Preoperative mFOLFIRINOX versus PAXG for stage I–III resectable and borderline resectable pancreatic ductal adenocarcinoma (PACT-21 CASSANDRA): results of the first randomisation analysis of a randomised, open-label, 2 × 2 factorial phase 3 trial

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Summary

Background Perioperative chemotherapy is a standard option for treatment of patients with resectable and borderline resectable pancreatic ductal adenocarcinoma (PDAC). This study aimed to assess the superiority of PAXG (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine) over mFOLFIRINOX (modified fluorouracil, leucovorin, irinotecan, and oxaliplatin) in this population.

Methods CASSANDRA is a randomised, open-label, 2×2 factorial phase 3 trial, involving 17 Italian academic hospitals. Eligible patients were aged 18–75 years with pathologically confirmed resectable or borderline resectable PDAC. Randomisation was performed by a central web-based system using R-code lists with a computerised algorithm. The design adopted a 1:1 randomisation, with a block stratification by centre and carbohydrate antigen 19-9. Participants were first randomly assigned PAXG (total daily capecitabine dose of 1250 mg/m² in a 625 mg/m² twice a day dosage and intravenous cisplatin 30 mg/m², nab-paclitaxel 150 mg/m², and gemcitabine 800 mg/m² every 14 days) or mFOLFIRINOX (intravenous fluorouracil 2400 mg/m², leucovorin 400 mg/m², irinotecan 150 mg/m², and oxaliplatin 85 mg/m² every 14 days) for 4 months, followed by a second randomisation to 2 months of additional chemotherapy either before or after surgery. The primary endpoint was event-free survival (EFS) in the intention-to-treat population and the safety population included all patients who received at least one cycle of the assigned therapy. The results of the first randomisation are reported here. The trial, registered on ClinicalTrials.gov (NCT04793932) and EudraCT (2020-003080-26 and 2024-519031-42-00), completed accrual and reached the necessary events for first randomisation primary analysis but follow-up of overall survival is ongoing.

Findings Between Nov 3, 2020, and April 24, 2024, 132 eligible patients were assigned to PAXG and 128 to mFOLFIRINOX. In the PAXG group, the median age was 65 years (IQR 60–70), 68 (52%) of 132 patients were female, and 64 (48%) were male. In the mFOLFIRNOX group, the median age was 63 years (IQR 57–69), 62 (48%) of 128 patients were female, and 66 (52%) were male. All 260 patients received at least one assigned chemotherapy administration. PAXG prolonged the median EFS compared with mFOLFIRINOX (16·0 months [95% CI 12·4–19·8] *vs* 10·2 months [8·6–13·5]; hazard ratio 0·63 [0·47–0·84]; p=0·0018). At least one grade 3 or worse adverse event was observed in 87 (66%) of 132 patients in the PAXG group and in 78 (61%) of 128 patients in the mFOLFIRINOX group, including one fatal event.

Interpretation PAXG significantly improved EFS compared with mFOLFIRINOX in resectable or borderline resectable PDAC. Preopertive PAXG could be considered a standard option for resectable or borderline resectable PDAC. Accordingly, preoperative PAXG should be considered as the standard comparator group for future trials in this setting.

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) accounts for about 3% of new cancer cases per year, is the third leading cause of cancer-related death, and yields the worst 5-year survival rate among solid tumours.[1] Only 10–20% of patients are surgical candidates, and surgery alone produces disappointing results, mainly due to early metastatic spread. Postoperative chemotherapy has been

