic cancer, the prognosis of this disease remains poor, even for patients who present with early-stage disease. We showed the safety and promising efficacy of using a combination of drugs in the neoadjuvant setting. Our results suggest that preoperative chemotherapy should be investigated further in a randomised, controlled phase 3 trial.

Results of the ESPAC-4 trial[5] suggested superiority of the combination of gemcitabine and capecitabine (median survival 28 months; 2-year overall survival 53·8%) over gemcitabine alone (25·5 months; 52·1%). The final results of the APACT trial (NCT01964430), which compares gemcitabine with nab-paclitaxel and gemcitabine, and PRODIGE-24 trial (NCT01526135), comparing gemcitabine with mFOLFIRINOX (modified regimen of fluorouracil, leucovorin, irinotecan, and oxaliplatin), might modify the standard of care (results expected in 2018, and 2019, respectively).

The rapid occurrence of distant metastases after surgical resection is consistent with the presence of subclinical disease dissemination at an earlier stage of the disease. Preoperative treatment for patients with resectable pancreatic cancer allows an optimal delivery of effective therapy, giving the drug treatment the full opportunity to eradicate micrometastatic disease, and can show if a given tumour is resistant to the selected drugs, thus offering the chance to choose alternative drugs, whenever available.

See Online for appendix

There are several advantages to such a course of action. Compared with adjuvant chemotherapy, upfront chemotherapy is not delayed by surgical complications or by slow recovery of performance status, which can be common after surgical resection. Only 51–54·3% of patients complete adjuvant chemotherapy regimens.[6,7] Furthermore, primary treatment might also increase the probability of real curative resections by reducing the risk of peritoneal tumour cell implantation during surgery because of intraoperative tumour spillage, nodal involvement, and positive resection margins.

To date, because of the absence of randomised trials, evidence favouring neoadjuvant treatment for resectable pancreatic ductal adenocarcinoma is scarce. We aimed to assess the role of combination chemotherapy in a preoperative setting for treatment of resectable pancreatic ductal adenocarcinoma. At the time of trial design (2010), the standard adjuvant chemotherapy after pancreatic ductal adenocarcinoma resection was gemcitabine, and the only combination chemotherapy showing superiority in metastatic disease over gemcitabine in a phase 3 trial was the PEFG regimen (cisplatin, epirubicin, fluorouracil, and gemcitabine),[8] which was subsequently modified in the PEXG regimen by including oral capecitabine instead of fluorouracil to increase patient compliance.[9] We selected this regimen for our study (PACT-15) because of its good efficacy and tolerability profile.

Methods

Study design and participants

We did this randomised, open-label, phase 2–3 trial in ten Italian hospitals (appendix). This trial conformed to the Declaration of Helsinki and was approved by the local ethics committees. We report the phase 2 part of the trial here (protocol is in the appendix).

Patients were eligible if they had previously untreated pancreatic adenocarcinoma; were aged 18–75 years; had a Karnofsky performance status of more than 60; had pathologically confirmed pancreatic ductal adenocarcinoma; were clinical stage I–II, according to the 2010 TNM classification;[10] had resectable disease defined as the absence of invasion of superior

mesenteric artery or vein, portal vein, coeliac artery, or hepatic artery; and had adequate bone marrow (white blood cells ≥3500 cells per µL, neutrophils ≥1500 cells per µL, platelets ≥100 000 per µL, and haemoglobin ≥10 g/dL), liver (alanine aminotransferase and aspartate aminotransferase ≤3 upper limit of normal [ULN]), and kidney function (serum creatinine ≤1·5 mg/dL). The enrolment of patients without a confirmed pathological diagnosis was allowed only when there had been at least one attempt at fine needle aspiration with a negative outcome, and imaging and clinical history were strongly suggestive for the diagnosis of adenocarcinoma. Criteria for exclusion were a personal history of other 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 for 5 years; pregnancy and lactation; symptomatic duodenal stenosis; concurrent treatment with other experimental drugs; any physiological, familiar, sociological, or geographic conditions that can potentially interfere with adherence to the protocol or to follow-up. Jaundice was not considered an exclusion criterion from the study and could be treated with an endoscopic or a percutaneous biliary stent. Written informed consent was obtained by the attending oncologist from each patient once eligibility was confirmed and after the patient's review of the protocol contents.

Randomisation and masking

Eligible patients were registered at a clinical research organisation (Mario Negri Institute, Milan, Italy) that conserved the randomisation list and was also responsible for local data entry by electronic clinical research forms, central data management monitoring accuracy, completeness, and reliability of the acquired data in a customised web-based database. Treatment was randomly allocated (1:1:1) with a minimisation algorithm (no block size), which stratified treatment allocation by centre and concentrations of carbohydrate antigen 19-9 (CA19-9 ≤5×ULN *vs* >5×ULN). Because of the nature of the interventions, patients were not masked to the assigned treatment. Investigators who administered treatment were masked to the randomisation sequence and knew the assigned treatment only after they had received informed consent from the patients and after they had obtained access to the web-based platform. Investigators who assessed outcomes and analysed results were also not masked to treatment allocation.

