# Neoadjuvant FOLFIRINOX versus neoadjuvant gemcitabine-based chemoradiotherapy in resectable and borderline resectable pancreatic cancer (PREOPANC-2): a multicentre, open-label, phase 3 randomised trial

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See Comment page 1267

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## Summary

**Background** The PREOPANC-2 trial aimed to evaluate whether neoadjuvant FOLFIRINOX improved overall survival compared with neoadjuvant gemcitabine-based chemoradiotherapy followed by adjuvant gemcitabine in patients with resectable or borderline resectable pancreatic ductal adenocarcinoma (PDAC).

**Methods** In this investigator-initiated, open-label, nationwide, phase 3 randomised trial, patients aged 18 years or older with resectable or borderline resectable PDAC and a WHO performance status of 0 or 1 were enrolled across 19 Dutch centres. Patients in the FOLFIRINOX (FFX) group received FOLFIRINOX (85 mg/m² intravenous oxaliplatin, 180 mg/m² intravenous irinotecan, 400 mg/m² intravenous leucovorin, followed by a 400 mg/m² intravenous fluorouracil bolus and then continuous infusion at 2400 mg/m² intravenously over 46 h every 14 days for eight cycles) followed by surgery without adjuvant treatment. Patients in the chemoradiotherapy (CRT) group received three cycles of neoadjuvant gemcitabine (1000 mg/m² intravenously on days 1, 8, and 15 of each 28-day cycle and on days 1 and 8 only for cycles one and three) combined with hypofractionated radiotherapy (36 Gy in 15 fractions) during the second cycle only, followed by surgery and four cycles of adjuvant gemcitabine. Randomisation (1:1) was done using a minimisation technique and stratified by resectability status (resectable *vs* borderline resectable disease) and centre. The primary endpoint was overall survival in the modified intention-to-treat population, after excluding ineligible patients. Data on race and ethnicity were not collected. This trial is registered with EudraCT (2017-002036-17) and is complete.

**Findings** From June 5, 2018, to Jan 28, 2021, 375 patients were randomly assigned to the FFX group (n=188) or the CRT group (n=187). Six patients (three per group) were excluded due to ineligibility (n=4) or immediate withdrawal of informed consent after randomisation (n=2). 208 (56%) of 369 patients were male and 161 (44%) were female. After a median follow-up of 42·3 months (IQR 35·7–48·7), median overall survival was 21·9 months (95% CI 17·7–27·0) in the FFX group versus 21·3 months (16·8–25·5) in the CRT group (HR 0·88 [95% CI 0·69–1·13], p=0·32). The most common grade 3–4 adverse events were neutropenia (43 [25%] of 175 in the FFX group *vs* 38 [22%] of 176 in the CRT group), diarrhoea (41 [23%] *vs* two [1%]), and leukopenia (14 [8%] *vs* 26 [15%]). Serious adverse events occurred in 85 (49%) patients in the FFX group compared with 75 (43%) in the CRT group (p=0·26). Adverse events of grades 3 or worse occurred in 117 (67%) patients in the FFX group versus 106 (60%) patients in the CRT group (p=0·20). Treatment-related deaths occurred in two (1%) patients in the FFX group (multi-organ failure and intestinal mucositis) and one (1%) patient in the CRT group (upper gastrointestinal haemorrhage).

**Interpretation** This randomised trial did not show a difference in overall survival between neoadjuvant FOLFIRINOX and neoadjuvant gemcitabine-based chemoradiotherapy in patients with resectable or borderline resectable PDAC. Both neoadjuvant treatment regimens may be considered in these patients.

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) has a very poor prognosis, with only minor improvements in overall survival over the past few decades.[1] The 5-year overall survival after upfront surgical resection of PDAC without adjuvant treatment is only 10%.[2] Evidence suggests PDAC

## Research in context

### Evidence before this study

The PREOPANC trial showed a 5-year overall survival benefit of 14% (20·5% *vs* 6·5%) for neoadjuvant gemcitabine-based chemoradiotherapy over upfront surgery in patients with resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC). Meanwhile, the multiagent FOLFIRINOX regimen was superior to gemcitabine monotherapy for patients with PDAC in the metastatic and adjuvant setting. Moreover, a patient-level meta-analysis showed promising results for neoadjuvant FOLFIRINOX in borderline resectable PDAC. We searched PubMed for randomised trials comparing neoadjuvant FOLFIRINOX to neoadjuvant gemcitabine-based chemoradiotherapy from database inception until Jan 1, 2017, without language restrictions, and did not identify a completed randomised trial for this comparison. We used the search terms "pancreatic cancer", "adenocarcinoma", "neoadjuvant", "neoadjuvant therapy", "chemotherapy", "chemoradiotherapy", "radiotherapy", "randomised", and "clinical trial".

### Added value of this study

To our knowledge, PREOPANC-2 is the first completed phase 3 randomised trial that compared FOLFIRINOX to gemcitabine-based chemoradiotherapy in the neoadjuvant setting in patients with resectable and borderline resectable PDAC. In view of the results, both neoadjuvant treatment regimens may be considered in patients with resectable and borderline resectable PDAC based on individual patient characteristics. This approach is a valuable alternative for patients in whom neoadjuvant FOLFIRINOX—the generally preferred regimen—is unsuitable.

### Implications of all the available evidence

Two phase 2 trials (SWOG 1505 and ESPAC-5F) investigated neoadjuvant FOLFIRINOX and gemcitabine-based neoadjuvant regimen in patients with resectable or borderline resectable PDAC. Neither trial showed a difference in overall survival between the regimens. The phase 3 PREOPANC-2 trial further supports that FOLFIRINOX and gemcitabine-based regimens can be used in the neoadjuvant setting. However, the superior overall survival of FOLFIRINOX over gemcitabine in the metastatic and adjuvant setting does not extrapolate to the neoadjuvant setting. Yet the available evidence does not exclude a long-term survival benefit of neoadjuvant FOLFIRINOX. In current guidelines, neoadjuvant therapy is recommended as the standard of care for borderline resectable PDAC and could be considered for resectable PDAC in selected patients or clinical trials. The phase 2 NORPACT-1 trial, including 140 patients with resectable PDAC, did not show an overall survival benefit from neoadjuvant FOLFIRINOX compared with upfront surgery with adjuvant FOLFIRINOX. The ongoing phase 3 ALLIANCE A021806 and PREOPANC-3 trials will further compare these treatment strategies.

is a systemic disease even when initial staging shows no metastases.[3]

Upfront surgery followed by adjuvant chemotherapy has long been the standard of care for patients with resectable and borderline resectable PDAC. The drawback of this approach is that about 45% of patients do not receive adjuvant systemic treatment due to surgical complications or frailty.[4,5] A neoadjuvant approach enables early systemic treatment of micrometastatic disease and increases the patients' chances of receiving systemic treatment. Moreover, patients with disease progression on neoadjuvant therapy are spared the morbidity of futile surgery.