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Research in context

Evidence before this study

From Jan 1, 2000, to June 29, 2020, we searched PubMed using the terms ("pancreatic ductal adenocarcinoma") AND (("neoadjuvant chemotherapy" OR "neoadjuvant chemo-radiotherapy") AND ("resectable" OR "borderline resectable")), limited to the English language. We filtered by article type "clinical trial" and "meta-analysis". In this scenario few phase 2 randomised trials emerged, as PACT15 (surgery upfront plus adjuvant gemcitabine or PEXG [cisplatin, epirubicin, capecitabine, and gemcitabine] *vs* perioperative PEXG) and Prep02 (surgery upfront plus adjuvant S-1 *vs* S-1 perioperative) both suggested the benefit of a neoadjuvant approach compared with primary surgery and adjuvant chemotherapy for patients with resectable pancreatic ductal adenocarcinoma (PDAC). Nevertheless, at that time, the only available phase 3 study, PREOPANC-1, performed in a mixed resectable and borderline resectable population, did not show a benefit of neoadjuvant gemcitabine plus radiotherapy compared with upfront surgery. Afterwards, the long-term, mature results of the study, reported in 2022 (while CASSANDRA was already ongoing), showed that preoperative chemoradiotherapy significantly prolonged survival over surgery. Thus, PREOPANC-1 provided evidence endorsing a neoadjuvant approach in patients with resectable and borderline resectable disease. Since then, several meta-analyses and additional phase 2 randomised studies were reported: NEONAX (surgery upfront followed by AG [nab-paclitaxel and gemcitabine] adjuvant *vs* AG perioperative) in patients with resectable disease and ESPAC5 (surgery plus adjuvant gemcitabine *vs* either short-course neoadjuvant mFOLFIRINOX, gemcitabine plus capecitabine, or chemoradiotherapy) in patients with borderline resectable disease, confirming neoadjuvant and perioperative therapy as a standard in these two settings. Conversely the NORPAC-1 trial (surgery upfront followed by adjuvant chemotherapy with mixed regimens *vs* 2-month preoperative chemotherapy with mixed regimens followed by surgery and postoperative chemotherapy) did not show significant differences between groups. Similarly, the SWOGS1505 phase 2 trial (perioperative nab-paclitaxel plus gemcitabine *vs* mFOLFIRINOX) for patients with resectable disease and the PREOPANC-2 phase 3 trial (neoadjuvant chemoradiotherapy and mFOLFIRINOX) for patients with resectable or borderline resectable disease showed no difference across regimens.

Added value of this study

Overall, cumulative evidence before and during the CASSANDRA trial showed that neoadjuvant therapy is a suitable standard approach in both resectable and borderline resectable PDAC, without evident differences among mFOLFIRINOX, nab-paclitaxel plus gemcitabine, capecitabine plus gemcitabine, or chemoradiation. To date, CASSANDRA and PREOPANC-2 are the only phase 3 studies testing the efficacy of different regimens in the field of resectable and borderline resectable PDAC. The CASSANDRA trial showed superiority of the PAXG regimen over mFOLFIRINOX in the setting of preoperative treatment of resectable and borderline resectable PDAC. Our findings supported not only that PAXG prolongs event-free survival, but also that it increases the rate of disease control, carbohydrate antigen 19-9 response, pathological complete response, pathological IA and IB stages, and node-negative resections, and reduces the incidence of intra or early postoperative metastases. According to subgroup analysis, the treatment effect consistently favoured PAXG across all the subpopulations. Furthermore, the PAXG regimen did not increase treatment-related toxicity and caused a clinically meaningful deterioration of quality of life in a smaller number of domains compared with mFOLFIRINOX.

Implications of all the available evidence

Neoadjuvant therapy should be indicated as standard-of-care for patients with non-metastatic PDAC before surgery. CASSANDRA sets PAXG as a new standard regimen for preoperative treatment of patients with resectable and borderline resectable PDAC.

shown to significantly prolong survival.[2,3] However, the detection of metastases during or after surgery, along with surgical complications, limits adjuvant chemotherapy use to about 65% of patients with initially resectable disease,[4,5] with only 65% completing the planned treatment.[5,6] The role of neoadjuvant therapy was explored in randomised phase 2 trials yielding promising results in both resectable and borderline resectable populations.[4,7,8] However, the anatomical resectability classification does not have prognostic validation[9] and is barely reproducible, even among experts.[10] To overcome this hindrance, The Dutch Pancreatic Cancer Group pragmatically enrolled resectable or borderline resectable patients into the phase 3 PREOPANC-1 trial, providing evidence of neoadjuvant therapy superiority over upfront surgery.[11]

In this context, the Pancreatic Adenocarcinoma Clinical Trials-21 (PACT-21) Chemotherapy Role Assessment in Stage I-III Surgically (Borderline) Resectable Pancreatic Adenocarcinoma: What Neoadjuvant Regimen? What Duration? Refinining the Therapeutic Approach (CASSANDRA) trial was initially designed as a phase 2 randomised trial aimed at selecting the best candidate for phase 3 testing between the PAXG (cisplatin, nab-paclitaxel, capecitabine, and gemcitabine) and the mFOLFIRINOX (modified fluorouracil, leucovorin, irinotecan, and oxaliplatin) regimens. Both regimens warranted evaluation because mFOLFIRINOX and FOLFIRINOX significantly prolonged survival compared with gemcitabine in patients with both metastatic and resected PDAC,[6,12] and encouraging results were reported for PAXG against

nab-paclitaxel plus gemcitabine in a randomised phase 2 study in stage II–III and IV disease.[13,14] During the conduct of the CASSANDRA trial, the phase 3 PREOPANC-2 trial (Netherlands Trial Register identifier: NTR7292, 2018-06-19) showed that mFOLFIRINOX and gemcitabine plus gemcitabine-based chemoradiation therapy followed by surgery yielded similar results in the resectable and borderline resectable population.[15] Accordingly, mFOLFIRINOX became a standard therapeutic option in the CASSANDRA trial population. Since the trial fulfilled the requirements for phase 3 definition,[16] the trial was reclassified accordingly after 224 (86%) of 260 patients were randomised. We aimed to analyse event-free survival (EFS) of PAXG compared with mFOLFIRINOX for first randomisation analysis.