Procedures

Patients were randomly assigned to receive surgery followed by adjuvant intravenous gemcitabine 1000 mg/m² on days 1, 8, and 15 every 4 weeks (arm A), or surgery followed by adjuvant PEXG (intravenous cisplatin 30 mg/m², epirubicin 30 mg/m², and gemcitabine 800 mg/m² on days 1 and 15 every 4 weeks and oral capecitabine 1250 mg/m² on days 1–28; arm B), or to preoperative and postoperative PEXG (arm C). In all groups, 6 months of treatment were planned (6 months of postoperative chemotherapy in arms A and B; 3 months of preoperative and 3 months of postoperative chemotherapy in arm C). Patients randomly assigned to group C could start the preoperative chemotherapeutic regimen if they had total bilirubin concentrations of 3 mg/dL or less. Treatment was stopped in cases of relapse or progressive disease, unacceptable adverse events, patient refusal, or medical decision.

In arm A, gemcitabine infusion was delayed in cases of grade 3–4 neutropenia or thrombocytopenia. In arms B and C, gemcitabine was administered at a dose intensity of 75% in cases of grade 2 neutropenia or grade 1 thrombocytopenia. Treatment was delayed for a maximum of 2 weeks in cases of grade 3–4 neutropenia, grade 2–4 thrombocytopenia, or anaemia. If recovery had not occurred within 2 weeks from the day of retreatment, the patient went off the study. In cases of grade 4 neutropenia or grade 3–4 thrombocytopenia, the gemcitabine dose was reduced to 75% in the subsequent cycles. In all three treatment groups, the treatment was delayed until recovery to at least grade 1 in cases of grade 3–4 non-haematological toxicity. Then, treatment could start again with the dose of the drugs deemed responsible for the toxicity reduced by 25%. In cases of multiple toxicities, the dose was tapered on the most severe grade of toxicity. Antiemetic therapy was given based on physician's opinion. Administration of growth factors was allowed in cases of grade 4 neutropenia, as long as it was not used concomitantly with capecitabine nor to permit subsequent administrations of chemotherapy in general at the scheduled times. Surgical or preoperative treatment had to begin within 4 weeks from randomisation and postoperative treatment within 2 months of the date of surgery. If the patient was not fully recovered by this time, treatment had to be definitively interrupted.

Contrast-enhanced CT scans of the chest, abdomen, pelvis, and tumour markers were done within 30 days before the date of the randomisation and repeated after surgery in all three groups, every three cycles of chemotherapy during treatment, every 3 months during the first year after randomisation, every 4 months during the second year, and every 6 months from the third year onwards, or whenever clinically indicated. An abdominal MRI was accepted as an alternative to abdominal CT scan.

Outcomes

The primary endpoint of the study was the proportion of patients who were event-free at 1 year, (with event-free being defined as freedom from progression, relapse, new tumour occurrence, distant metastases, or death), based on local investigator assessment. We also assessed

efficacy in terms of event-free survival (defined as the time from the day of randomisation to disease progression, relapse, new tumour occurrence, distant metastases, or death for any cause, whichever occurred first) and overall survival (defined as the time interval between randomisation and the date of death or of last follow-up visit). The secondary endpoints were the proportion of patients who were resectable; surgical complications and mortality; the percentage of patients with N0 and R0 after surgery; tolerance of treatments; the proportion of patients who achieved radiological response (only in the preoperative arm) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines;[11] the proportion of patients who achieved