The PREOPANC trial showed a long-term overall survival benefit of a neoadjuvant approach in patients with resectable and borderline resectable PDAC.[6,7] Neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery was superior to upfront surgery with adjuvant gemcitabine (hazard ratio [HR] 0·73, 95% CI 0·56–0·96; p=0·025).[7] A meta-analysis of seven randomised controlled trials (RCTs) confirmed the superiority of neoadjuvant therapy compared with upfront surgery for resectable and borderline resectable PDAC (HR 0·66, 95% CI 0·52–0·85, p=0·001).[5] Gemcitabine-based neoadjuvant regimens were used across all trials, with neoadjuvant radiotherapy included in five.

Meanwhile, the FOLFIRINOX regimen was superior to gemcitabine monotherapy for patients with PDAC in both metastatic and adjuvant settings.[8,9] We hypothesised that FOLFIRINOX could also improve outcomes when administered in the neoadjuvant setting. The PREOPANC-2 trial aimed to investigate whether neoadjuvant FOLFIRINOX would improve overall survival as compared with neoadjuvant gemcitabine-based chemoradiotherapy with adjuvant gemcitabine in patients with resectable and borderline resectable PDAC.

## Methods

### Study design and participants

The PREOPANC-2 trial was an investigator-initiated, nationwide, phase 3 randomised trial performed at 19 centres of the Dutch Pancreatic Cancer Group.

Eligible patients were 18 years or older, had histologically or cytologically confirmed resectable or borderline resectable PDAC without evidence of distant metastases, and had a WHO performance status of 0 or 1. Resectability was determined on multiphase CT imaging within 4 weeks before randomisation. Resectable PDAC was defined according to the Dutch Pancreatic Cancer Group criteria as no arterial involvement (celiac trunk, superior mesenteric artery, or common hepatic artery) and less than 90° venous involvement (superior mesenteric vein, portal vein, or

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See Online for appendix

both). Borderline resectable PDAC was defined as arterial involvement less than 90°, venous involvement of 90–270° without venous occlusion, or both. Exclusion criteria were previous treatment for PDAC, comorbidity or previous treatments precluding study treatments, and pregnancy. Advanced age was not an exclusion criterion. A history of other cancers was allowed provided there was no evidence of disease, and the cancer was diagnosed more than 3 years before the diagnosis of pancreatic cancer, or if the patient had a life expectancy of more than 5 years from the date of inclusion. An MRI to rule out small liver metastases was not routinely used. The complete list of inclusion and exclusion criteria is described in the study protocol (appendix).

The study protocol was approved by the Medical Ethics Review Committee Erasmus MC (MEC 2018-004) and registered with EudraCT (2017-002036-17). The study was conducted according to the principles of the Declaration of Helsinki. The study protocol was published previously[10] and is available online (appendix). All patients provided written informed consent.

### Randomisation and masking

Patients were randomly assigned (1:1) to neoadjuvant FOLFIRINOX followed by surgery without adjuvant treatment (FFX group) or neoadjuvant gemcitabine-based chemoradiotherapy followed by surgery and adjuvant gemcitabine (CRT group). Random assignment was performed using a minimisation technique with stratification for resectability status (resectable *vs* borderline resectable disease) and centre. Randomisation was performed by authorised individuals within the research team from participating centres. Patients were allocated through the internet-based randomisation tool ALEA Clinical (ALEA Clinical Services, Abcoude, Netherlands), and the assigned treatment group was sent immediately by email to local investigators. The study was open-label and no masking was used.

### Procedures

Patients allocated to neoadjuvant FOLFIRINOX (FFX group) were scheduled to receive eight cycles of neoadjuvant full-dose FOLFIRINOX. No adjuvant chemotherapy was scheduled. FOLFIRINOX was administered every 14 days and consisted of 85 mg/m² of intravenous oxaliplatin, 400 mg/m² of intravenous leucovorin, 180 mg/m² of intravenous irinotecan, followed by a bolus of 400 mg/m² intravenous fluorouracil, followed by a continuous intravenous infusion of fluorouracil at a dose of 2400 mg/m² over 46 h. Dose modification from the start of treatment was allowed at the treating physician's discretion. Testing of the *DPYD* gene and primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) medication, either pegfilgrastim or filgrastim, after every cycle of FOLFIRINOX, were strongly recommended.

Patients allocated to neoadjuvant chemoradiotherapy (CRT group) were scheduled to receive three cycles of neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions for 3 weeks) added to the second cycle only, and four adjuvant cycles of gemcitabine. Gemcitabine was given weekly (days 1, 8, and 15) of each 28-day cycle at a dose of 1000 mg/m² intravenously. The first and third cycles were modified to a 3-week course (days 1 and 8). The gemcitabine dose alongside radiotherapy remained the same.

In both groups, dose adjustments were based on the maximum graded toxicity within the previous cycle, with dose adjustments as described in the study protocol (appendix). Treatment was discontinued prematurely for unacceptable toxicity (according to the protocol or at the treating physician's discretion), disease progression, death, or at the patient's request. The scheduled neoadjuvant treatment duration was 16 weeks for the FFX group and 10 weeks for the CRT group. The scheduled total treatment duration was 22 weeks for the FFX group and 40 weeks (including up to 12 weeks until the start of adjuvant treatment) for the CRT group.

A restaging CT scan was performed after four cycles of FOLFIRINOX and in both groups after the last cycle of neoadjuvant therapy. Surgery was scheduled within 3–6 weeks after the last chemotherapy cycle. Resection was performed according to the consensus statement of the International Study Group on Pancreatic Surgery (ISGPS).[11] Scheduled adjuvant treatment was started within 12 weeks after resection.

Patients were scheduled for follow-up every 3 months during the first 2 years and every 6 months during years 3–5, calculated from the date of randomisation. Follow-up included a CT scan with tumour marker analysis (serum cancer antigen 19-9 [CA-19] and carcinoembryonic antigen) every 6 months after randomisation during the first 2 years and yearly thereafter until disease recurrence or to a maximum of 5 years after randomisation in patients without recurrence. Data on subsequent anti-cancer treatments after recurrence or progression were not collected. Sex was self-reported. Data on race and ethnicity were not collected.

### Outcomes

The primary endpoint was overall survival, defined as the time between randomisation and death from any cause. Secondary endpoints were progression-free survival, locoregional failure-free interval, distant metastases-free interval, disease-free survival, locoregional recurrence-free interval, treatment start rate, treatment completion rate, dose intensity, dose reduction rate, staging laparoscopy rate, staging laparoscopy yield, surgical exploration rate, resection rate, pathology results (ie, margin-negative [R0] resection, lymph node-negative [N0] resection, tumour size, and pathological response), postoperative complications, clinical response rate, tumour marker (carcinoembryonic antigen and

CA 19-9) response, adverse events, quality of life, cost-effectiveness, and biomarkers in serum and resected tumours. Progression-free survival was defined as survival without any locoregional progressive or recurrent disease, distant metastases, or secondary pancreatic cancer, calculated from the date of randomisation. Death was also considered an event for progression-free survival. Locoregional failure-free interval was defined as the time without locoregional failure after randomisation. Distant metastases-free interval was defined as the time without distant metastases after randomisation. Disease-free survival was defined as the time between randomisation and locoregional recurrence, occurrence of distant metastases, second pancreatic cancer, or death. Locoregional recurrence-free interval was defined as the time between randomisation and locoregional recurrence. Treatment start rate was defined as the percentage of patients who received at least one cycle of study chemotherapy. Treatment completion rate was defined as the percentage of patients who completed all cycles of study chemotherapy. Dose intensity was defined as the amount of drug delivered as a percentage of planned dose according to the protocol. Staging laparoscopy rate was defined as the percentage of patients that underwent a staging laparoscopy. Staging laparoscopy yield was defined as the percentage of patients that underwent staging laparoscopy and were diagnosed with metastatic or locally unresectable disease during this procedure. Surgical exploration rate was defined as the percentage of patients that underwent surgical exploration (open or minimally invasive), regardless of whether a resection was performed. Resection rate was defined as the proportion of patients that underwent a curative-intent pancreatic resection. Margin-negative (R0) resection was defined as the percentage of patients that underwent a resection with 1 mm or less between the inked margin and the tumour cells.[12] Lymph-node (N0) negative resection was defined as the percentage of patients that underwent a resection with negative lymph nodes in the surgical specimen. Pathological response was determined using the modified three-tier Histological Tumour Regression Grading (HTRG) scheme.[13] Postoperative complications were defined according to the Clavien-Dindo classification and definitions of post-pancreatic surgery complications (pancreatic fistula, delayed gastric emptying, and bleeding) by the International Study Group on Pancreatic Surgery. Clinical response rate was defined according to Response Evaluation Criteria in Solid Tumors criteria (version 1.1). Tumour marker response was defined as the change in CA 19-9 and carcinoembryonic antigen after neoadjuvant chemoradiotherapy and after four and eight cycles of neoadjuvant FOLFIRINOX compared with baseline. Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE; version 4.03). Only grade 3, 4, and 5 adverse events were collected. Serious adverse events were defined as any medical occurrence that resulted in death,

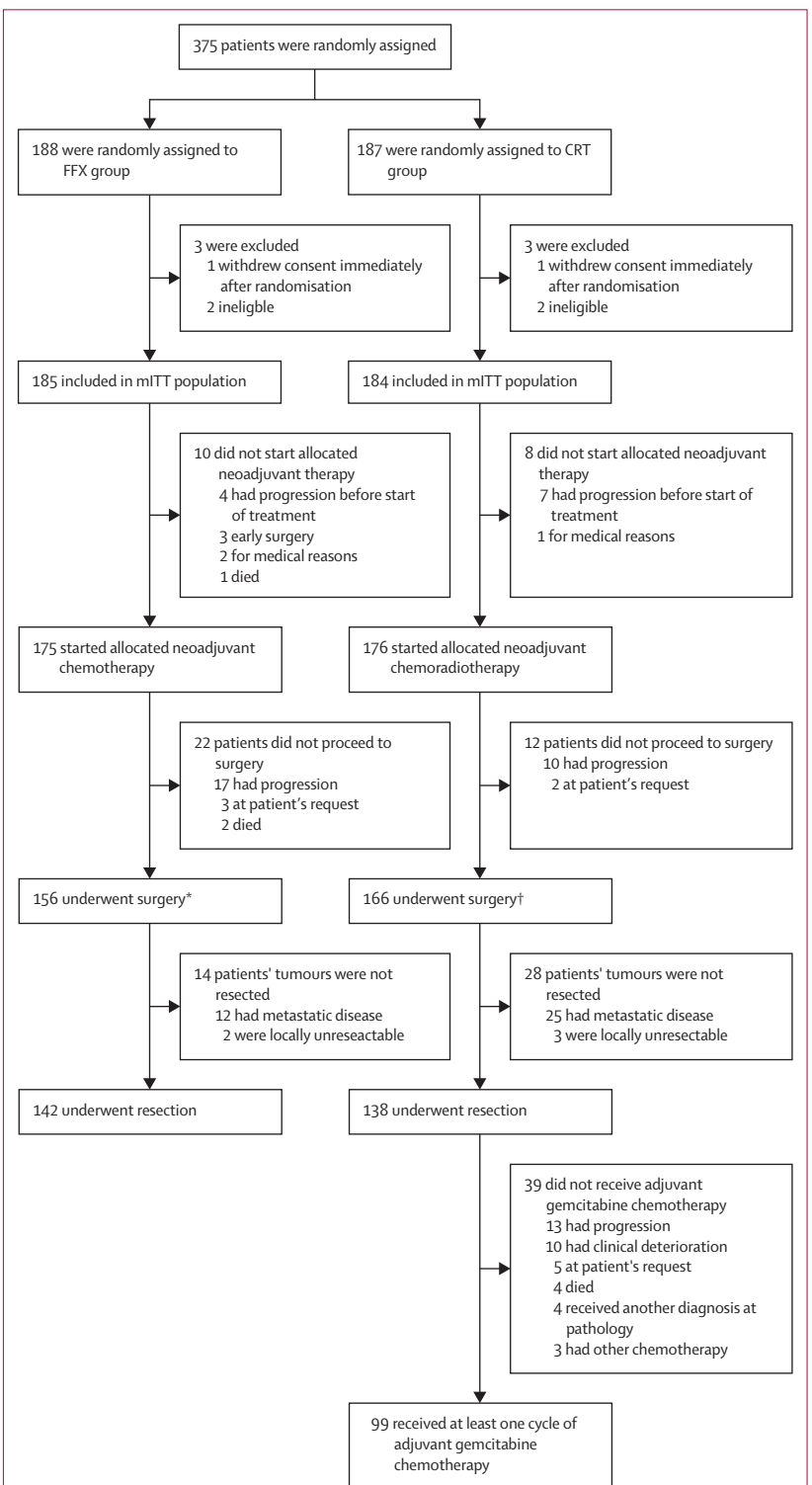


***Figure 1:*** **Trial profile**
CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX. mITT=modified intention-to-treat. *3 patients underwent surgery without FFX. †2 patients underwent surgery without CRT.

was life-threatening, required hospital admission or extension of ongoing hospital stay, resulted in substantial disability, or any other important medical event likely to affect the safety of participants, occurring from randomisation until 30 days after the last chemotherapy. Two or more serious adverse events or two or more adverse events at grade 3 or above were analysed as additional non-prespecified outcomes, as well as the prevalence of serious adverse events by age group (<75 years *vs* ≥75 years). We are in the process of collecting data on quality of life, cost-effectiveness, and biomarkers and will describe the results in separate manuscripts. Additionally, data from this study regarding laparoscopy rate, laparoscopy yield, surgical complications, recurrence (including locoregional failure-free interval, distant metastases-free interval, disease-free survival, and locoregional recurrence-free interval), clinical response rate, tumour marker response, and reasons for dose reductions, will be reported separately.