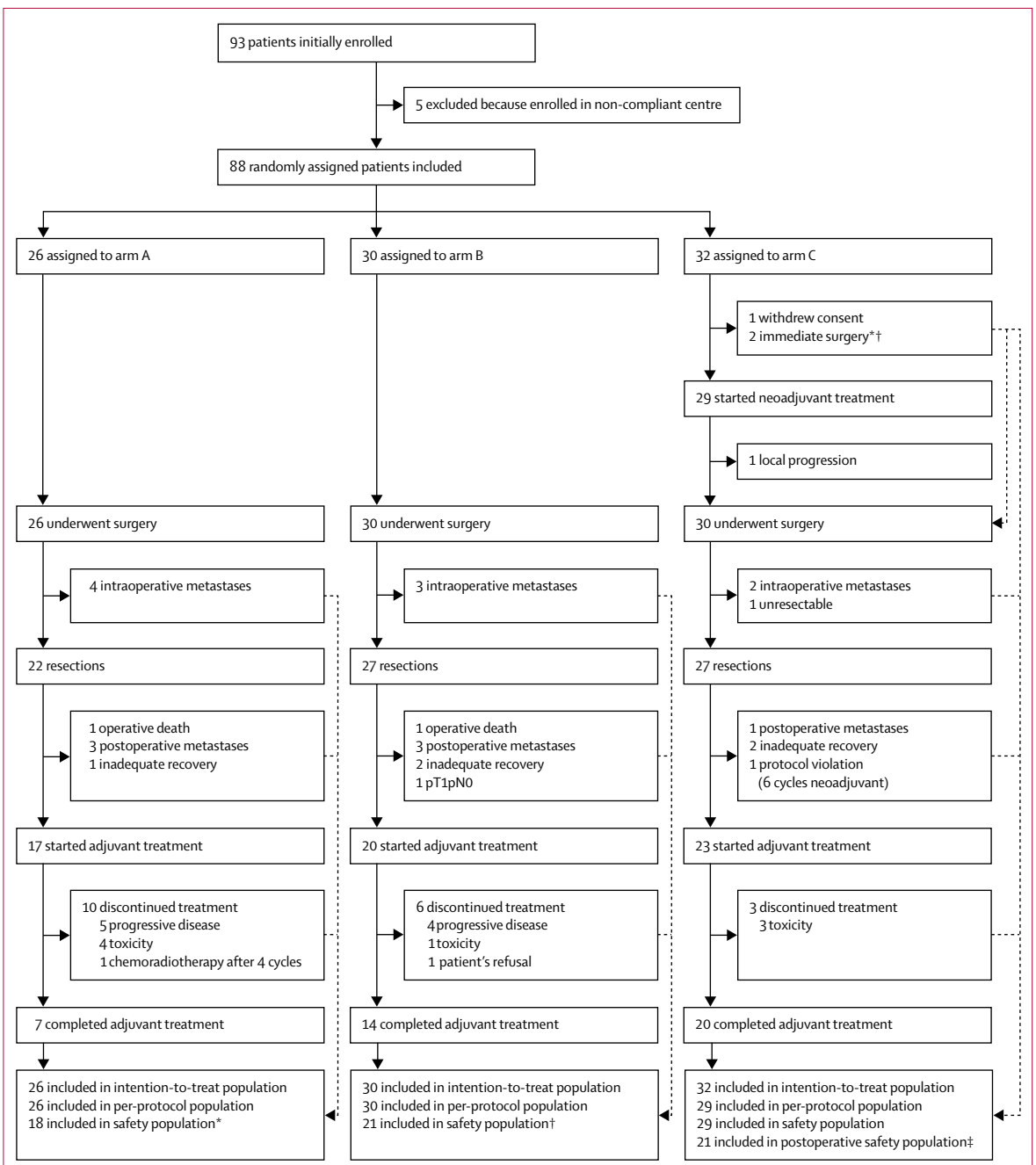

Figure 1: **Trial profile**
One patient received adjuvant gemcitabine after immediate surgery and was included in the safety population of arm A. †One patient received adjuvant PEXG after immediate surgery and was included in the safety population of arm B. ‡Two patients did not receive preoperative PEXG and were included in arm A and arm B†.

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complete pathological response (only in the preoperative arm); and biochemical response (only in the preoperative arm), defined as the percentage of CA19-9 variation at nadir with respect to basal values in patients with basal concentrations higher than normal laboratory concentrations, after normalisation of serum bilirubin concentrations. In this regard, patients were defined as non-responders (CA 19-9 variation <50%), minor responders (CA 19-9 variation between 50% and 89%), and major responders (CA 19-9 variation >89%).[12]

Side-effects of treatment were monitored separately for each cycle. The worst toxicity observed for each patient was registered and classified according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.

The outcome of surgery in different treatment arms was recorded. Surgical complications were defined according to International Study Group of Pancreatic Surgery definitions[13–15] and graded according to the Clavien-Dindo classification.[16] Operative mortality was defined as in-hospital mortality, irrespective of duration; complications or death occurring during readmissions within 30 days after discharge were also recorded.

Statistical analysis

We designed the study as a calibrated phase 2 clinical trial[17] and analysed each experimental arm separately. We verified the null hypothesis, that the proportion of patients alive without relapse would be 20%, against the alternative hypothesis with a one-tailed test. The total number of patients to consider for each group was 24. If more than 16 events were recorded, the treatment arms would not be considered active enough; by contrast, if less than 16 events were recorded, the null hypothesis was to be rejected and the treatment considered active. This design has an error of 10% and a power of 80% under the alternative hypothesis of 40%. If no treatment arm had achieved the minimum accepted level, the study was to be interrupted and the phase 3 trial not done. If only one experimental arm achieved the minimum accepted level, the phase 3 trial was to be done, but we would compare the standard treatment arm to the positive experimental arm. If both arms B and C achieved the minimum accepted level, they were to be compared with a χ^2 test to select the one deserving further evaluation. If no difference was found between these arms, we were to select which regimen to study in the phase 3 trial on the basis of feasibility and safety.

We evaluated the proportion of patients who were event-free at 1 year in the per-protocol population, including all patients satisfying eligibility criteria who were randomly assigned and who did not show major violation of the protocol. We considered major protocol violation when patients in group A and group B did not undergo resection for reasons other than disease failure, or when patients in group C did not receive at least one cycle of preoperative chemotherapy for reasons other than disease failure.

	Group A (n=26)	Group B (n=30)	Group C (n=32)
Sex			
Male	14 (54%)	13 (43%)	25 (78%)
Female	12 (46%)	17 (57%)	7 (22%)
Age (years)	65 (37–74)	68 (49–75)	64 (39–75)
Karnofsky performance status >80	24 (92%)	27 (90%)	29 (91%)
Baseline CA19-9			
>5 × ULN	9 (36%)*	16 (53%)	15 (48%)*
>ULN	18 (72%)*	24 (80%)	23 (74%)*
Baseline CA19-9	179 (39–3337)	240 (40–12000)	173 (43–4510)
Cancer site			
Pancreatic head	25 (96%)	26 (87%)	28 (88%)
Pancreatic body	0	3 (10%)	2 (6%)
Pancreatic tail	1 (4%)	1 (3%)	2 (6%)
Jaundice at diagnosis	21 (81%)	24 (80%)	23 (72%)
Biliary drainage at diagnosis	13 (50%)	15 (50%)	21 (66%)
Lack of pathological confirmation at enrolment	0	1 (3%)	1 (3%)

Data are n (%) or median (range). CA19-9=carbohydrate antigen 19-9. *Data for one patient were unknown.