### Statistical analysis

Sample size calculation was performed for the primary endpoint of overall survival. We estimated the median overall survival in the comparator (CRT) group to be 17 months, based on the initial results of the PREOPANC trial.[14] The calculated sample size was 368 patients (with 252 events), assuming an improvement in overall survival for the intervention (FFX) group to 24 months at a hazard ratio (HR) of 0·70, with 80% power and a two-sided alpha significance level of 0·05, a 3-year enrolment time (monthly accrual 10 patients), and 18 months of follow-up after inclusion of the last patient. Patients alive at the last follow-up were censored.

| | FFX group (n=185) | CRT group (n=184) |
|---|---|---|
| Age, years | 66 (59–72) | 68 (61–73) |
| <65 | 88 (48%) | 68 (37%) |
| 65–74 | 70 (38%) | 84 (46%) |
| ≥75 | 27 (15%) | 32 (17%) |
| Sex | | |
| Male | 115 (62%) | 93 (51%) |
| Female | 70 (38%) | 91 (49%) |
| Resectability status | | |
| Resectable | 120 (65%) | 121 (66%) |
| Borderline resectable | 65 (35%) | 63 (34%) |
| WHO status | | |
| 0 | 112 (61%) | 110 (60%) |
| 1 | 73 (39%) | 74 (40%) |
| CA 19–9, U/mL | 164 (52–471) | 193 (51–622) |
| <500 | 135/175 (77%) | 122/175 (70%) |
| ≥500 | 40/175 (23%) | 53/175 (30%) |
| Tumour size at baseline, mm | 29 (23–35) | 30 (23–36) |
| <30 | 87/161 (54%) | 71/152 (47%) |
| ≥30 | 74/161 (46%) | 81/152 (53%) |
| Location | | |
| Head | 154 (83%) | 158 (86%) |
| Other | 31 (17%) | 26 (14%) |

Data are median (IQR) or n (%). CA 19–9=cancer antigen 19–9. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX.

***Table 1:*** **Baseline characteristics in the modified intention-to-treat population**

The cutoff date for this analysis was Dec 14, 2023. All primary efficacy analyses were performed according to the modified intention-to-treat (mITT) principle. Patients initially randomised but ineligible in hindsight based on information available before randomisation were excluded from all analyses. The adverse events were analysed using the safety population, comprising all patients who received at least one cycle of chemotherapy, analysed as treated and independent of the treatment stage (ie, neoadjuvant or adjuvant). Pathology results were analysed using the patients who underwent surgical resection; patients with a final pathology diagnosis other than PDAC were not included in these analyses.

Categorical variables were compared using Fisher's exact or Chi-square test, and continuous variables were compared using the Mann-Whitney U test. The primary endpoint of overall survival was compared using a stratified Cox proportional hazards model. Treatment effect was expressed using an HR with a corresponding 95% CI. The proportional hazards assumption was tested using the Grambsch–Therneau test. Survival probabilities were estimated using the Kaplan-Meier method. Other time-to-event outcomes were compared using Cox proportional hazards models, and survival curves were constructed using the Kaplan-Meier method. A test for interaction was used to assess the heterogeneity of the treatment effect for the prespecified subgroups of age (<65 years *vs* ≥65 years), sex (male *vs* female), resectability (resectable *vs* borderline resectable), WHO status (0 *vs* 1), CA 19-9 level (<500 *vs* ≥500 U/mL), tumour size (<30 *vs* ≥30 mm), and tumour location (head *vs* other). Additionally, overall survival was investigated in patients who underwent a resection versus those who did not. All tests were two-sided with a statistical significance level of 0·05. Adjustment for multiplicity was not performed. Analyses were performed using R statistical package (version 4.3.2).

An independent Data Safety Monitoring Board was appointed to monitor feasibility, mortality, and serious adverse events, including suspected unexpected serious adverse reactions, with evaluation after a total of 50 patients and 100 patients had completed their allocated treatment. Independent data managers collected data according to study-specific data entry guidelines. Additionally, independent monitors periodically visited each participating centre to check compliance with the study protocol.

### Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

From June 5, 2018, to Jan 28, 2021, 375 patients were randomly assigned. Six patients (three per group) were excluded because of ineligibility (n=4) or withdrawal of informed consent immediately after randomisation (n=2; appendix p 2). The resultant mITT population consisted of 369 patients, who were allocated to receive either neoadjuvant FOLFIRINOX (FFX group; n=185) or neoadjuvant chemoradiotherapy (CRT group; n=184; figure 1). Baseline characteristics of patients can be found in table 1. 208 (56%) of 369 patients were male and 161 (44%) were female. The recruitment rate per centre is provided in the appendix (p 8).

After a median follow-up of 42·3 months (IQR 35·7–48·7), 258 (70%) of 369 patients had died—125 (68%) of 185 in the FFX group and 133 (72%) of 184 in the CRT group. The median overall survival was 21·9 months (95% CI 17·7–27·0) in the FFX group and 21·3 months (16·8–25·5) in the CRT group (HR 0·88 [95% CI 0·69–1·13], p=0·32; figure 2A). There was no evidence for non-proportional hazards (p=0·96). The estimated overall survival was 76% (95% CI 70–82) at 1 year and 36% (30–44) at 3 years for the FFX group, versus 70% (63–77) at 1 year and 33% (27–41) at 3 years for the CRT group. Prespecified subgroup analyses of overall survival for baseline characteristics showed no evidence for treatment effect heterogeneity (figure 3). In patients with resectable PDAC, median overall survival was 21·5 months (95% CI 17·9–28·3) in the FFX group versus 22·5 months (17·4–28·1) in the CRT group (HR 0·93, 95% CI 0·69–1·26, p=0·64). In patients with borderline resectable PDAC, median overall survival was 23·4 months (14·8–31·7) in the FFX group versus 17·0 months (12·3–28·7) in the CRT group (0·80, 0·53–1·21, p=0·30; figure 2B). Figure 2C presents the survival curves for patients who did and did not undergo resection for both groups. The median progression-free survival was 12·1 months (11·3–15·0) in the FFX group versus 11·9 months (10·0–13·7) in the CRT group (0·84, 0·67–1·06, p=0·14; figure 2D).

In total, 175 (95%) of 185 patients started allocated neoadjuvant treatment in the FFX group and 176 (96%) of 184 patients started allocated neoadjuvant treatment in the CRT group. The median time between randomisation and start of neoadjuvant treatment was 13 days (IQR 9–17) in the FFX group and 12 days (8–17) in the CRT group. The most common reason for not starting neoadjuvant treatment was early disease progression (11 [61%] of