Table 1: **Baseline characteristic of the patients**

We did the safety analysis for the safety population, defined as all patients receiving at least one dose of study treatment. Operative morbidity and mortality were evaluated on the population of patients who underwent surgical resection.

Event-free survival and overall survival were assessed by Kaplan-Meier analyses in the intention-to-treat population. We also analysed the ratio of objective radiological and biochemical responses, number of resections, percentages of patients with N0 and R0, and patient characteristics in the intention-to-treat population, including all patients who satisfied eligibility criteria and were randomly assigned, on the basis of the assigned treatment at the time of randomisation, regardless of whether the patient actually received any drug.

We did all analyses using Statistica (version 12.0; statistical package for Windows). This study is registered with ClinicalTrials.gov, number NCT01150630.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between Oct 5, 2010, and May 30, 2015, 93 eligible patients were enrolled and randomised (figure 1). One participating institution that enrolled five patients (four randomly assigned to group A and one to group B), was not compliant with the protocol criteria and study conduct. Thus, no patients at this institution received the assigned treatment, and all patients were lost to follow-up. This site and the five patients enrolled were excluded from analyses.

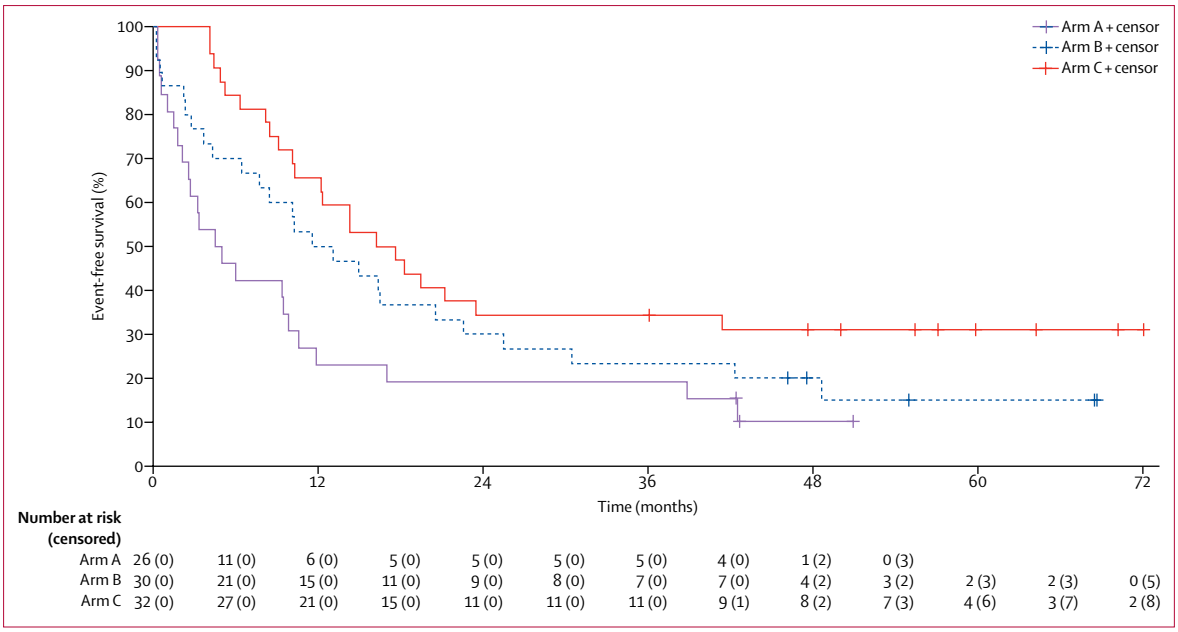

Figure 2: **Event-free survival**

The intention-to-treat population comprised of 88 patients; 26 patients randomly assigned to receive adjuvant gemcitabine (group A), 30 to receive adjuvant PEXG (group B), and 32 to receive preoperative and postoperative PEXG (group C). The baseline demographics and clinical characteristics of the patients are shown in table 1. All patients enrolled in group A and group B received the assigned treatment (ie, surgery upfront), and therefore, the intention-to-treat and per-protocol populations overlapped in these two groups. In group C, two patients underwent immediate resection because of failure to palliate jaundice and one patient did not undergo any treatment because of withdrawal of consent after randomisation. Accordingly, the per-protocol population comprised of 29 patients in group C (figure 1).

At the final analysis (Feb 28, 2018), with a median follow-up of 55·4 months (IQR 47·8–69·4), 23 (88%) events had been observed in group A, 25 (83%) in group B, and 22 (69%) in group C (figure 2). In the per-protocol population, six (23%, 95% CI 7–39) of 26 patients in group A were event-free at 1 year, as were 15 (50%, 32–68) of 30 in group B and 19 (66%, 49–83) of 29 in group C.