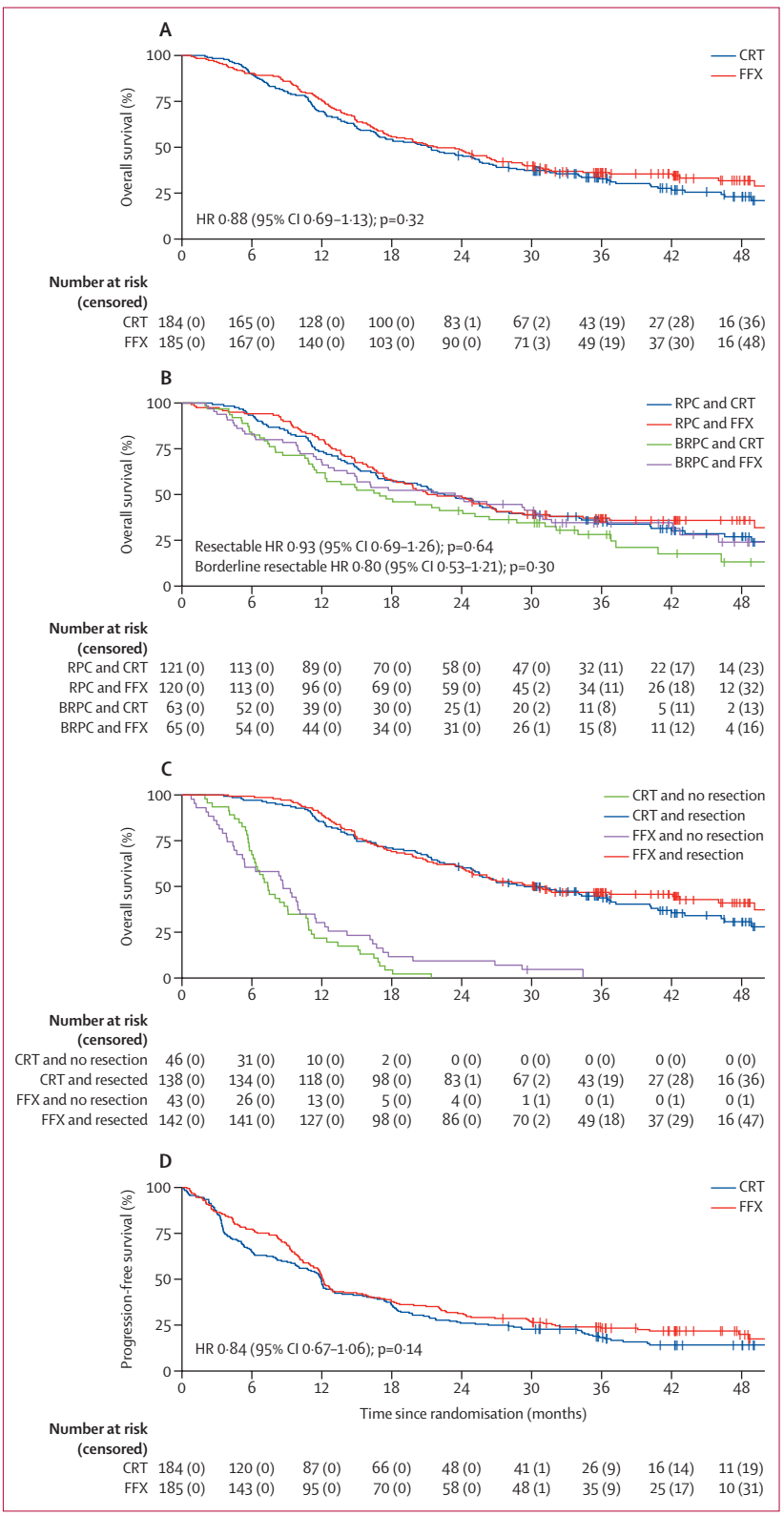


***Figure 2:*** **Overall and progression-free survival in the modified intention-to-treat population and prespecified subgroups**

(A) Overall survival by treatment group. (B) Overall survival by resectability status and treatment group. (C) Overall survival by resection status and treatment group (descriptive analysis). (D) Progression-free survival by treatment group. BRPC=borderline resectable pancreatic cancer. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX. RPC=resectable pancreatic cancer.

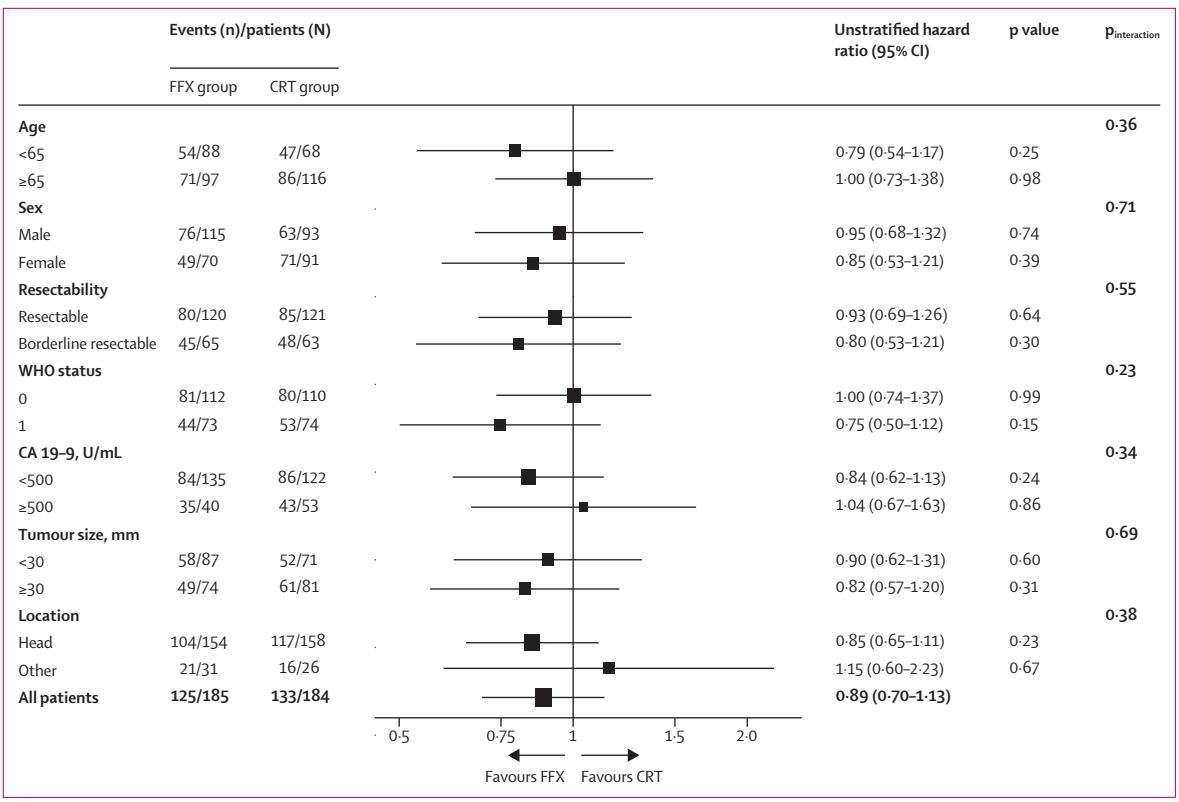


***Figure 3:*** **Forest plot of treatment effect on overall survival according to baseline characteristics in the modified intention-to-treat population**
CA 19-9=cancer antigen 19-9. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX.

18 patients; figure 1). In the FFX group, 150 patients (81%) completed at least four cycles of neoadjuvant chemotherapy, and 114 (62%) completed all eight cycles. At least one dose of granulocyte colony-stimulating factor was administered to 120 (69%) of 175 patients in the FFX group. In the CRT group, 170 (92%) patients started radiotherapy, 167 (91%) completed radiotherapy, and 162 (88%) completed all scheduled neoadjuvant chemoradiotherapy. Overall, 114 patients (62%) in the FFX group completed all scheduled systemic treatment versus 72 patients (39%) in the CRT group (p<0·0001; appendix p 9).

Median total duration of neoadjuvant therapy was 16 weeks (IQR 10–17) in the FFX group and 10 weeks (10–10) in the CRT group. In the FFX group, 143 (82%) of 175 patients required dose reductions as compared with 47 (27%) of 176 patients in the CRT group (p<0·0001). Median relative dose intensity of neoadjuvant chemotherapy was 0·81 (0·69–0·96) in the FFX group and 0·92 (0·85–0·94) in the CRT group (p=0·0042).

After neoadjuvant treatment, 156 (84%) of 185 patients in the FFX group had surgery versus 166 (90%) of 184 patients in the CRT group (p=0·090). The median time between the end of neoadjuvant treatment and surgery was 41 days (IQR 34–51) in the FFX group and 38 days (30–46) in the CRT group. The most common reason for not proceeding to surgery was disease progression (17 [10%] of 175 patients in the FFX group compared with 10 [6%] of 176 patients in the CRT group [figure 1]). Resection was performed in 142 (77%) of 185 patients in the FFX group versus 138 (75%) of 184 patients in the CRT group (p=0·69). Resection rates by resectability status and the number of vascular resections are presented in the appendix (pp 3–4). In a post-hoc analysis, reasons for abandoning resection were occult metastatic disease (12 [8%] of 156 patients in the FFX group versus 25 [15%] of 166 patients in the CRT group [p=0·038]) and locally unresectable disease (two patients [1%] in the FFX group versus three patients [2%] in the CRT group [p=0·70]). Five patients underwent surgery without neoadjuvant study treatment (three in the FFX group, two in the CRT group). Two patients in the CRT group switched to neoadjuvant FOLFIRINOX following local progression after CRT, both of whom subsequently underwent successful resection. None of the patients in the FFX group switched to CRT. In a post-hoc exploratory analysis, postoperative mortality within 30 days after resection was 0 of 142 for the FFX group versus 3 (2%) of 138 for the CRT group (p=0·12). In a post-hoc exploratory analysis, corresponding mortality at 90 days was two (1%) of 142 for the FFX group versus four (3%) of 138 for the CRT group (p=0·44).

In the CRT group, adjuvant gemcitabine chemotherapy was initiated in 99 (72%) of 138 patients who underwent resection after CRT and 54% of all 184 patients randomly assigned to CRT). 74 patients completed all four cycles of

adjuvant gemcitabine chemotherapy—54% of those who underwent a resection after CRT and 40% of all patients randomised to CRT. The most common reasons for not receiving adjuvant chemotherapy were disease progression at postoperative restaging in 13 (9%) of 138 patients who had a resection and clinical deterioration in 10 (7%) of 138 patients (figure 1).

The pathology outcomes of patients with PDAC are listed in table 2. 263 (94%) of 280 patients had postoperative histopathology confirming PDAC. In 17 patients (6%), histopathology revealed other diagnoses—nine (3%) patients had distal cholangiocarcinoma, four (1%) had ampullary carcinoma, and four (1%) had non-malignant disease (appendix p 5). No difference was found between the treatment groups regarding the number of patients who underwent an R0 resection (78 [60%] of 131 patients in the FFX group *vs* 88 [67%] of 131 patients in the CRT group, p=0·25) or had a pathological complete response (11 [10%] of 107 patients in the FFX group *vs* 6 [5%] of 121 patients in the CRT group, p=0·28). The number of ypN0 resections was higher in the CRT group (76 [58%] of 132 patients) compared with the FFX group (62 [47%] of 131 patients; p=0·0073) .

Adverse events of grade 3 or worse occurred in 117 (67%) of the 175 patients in the safety population in the FFX group versus 106 (60%) of 176 patients in the CRT group (p=0·20). Two or more adverse events of grade 3 or above were observed in 80 patients (46%) in the FFX group versus 59 patients (34%) in the CRT group (exploratory analysis p=0·020; appendix p 10). Treatment-related deaths occurred in two patients (1%) in the FFX group (multi-organ failure and intestinal mucositis) versus one (1%) in the CRT group (upper gastrointestinal haemorrhage; p=0·62). Adverse events of grades 3 or above occurring in more than 5% of patients in either treatment group are listed in table 3. The most common grade 3–4 adverse events were neutropenia (43 [25%] of 175 patients in the FFX group *vs* 38 [22%] of 176 in the CRT group), diarrhoea (41 [23%] *vs* two [1%]), and leukopenia (14 [8%] *vs* 26 [15%]). Serious adverse events occurred in 85 patients (49%) in the FFX group versus 75 patients (43%) in the CRT group (p=0·26). Two or more serious adverse events were observed in 32 patients (18%) in the FFX group versus 20 patients (11%) in the CRT group (exploratory analysis p=0·068; appendix p 11). In the FFX group, serious adverse events were observed in 15 (58%) of 26 patients aged 75 years or older and in 70 (47%) of 149 patients aged younger than 75 years (appendix p 6). In the CRT group, serious adverse events were observed in 11 (35%) of 31 patients aged 75 years or older and in 64 (44%) of 145 patients aged younger than 75 years.

## Discussion

This nationwide phase 3 randomised trial found no overall survival difference between neoadjuvant FOLFIRINOX and neoadjuvant gemcitabine-based chemoradiotherapy

| | FFX group (n=131) | CRT group (n=132) | p value |
|---|---|---|---|
| Tumour size, mm* | 25 (16–35) | 25 (20–35) | 0·60 |
| Tumour regression | | | 0·28 |
| No viable tumour | 11/107 (10%) | 6/121 (5%) | .. |
| <5% viable tumour cells | 12/107 (11%) | 17/121 (14%) | .. |
| ≥5% viable tumour cells | 84/107 (79%) | 98/121 (81%) | .. |
| Tumour stage | | | 0·49 |
| ypT0 | 10/130 (8%) | 7 (5%) | .. |
| ypT1 | 37/130 (28%) | 33 (25%) | .. |
| ypT2 | 66/130 (51%) | 79 (60%) | .. |
| ypT3 | 17/130 (13%) | 13 (10%) | .. |
| Nodal stage | | | 0·0073 |
| ypN0 | 62 (47%) | 76 (58%) | .. |
| ypN1 | 43 (33%) | 47 (36%) | .. |
| ypN2 | 26 (20%) | 9 (7%) | .. |
| Margin status | | | 0·25 |
| R0 | 78 (60%) | 88/131 (67%) | .. |
| R1 | 52 (40%) | 43/131 (33%) | .. |
| R2 | 1 (1%) | 0 | .. |
| Perineural invasion | | | 0·47 |
| Present | 76/126 (60%) | 72/129 (56%) | .. |
| Absent | 50/126 (40%) | 57/129 (44%) | .. |

Data are n (%) or median (IQR). Tumour stage and nodal status were defined according to the eighth edition of the TNM classification.[15] Perineural invasion and tumour regression as assessed by investigators. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX. * Tumour size was available for 130 patients in the FFX group.