Median event-free survival was 4·7 months (95% CI 0·9–8·9) in group A and 12·4 months (5·4–19·4) in group B (figure 2). In group C, median event-free survival was 16·9 months (3·7–28·7) in the intention-to-treat population (figure 2); in the per-protocol population it was 16·2 months (3·7–28·7). For all groups, the main site of tumour failure was a distant site (table 2).

By Feb 28, 2018, 21 patients (81%) in group A, 23 (77%) patients in group B, and 17 (53%) patients in group C had died. Median overall survival was 20·4 months (95% CI 14·6–25·8) for patients randomly assigned to group A, 26·4 months (15·8–26·7) for patients randomly assigned to group B, and 38·2 months (27·3–49·1) for patients randomly assigned to group C (figure 3). In the per-protocol population of group C, median overall survival was 39·8 months (95% CI 28·8–50·8). Intention-to-treat estimates of 3-year overall survival were 35% (95% CI 17–53) in group A, 43% (25–61) in group B, and 55% (38–72) in group C. 3-year overall survival in the per-protocol population of group C was 58% (40–76). Intention-to-treat estimates of 5-year overall survival were 13% (95% CI 0–26) in group A, 24% (9–39) in group B, and 49% (32–66) in group C. 5-year overall survival in the per-protocol population of group C was 50% (32–68).

During surgery, seven patients (13%) in the two adjuvant groups were found to have intraoperative metastases and did not undergo resection (figure 1). The proportion of patients who underwent resection was 88% (49 of 56 patients) in the pooled adjuvant groups (22 [85%] in group A and 27 [90%] in group B; figure 1). In the preoperative treatment group, apart from the patient who withdrew consent, one additional patient did not undergo surgery because of local progression (figure 1). Two patients (6%) were not resected because of intraoperative metastases and one patient (3%) because of local unresectability (figure 1). Of the patients who underwent resections, one patient (5%) in group A, one (4%) in group B, and none in group C died because of surgical complications (table 2). Most resected specimens were pT3 and pN1 (table 3). The number of liver metastases among patients receiving adjuvant therapy appeared to be almost halved after combination therapy compared with adjuvant gemcitabine (14 [64%] of 22 in group A *vs* seven [33%] of 21 in group C; table 2).

	Group A (n=26)	Group B (n=30)	Group C (n=32)
Interval between randomisation and start of assigned treatment (days)	10 (1–25)	10 (1–25)	12 (1–45)
Type of resection			
Pancreaticoduodenectomy	16/22 (73%)	18/27 (67%)	17/27 (63%)
Total pancreatectomy	5/22 (23%)	6/27 (22%)	5/27 (19%)
Distal pancreatectomy	1/22 (4%)	3/27 (11%)	5/27 (19%)
Surgery while jaundiced	8/22 (36%)	9/27 (33%)	2/27 (7%)
Vein resections	2/22 (9%)	2/27 (7%)	0
Overall mortality	1/22 (5%)	1/27 (4%)	0
Overall morbidity	14/22 (64%)	17/27 (63%)	16/27 (59%)
Minor complications (Clavien-Dindo I–II)	9/22 (41%)	12/27 (44%)	13/27 (48%)
Major complications (Clavien-Dindo III–IV)	5/22 (23%)	5/27 (19%)	3/27 (11%)
Pancreatic fistula	3/22 (14%)	3/27 (11%)	3/27 (11%)
Relaparotomy	2/22 (9%)	1/27 (4%)	1/27 (4%)
30-day readmission (or emergency room visit)	0	2/27 (7%)	4/27 (15%)
Length of stay (days)	15·9 (13·8)	15·7 (13·3)	15·2 (13·5)
Start of adjuvant treatment (days)	53 (32–75)	54 (39–70)	52 (31–81)
Number of failures	23	25	22
Site of failure*			
Local	3/22 (14%)	5/24 (21%)	4/21 (19%)
Distant	15/22 (68%)	13/24 (54%)	13/21 (62%)
Both local and distant	4/22 (18%)	6/24 (25%)	4/21 (19%)
Liver	14/22 (64%)	10/24 (42%)	7/21 (33%)

Data are n/N (%), median (range), or mean (SD). *Data for one patient in each group were unknown.