***Table 2:*** **Pathology results in the surgery population with postoperative pathology confirming pancreatic adenocarcinoma**

| | FFX group (n=175) | | | CRT group (n=176) | | |
|---|---|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 5 (deaths) | Grade 3 | Grade 4 | Grade 5 (deaths) |
| Alanine aminotransferase increased | 4 (2%) | 0 | 0 | 11 (6%) | 0 | 0 |
| Aspartate aminotransferase increased | 4 (2%) | 0 | 0 | 10 (6%) | 0 | 0 |
| Biliary tract infection | 11 (6%) | 0 | 0 | 7 (4%) | 0 | 0 |
| Dehydration | 15 (9%) | 0 | 0 | 3 (2%) | 0 | 0 |
| Diarrhoea | 41 (23%) | 0 | 0 | 2 (1%) | 0 | 0 |
| Fatigue | 9 (5%) | 0 | 0 | 7 (4%) | 0 | 0 |
| Febrile neutropenia | 10 (6%) | 0 | 0 | 2 (1%) | 0 | 0 |
| GGT increased | 11 (6%) | 1 (1%) | 0 | 19 (11%) | 4 (2%) | 0 |
| Hyperglycaemia | 9 (5%) | 1 (1%) | 0 | 4 (2%) | 1 (1%) | 0 |
| Hypertension | 9 (5%) | 0 | 0 | 4 (2%) | 0 | 0 |
| Hypokalaemia | 21 (12%) | 2 (1%) | 0 | 4 (2%) | 1 (1%) | 0 |
| Multi-organ failure | 0 | 0 | 1 (1%) | 0 | 0 | 0 |
| Nausea | 14 (8%) | 0 | 0 | 11 (6%) | 0 | 0 |
| Neutropenia | 24 (14%) | 19 (11%) | 0 | 26 (15%) | 12 (7%) | 0 |
| Small intestinal mucositis | 4 (2%) | 2 (1%) | 1 (1%) | 1 (1%) | 0 | 0 |
| Upper gastrointestinal haemorrhage | 0 | 0 | 0 | 0 | 0 | 1 (1%) |
| Vomiting | 13 (7%) | 0 | 0 | 5 (3%) | 0 | 0 |
| Leukopenia | 9 (5%) | 5 (3%) | 0 | 24 (14%) | 2 (1%) | 0 |

Overview of the number of patients with grade 3–5 adverse events with an incidence of 5% or more in either treatment group. CRT=gemcitabine-based chemoradiotherapy. FFX=FOLFIRINOX. GGT=gamma-glutamyltransferase.

***Table 3:*** **Common grade 3–4 adverse events and all grade 5 adverse events in the safety population**

with adjuvant gemcitabine in patients with resectable and borderline resectable PDAC. Furthermore, secondary endpoints, including progression-free survival, resection percentage, R0 resection percentage, and complete pathological response, showed no statistically significant differences between the two treatment groups. Only the proportion of ypN0 resections was significantly higher in the CRT group than in the FOLFIRINOX group. No difference was found in the proportion of patients with at least one adverse event or serious adverse event at grades 3 or worse, although patients in the FFX group had a higher proportion of two or more adverse events at grades 3 or worse.

The long-term results of the PREOPANC trial showed superior overall survival for neoadjuvant CRT (5-year overall survival 20·5% versus 6·5%; HR 0·73 [95% CI 0·56–0·96], p=0·025).[7] Subsequently, the superiority of a neoadjuvant approach in this setting was confirmed in a meta-analysis including seven RCTs comprising 938 patients.[5] In subgroup analyses, the superiority of the neoadjuvant approach was more evident in the borderline resectable setting (HR 0·61 [95% CI 0·44–0·85], p=0·004) compared with the resectable setting (0·77 [0·53–1·12], p=0·18). International guidelines, therefore, recommend neoadjuvant therapy as the standard of care for patients with borderline resectable PDAC and as a treatment option for resectable PDAC.[16,17] However, these guidelines provide no strong recommendations regarding the preferred neoadjuvant treatment regimen. Neoadjuvant FOLFIRINOX is often preferred over gemcitabine-based treatment by clinicans for patients with a good performance status. This recommendation has not been based on RCTs in the neoadjuvant setting but reflects an extrapolation of superior results with FOLFIRINOX compared with gemcitabine monotherapy in the metastatic and adjuvant setting.[8,9] The results of the current trial could be of particular value in patients for whom neoadjuvant (modified) FOLFIRINOX is considered unsuitable.

Five small, phase 2, randomised trials also compared two neoadjuvant regimens for PDAC. The SWOG S1505 trial investigated perioperative (12 weeks preoperative, 12 weeks postoperative) modified FOLFIRINOX and gemcitabine plus nab-paclitaxel in 102 patients with resectable PDAC and found a median overall survival of 23·2 months (95% CI 17·6–45·9) for FOLFIRINOX versus 23·6 months (95% CI 17·8–31·7) for gemcitabine plus nab-paclitaxel.[18] The ESPAC-5F trial investigated upfront surgery and neoadjuvant treatment with either capecitabine-based CRT, FOLFIRINOX, or gemcitabine with capecitabine in 90 patients with borderline resectable PDAC and found similar rates of overall survival across the neoadjuvant treatment groups.[19] Two small Japanese randomised phase 2 trials (JASPAC-04 and CSGO-HBP-015) found similar overall survival rates comparing neoadjuvant gemcitabine with S-1 to gemcitabine with radiotherapy or nab-paclitaxel.[20,21] The PANACHE01 trial investigated neoadjuvant mFOLFIRINOX, neoadjuvant FOLFOX, and upfront surgery in 153 patients. The median overall survival was 31·3 months (95% CI 21·5–not reached) after neoadjuvant mFOLFIRINOX and 31·8 months (23·8–not reached) after neoadjuvant FOLFOX.[22] The present trial was adequately powered but did not show a difference in overall survival when comparing neoadjuvant FOLFIRINOX with gemcitabine-based CRT.

Almost all secondary endpoints in this study showed no statistically significant differences between the treatment groups. Despite the longer scheduled duration of neoadjuvant treatment in the FFX group (16 versus 10 weeks), the proportion of patients who underwent a resection was similar. The proportion of R0 resections was similar between the groups. Only the N0 resection percentage was superior in the CRT cohort, which did not translate into superior overall survival. A meta-analysis of RCTs showed a higher R0 resection percentage after neoadjuvant treatment compared with upfront surgery in patients with resectable or borderline resectable PDAC (40% versus 29%; p<0·001).[5] Five of seven included RCTs used neoadjuvant chemoradiotherapy. The NORPACT-1 trial compared neoadjuvant FOLFIRINOX (four cycles) with upfront surgery in 140 patients with resectable PDAC. The neoadjuvant approach had superior surgical margin and nodal status, which again did not translate into superior overall survival.[23] Apparently, nodal and margin status are inadequate surrogate outcomes for overall survival in the neoadjuvant setting.

The first unexpected outcome of the PREOPANC-2 trial was that superior overall survival after neoadjuvant FOLFIRINOX compared with gemcitabine-based CRT could not be shown. The second unexpected outcome was that the proportions of patients with at least one adverse event or serious adverse event at grade 3 or worse severity were similar between both groups. This finding was unexpected because FOLFIRINOX was more toxic compared with gemcitabine in the metastatic setting.[8] Increased toxicity in the FFX group was found only for a higher percentage of patients with two or more adverse events at grades 3 or worse.