Table 2: **Treatment details, types of surgery, and outcomes**

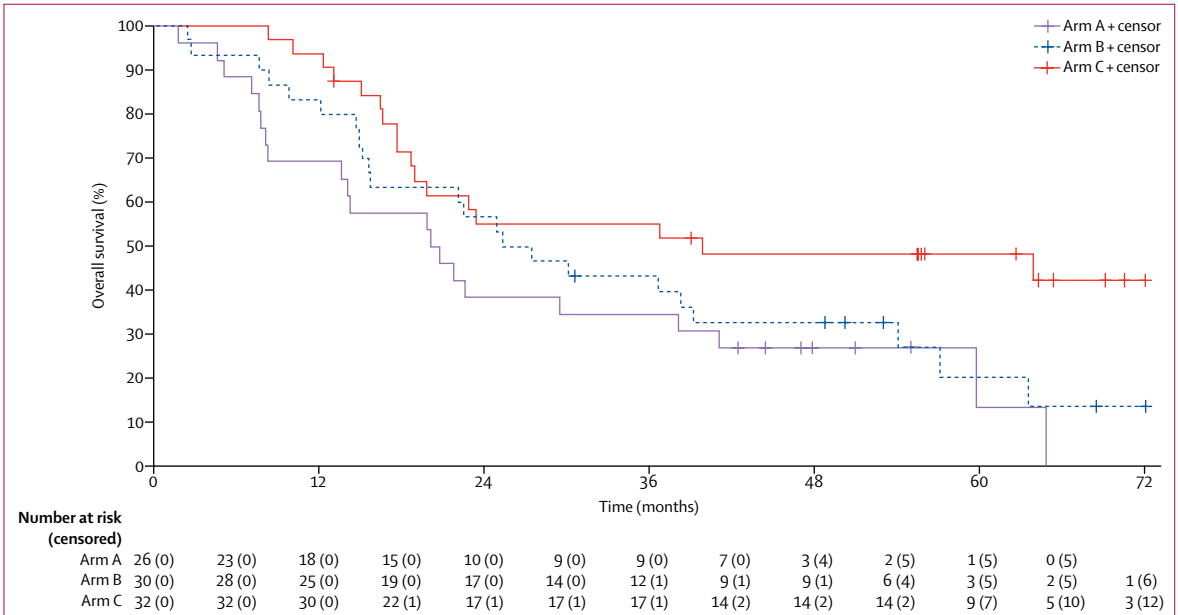

Figure 3: **Overall survival**

In addition to the nine patients with intraoperative metastases, metastases were detected at postoperative CT assessment in three patients in group A, three patients in group B, and one patient in group C (figure 1). Of the 16 patients with intraoperative or postoperative metastases, 13 (23%) patients randomly assigned to immediate surgery and three (9%) patients in the preoperative chemotherapy group had metastatic disease

	Group A (n=22)	Group B (n=27)	Group C (n=27)
pT1	1 (5%)	1 (4%)	4 (15%)
pT2	1 (5%)	0	1 (4%)
pT3	20 (91%)	26 (96%)	22 (81%)
pN0	6 (27%)	7 (26%)	13 (48%)
pN1	16 (73%)	20 (74%)	14 (52%)
Node ratio	16·3% (4–77)	13·6% (3–64)	13·9% (5–29)
R0	6 (27%)	10 (37%)	17 (63%)
R1	16 (73%)	17 (63%)	10 (37%)
Grade 3	13 (59%)	16 (59%)	7 (26%)
Tumour size (cm)	2·5 (1·5–5·0)	2·1 (1·5–7·0)	2·0 (0·0–6·0)
Pathological response[18]			
Marked	NA	NA	9/25 (36%)
Moderate	NA	NA	8/25 (32%)
Poor	NA	NA	8/25 (32%)

Data are n (%), median (range), or n/N (%). Pathological response was calculated for 25 patients receiving preoperative chemotherapy. NA=not applicable.

Table 3: **Pathological characteristics in patients who underwent resection**

that was undetected at baseline CT scan (figure 1). All patients with metastatic disease were subsequently treated with combination chemotherapy (in group A: four PEXG, one FOLFIRINOX, one nab-paclitaxel and gemcitabine [AG], and one clinical phase 3 trial; in group B: four PEXG, one AG, and one FOLFIRINOX; in group C: one FOLFIRINOX, one AG, and two cyclophosphamide–irinotecan [aditoinal patient had unresectable disease]).

In group A, among 18 patients who were potential candidates for adjuvant gemcitabine, clinical conditions did not adequately recover after surgery in one patient (6%), for whom adjuvant treatment was therefore omitted (figure 1). Adjuvant gemcitabine treatment was not completed in ten patients (figure 1) and dose intensity was 84%.

In group B, among 23 patients who were candidates for receiving adjuvant PEXG, two patients (9%) did not receive the assigned therapy because they did not adequately recover after surgery and one patient did not receive treatment because treating oncologists deemed adjuvant chemotherapy unnecessary after a pathological examination showed a pT1pN0 tumour (figure 1). Adjuvant treatment was interrupted before the sixth cycle in six patients (figure 1). Dose intensity was 83% for cisplatin, 81% for epirubicin, 80% for capecitabine, and 76% for gemcitabine.

In group C, 29 (91%) patients received preoperative chemotherapy (figure 1). After surgery, among 26 patients who were candidates for receiving the adjuvant part of the treatment, three did not receive further chemotherapy: two patients (8%) did not adequately recover and one patient (4%) who had received six cycles preoperatively (figure 1). For the two patients in group C who underwent immediate surgery, one (4%) received adjuvant PEXG for six cycles and the other received gemcitabine only because of a minor protocol violation (figure 1). Adjuvant chemotherapy was interrupted before completion in three patients due to toxicity (figure 1). Dose intensity was higher before surgery than after: 89% versus 75% for cisplatin, 87% versus 75% for epirubicin, 86% versus 72% for capecitabine, and 82% versus 63% for gemcitabine.

No chemotherapy toxicity-related deaths were observed (table 4). Serious adverse events were reported in five patients (29%) in group A, five patients (24%) in group B, 11 patients (38%) in group C before surgery, and two patients (10%) in group C after surgery. The main grade 3 toxicities were neutropenia (five [28%] of 18 in group A, eight [38%] of 21 in group B, eight [28%] of 29 in group C before surgery, and ten [48%] of 21 in group C after surgery), anaemia (one [6%] in group A, four [19%] in group B, eight [28%] in group C before surgery, and five [24%] in group C after surgery), and fatigue (one [6%] in group A, three [14%] in group B, two [7%] in group C before surgery, and one [5%] in group C after surgery). The main grade 4 toxicity reported was neutropenia (two [11%] in group A and four [19%] in group B; table 4). Febrile neutropenia was observed in one patient (3%) before surgery in group C (table 4).

Radiological response was assessed in 26 patients in group C. According to RECIST criteria,[11] a partial response was observed in eight (31%) patients, stable disease in 17 (65%) patients, and progressive disease in one (4%). CA19-9 response was assessed in 22 (96%) of the 23 patients in group C with elevated baseline values. A reduction of more than 89% was reported in one patient (5%), between 50% and 89% in 12 patients (55%), and of less than 50% in nine patients (41%). Median CA19-9 reduction was 62% (IQR 35–74).

Discussion

The findings of the phase 2 part of PACT-15 suggest that a combination of drugs is safe and effective in patients with resectable pancreatic adenocarcinoma, and more importantly, that the neoadjuvant administration of an effective combination regimen appears to give an additional therapeutic benefit over that gained with adjuvant-only administration. Both preoperative and adjuvant PEXG resulted in more than 40% of patients being event-free at 1 year, meeting the predefined criteria for success. 3-year and 5-year overall survival with adjuvant therapy were in line with results from a previous phase 2 adjuvant trial that used a similar four-drug regimen (PEFG, with fluorouracil instead of capecitabine).[19] However, we believe the most relevant results of our study are the median survival (38·2 months) and 3-year and 5-year overall survival (55% and 49%, respectively) observed in patients who received neoadjuvant PEXG. Notably, the administration of PEXG in the neoadjuvant and adjuvant setting for the same overall duration as in the adjuvant setting only was associated with different survival outcomes.

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	Group A (n=18)			Group B (n=21)			Group C before surgery (n=29)			Group C after surgery (n=21)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Anaemia	12 (67%)	1 (6%)	0	13 (62%)	4 (19%)	0	19 (66%)	8 (28%)	0	10 (48%)	5 (24%)	0
Neutropenia	3 (17%)	5 (28%)	2 (11%)	5 (24%)	8 (38%)	4 (19%)	9 (31%)	8 (28%)	0	7 (33%)	10 (48%)	0
Febrile neutropenia	0	0	0	0	0	0	0	0	1 (3%)	0	0	0
Thrombocytopenia	3 (17%)	0	0	8 (38%)	1 (5%)	0	13 (45%)	0	1 (3%)	10 (48%)	1 (5%)	0
Hypertransaminasaemia	0	1 (6%)	0	0	0	0	0	0	0	0	0	0
Fatigue	9 (50%)	1 (6%)	0	9 (43%)	3 (14%)	0	10 (34%)	2 (7%)	0	8 (38%)	1 (5%)	0
Abdominal pain	0	1 (6%)	0	0	1 (5%)	0	0	1 (3%)	0	0	0	0
Vomiting	6 (33%)	0	0	8 (38%)	0	0	3 (10%)	1 (3%)	0	1 (5%)	0	0
Hyporexia	0	0	0	1 (5%)	0	0	0	0	0	0	0	0
Hand-foot syndrome	0	0	0	6 (29%)	0	0	6 (21%)	1 (3%)	0	3 (14%)	2 (10%)	0
Atrial Fibrillation	0	1 (6%)	0	0	0	0	0	0	0	0	0	0
Venous thromboembolism	0	0	0	0	1 (5%)	0	0	0	0	0	0	0
Osseous fracture	0	0	0	0	0	0	0	0	0	0	1 (5%)	0

Table 4: **Treatment-related adverse events**

The outcome observed with adjuvant gemcitabine monotherapy might appear worse than expected from previous adjuvant trials,[3–5,20] in which the proportion of patients with 1-year event-free survival was approximately twice that seen in our trial. We must consider that the participants enrolled in our study were patients with a preoperative diagnosis of resectable pancreatic ductal adenocarcinoma. Therefore, our study population was different from previous trials of adjuvant chemotherapy. These previous trials included populations that were highly selected, from which patients with intraoperative or postoperative metastases, serious surgical complications, and inadequate recovery after surgery were excluded—ie, only 37 of 56 (66%) patients randomly assigned to a surgery-first approach in the present trial would have been enrolled in these previous trials. Pancreatic surgery is challenging for patients and surgeons alike, and is associated with frequent and serious morbidity and high mortality. Even high-volume centres report 30–50% morbidity for pancreaticoduodenectomy,[21] including prolonged length of hospital stay, high 30-day readmission rates, long recovery, and serious complications, such as pancreatic fistula, biliary leak, or delayed gastric-emptying syndrome. Furthermore, the quality of life for patients who undergo surgery is frequently impaired by the onset of endocrine and exocrine insufficiencies that make many of these patients unfit for adjuvant chemotherapy for prolonged periods of time or even forever. The patients enrolled in PACT-15 were randomly assigned before any therapeutic procedure and are more representative of a real-life population at time of initial diagnosis. This process alone might explain why the adjuvant gemcitabine monotherapy group had such poor event-free survival.