The optimal duration of neoadjuvant FOFLIRINOX is currently unclear. The number of scheduled neoadjuvant cycles with FOLFIRINOX varied from four in the ESPAC-5F and NORPACT-1 trials to six in the SWOG S1505 trial versus eight in the present PREOPANC-2 trial.[18,19,23] Treatment adherence to neoadjuvant FOLFIRINOX varied considerably across trials. The percentage of patients completing four cycles of neoadjuvant FOLFIRINOX was higher in the PREOPANC-2 trial (81%) compared with the NORPACT-1 trial (46%), but similar to the ESPAC-5F trial (79%). In the SWOG S1505 trial, more patients (84%) received at least six cycles than in the PREOPANC-2 trial (68%). In a small single-centre phase 2 trial, 79% of patients received all eight scheduled neoadjuvant FOLFIRINOX cycles,

compared with only 62% in the present study.[24] The lower completion proportion of all scheduled treatment can be explained by full-dose rather than modified dose FOLFIRINOX, broad inclusion criteria (eg, no age restrictions with 16% of participants in this study aged ≥75 years), and the setting of a nationwide trial in a country with universal health-care coverage.

The rationale for radiotherapy in resectable PDAC is local disease control with a higher proportion of R0 resections. The role of radiotherapy for PDAC, however, remains uncertain. Radiotherapy in the PREOPANC and PREOPANC-2 trials was a component of the neoadjuvant CRT regimen. Therefore, based on these trials, no conclusion regarding the added overall survival benefit of subsequent radiotherapy following systemic treatment can be drawn. The ALLIANCE A021501 phase 2 trial is currently the only published trial that directly compared neoadjuvant FOLFIRINOX with or without hypofractionated radiotherapy, including 126 patients with borderline resectable PDAC.[25] The median overall survival favoured the group without radiotherapy, but the study design did not allow for a direct comparison between the treatment groups. Furthermore, the PANDAS-PRODIGE44 trial comparing mFOLFIRINOX alone or followed by capecitabine-based CRT (50·4 Gy in 28 fractions) showed no difference in overall survival.[26] Ongoing RCTs, including the BRPCNCC-1 trial (NCT03777462), will provide more evidence regarding the additional benefit of neoadjuvant radiotherapy.

The results of the current study should be interpreted considering several limitations. First, the cohort was heterogeneous, including both patients with resectable (65%) and borderline resectable disease (35%). However, the Dutch Pancreatic Cancer Group definition for resectability only allowed for venous contact up to 270° and arterial contact up to 90°. That is, these patients only had limited borderline disease compared with the National Comprehensive Cancer Network definitions. Second, no centralised review of radiological or pathological data was performed. However, radiology reports have been standardised nationwide, patients were randomised in PDAC expertise centres or discussed with PDAC expertise centres at multidisciplinary tumour boards, and pathology specimens were evaluated by experienced pathologists. Finally, toxicity in the FFX group might have been increased because patients were scheduled for full-dose FOLFIRINOX, while other recently published trials scheduled patients for modified dose FOLFIRINOX.[22]

A key strength of the PREOPANC-2 trial is that it is a nationwide study including about 60% of all eligible patients in the Netherlands during the inclusion period. Limited exclusion criteria (eg, no upper age limit) further improved the generalisability of the results. Moreover, treatment compliance was good, considering 150 (81%) of 185 patients received at least four cycles of FOLFIRINOX, and 162 (88%) of 184 received all neoadjuvant CRT. Finally, the primary endpoint of this randomised phase 3 trial was overall survival rather than surrogate endpoints.

Future research should focus on the search for predictive biomarkers for the treatment effects of FOLFIRINOX and gemcitabine-based CRT.[27,28] The extensive longitudinal blood and tissue collection within the PREOPANC-2 trial will allow for searching and validating predictive biomarkers.[29] Another remaining question is whether neoadjuvant FOLFIRINOX confers superior overall survival compared with upfront surgery with adjuvant FOLFIRINOX in patients with resectable PDAC.[30] The NORPACT-1 trial was the first randomised controlled trial to address this question.[23] A difference in median overall survival could not be shown, but the sample size was small, and many patients received two or fewer cycles of neoadjuvant FOLFIRINOX. The ongoing ALLIANCE A021806 trial (NCT04340141) and PREOPANC-3 trial (NCT04927780) aim to answer this question definitively.[31]

In conclusion, the PREOPANC-2 trial did not show a benefit in overall survival for neoadjuvant FOLFIRINOX as compared with neoadjuvant gemcitabine-based chemoradiotherapy followed by adjuvant gemcitabine chemotherapy in patients with resectable and borderline resectable PDAC. Based on these results, both treatment regimens may be considered in these patients.

#### Contributors

BGK, MGB, JWW, MYVH, and GvT conceived and designed the trial. QPJ, JLvD, MLvB, BAB, HB, KPB, SAB, AMEB, ORB, PPLOC, CHJvE, JWBdG, BCMH, IHJTdH, TMK, GK, MBvdK, MSLL, OJLL, SACL, MDPL, LJMM, JSDM, VBN, JJMEN, GAP, HCvS, MWJS, EV, JdV-G, RFdW, BMZ, MYVH, GvT, MGB, JWW, and BGK participated in patient recruitment and trial conduct. QPJ, JLvD, BvdH, and BGK participated in data analysis and interpretation and performed the statistical analysis. QPJ and JLvD directly accessed and verified the underlying data reported in the manuscript. QPJ, JLvD, and BGK participated in data analysis and interpretation and prepared and wrote the initial draft of the report. QPJ and BGK collated changes proposed by all of the authors into the final draft manuscript before final approval by all of the named coauthors. All authors gave final approval of the version to be published.

#### Declaration of interests

MGB has received institutional research grants from the Dutch Cancer Society, ZonMw, Oncosil, MLDS, Deltaplan, and Intuitive Surgical. CHJvE has served as a consultant for AIM Immunotech. BCMH has received honoraria for lectures from Prevents and for data safety monitoring board membership from Amgen. IHJTdH has received institutional research grants from Roche and RanD Biotech. GK is director of the Cancer Center Amsterdam Foundation and director of the ADORE Foundation. BvdH has received honoraria for data safety monitoring board membership from Intergroupe Francophone du Myélome. MDPL has received institutional research grants from Medtronic and Galvani Bioelectronics. JdV-G has received institutional research funding from Servier. JWW has served as a consultant for MSD, AstraZeneca, and Servier, and has received institutional research funding from Servier, MSD, and Nordic. BGK has received institutional research grants from the Dutch Cancer Society and ZonMw for the current investigator-initiated study. All other authors declare no competing interests.

#### Data sharing

De-identified data from this study will be made available to the corresponding author upon reasonable request. Requests will be subject to review and approval by the leading study board of the PREOPANC-2 study group and institutional review boards (if appropriate). All requests should fulfil the following access criteria: all research is conducted with

PREOPANC-2 investigators' support after approval of a proposal by the leading study board of the PREOPANC-2 study group and with a signed data access agreement. The full PREOPANC-2 study protocol, case report form, and informed consent form are available upon reasonable request.

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