Our results suggest that chemotherapy does not increase the risk of surgical complications when administered before rather than after the surgical procedure and it does not compromise postoperative recovery. Moreover, the neoadjuvant timing seems to allow for administration of more cycles of chemotherapy.

Neoadjuvant treatment for pancreatic ductal adenocarcinoma has a strong rationale, even in comparison with other solid tumour candidates for drug therapy before surgery, because it allows an individual assessment of sensitivity to drugs that has direct relevance for subsequent decision making. Surgery is unlikely to provide real benefit for the sizeable proportion of patients with chemoresistant, aggressive, and rapidly progressing disease. Additionally, neoadjuvant administration can anticipate, by several months, the exposure of sensitive pancreatic ductal adenocarcinomas and microscopic metastatic foci to effective drugs; the use of these drugs in the adjuvant setting might instead be very delayed or even impossible because of slow recovery and surgical complications.

Previous studies[22–27] of neoadjuvant therapy in patients with resectable pancreatic ductal adenocarcinoma reported a RECIST response in only 9·5–12% of patients, a median decrease of CA19-9 concentrations of 26%, and disease progression in 8–36% patients. Of the patients who were initially resectable, only 57–82%, were actually resected after neoadjuvant therapy and the median survival was between 15·1 months and 28·3 months (23–23·3 months in resected patients).[22–27] These results can be viewed as disappointing and are probably related to suboptimal activity of the adopted chemotherapeutic regimens, and to the choice of administering chemoradiotherapy regimens with limited possibility of adequate control of systemic disease.

Combination regimens[8,9,28,29] that can yield more objective responses and prolonged control of locally advanced and metastatic disease are probably much better candidates for use in the preoperative setting than treatment with single-agent chemotherapy, chemoradiation, or outdated combination chemotherapy

regimens. The results of the present trial suggest that the upfront use of a more effective chemotherapy regimen might reduce the risk of progression during the preoperative phase or during the first 3 months of the adjuvant phase, might increase radiological response rate, and might decrease CA19-9 concentrations. Consistent with retrospective data from the National Cancer Database,[30] showing that neoadjuvant chemotherapy was associated with more patients achieving a lower pathological T and N stage and positive resection margins than those patients who were resected without neoadjuvant therapy, the proportion of patients with N1 disease and R1 resections in the two adjuvant groups in our study appear higher than one might expect from previous trials,[3,4] but are in line with the ESPAC-4 trial results[5] and were numerically lower in group C than in groups A and B, possibly a reflection of downstaging from neoadjuvant chemotherapy. Notably, the number of liver metastases among patients receiving adjuvant therapy appears to be halved after combination therapy compared with adjuvant gemcitabine. Such effects might have affected the lower probability of finding metastases intraoperatively or postoperatively as compared with immediate surgery, and we propose that they also contributed to the promising survival outcome associated with the neoadjuvant approach.

Whether a longer duration of neoadjuvant chemotherapy or the use of a different regimen would achieve better results is a matter of speculation. Possibly relevant to the duration of therapy and the use of a different regimen is our previous investigation of patients with stage III and IV disease, in whom partial responses were reported in 58–63% of patients treated with PDXG (cisplatin, docetaxel, capecitabine, and gemcitabine) and PAXG,[9,31] compared with 33–45% of patients treated with the same PEXG regimen used for a longer time[9,32] and 31% with 3 months of PEXG in the current series.

We believe the results of PACT-15 provide the strongest available evidence to date of the efficacy of neoadjuvant chemotherapy in patients with resectable pancreatic cancer. The study had a phase 2 design and the results cannot be viewed as conclusive. Despite this limitation, the reported advantage of neoadjuvant chemotherapy challenges the belief that the only curative chance for pancreatic cancer is upfront surgery, and could lead to a major departure from the traditional approach, in which initial chemotherapy can give patients an increased chance of therapeutic benefit and eventual cure. During the phase 2 part of the PACT-15 trial, the standard-of-care scenario for adjuvant therapy changed and chemotherapy regimens that are apparently more active or based on more robust evidence than the PEXG regimen are now available for the metastatic disease setting. Accordingly, we decided to not continue with the phase 3 part of the PACT-15. However, we are planning to do a confirmatory phase 3 trial in which the comparator arm is yet to be identified. We will take into account the results of the ESPAC-4 trial[5] and will base our decision on the expected final results of the APACT and PRODIGE-24 adjuvant trials and of the SWOG S1505 trial (NCT02562716; estimated completion date October, 2019), which will compare preoperative and postoperative chemotherapy with FOLFIRINOX with nab-paclitaxel-gemcitabine for patients with resectable disease.

Contributors

MR, GB, SZ, AZ, LR, RC, DP, SM, CD, MC, CP, PGA, MF, and LG contributed to the literature search, study design, data analysis and interpretation, and writing and approval of manuscript. VT did the statistical analysis and contributed to study design and writing and approval of manuscript. MR, GB, SZ, AZ, LR, RC, DP, SM, MC, CP, PM, and DC contributed to patient registration and treatment, data collection, data interpretation, and writing and approval of the manuscript. MR guarantees the integrity, accuracy, completeness of data analyses and adherence to protocol.

Declaration of interests

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