Methods

Study design

This randomised, open-label, 2×2 factorial phase 3 trial (PACT-21 CASSANDRA) was designed under the auspices of the Associazione Italiana Studio Pancreas, approved by the independent ethics committee at each participating institution (appendix pp 2–3), and conducted at 17 Italian academic hospitals in accordance with the International Conference on Harmonization E6 requirements for Good Clinical Practice and with the ethical principles outlined in the Declaration of Helsinki.[17] A data and safety monitoring board was not planned for this study because it was originally designed as a phase 2 trial. The appendix contains the study protocol (pp 19–95) and the statistical analysis plan (pp 96–108). The trial, registered on ClinicalTrials.gov (NCT04793932) and EudraCT (2020-003080-26 and 2024-519031-42-00), has completed accrual and reached the necessary events for first randomisation primary analysis but follow-up of overall survival is ongoing.

The trial was registered 3 months and 15 days late on the ClinicalTrials.gov platform. The first patient was randomised on Nov 3, 2020, and seven patients were enrolled before the registration on March 10, 2021. Autumn, 2020, was difficult in Italy due to the second wave of COVID-19 outbreak and some communication and supervision shortages led to missing this deadline due to good faith human mistakes. The small number of patients who were enrolled before registration guarantees that no attempt at selective or biased reporting of research outcomes was made. Furthermore, patients and the public were informed of the existence of the trial by patients' associations that supported it.

Patients

Eligible patients were aged 18–75 years and had a Karnofsky performance-status score of 70 or more, stage I–III disease according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual,[18] pathologically confirmed PDAC that was considered to be resectable or borderline resectable by local investigators according to National Comprehensive Cancer Network Guidelines, and biologically defined according to the international consensus on definition and criteria of borderline resectable PDAC (carbohydrate antigen 19-9 [CA19-9] of 500 IU/mL or more).[19,20] Self-reported sex (open question) and race (open question) data were collected at clinical review but no ethnicity data were collected due to expected uniformity in the Italian population. A protocol amendment aimed at improving trial external validity was introduced after 21 patients were randomised, allowing the enrolment of participants with dihydropyrimidine-dehydrogenase (DPYD) and uridine-5□-diphospho-glucuronosyltransferase (UGT) dysfunctional polymorphism. Full eligibility criteria are provided in the trial protocol (appendix pp 19–93). All the patients provided written informed consent before study initiation.

Randomisation

Patients were randomly assigned in a 1:1 ratio to receive PAXG or mFOLFIRINOX. Patients without progression or limiting toxicity after 4 months of chemotherapy were further randomised in a 1:1 ratio to receive a further 2 months of the same chemotherapy either before or after surgery. Results of the first randomisation are reported here. The results of the second randomisation will be reported in a separate manuscript.

See Online for appendix

Randomisation lists were written using R code (package randomizeR) and stratified according to centre and CA19-9 serum level (equal or inferior to five times the upper limit of the normal range) for the first randomisation or according to previously assigned treatment for the second randomisation. Both randomisations used 1:1 ratios and blocks that were variable from two to four. The size of blocks randomly varied to guarantee balancing within strata while preserving randomisation concealment. The list was generated at the study start by a consultant statistician who was not in charge of the analysis, integrated into the central clinical research organisation independent web-based platform, and associated with the relevant centre. A randomisation button was defined in the electronic case report form structure. Based on the conditions associated with each randomisation button, the system selected a specific layer from the list and then associated the patient to the first available free position within the randomisation layer. Patient recruitment was overseen by the study investigators of each centre and randomisation was performed by the local clinical trial assistant who was not involved in the rest of the trial.

Procedures

Patients were randomly assigned to receive PAXG (oral capecitabine total daily dose of 1250 mg/m² in 625 mg/m² twice daily dosage and 30–40 min intravenous infusion of nab-paclitaxel 150 mg/m², 60–80 min intravenous

infusion of gemcitabine 800 mg/m², and 60 min intravenous infusion of cisplatin 30 mg/m² every 14 days) or mFOLFIRINOX (2 h intravenous infusion of oxaliplatin 85 mg/m², 2 h intravenous infusion of leucovorin 400 mg/m², 90 min intravenous infusion of irinotecan 150 mg/m², and continuous 46 h intravenous infusion of fluorouracil 2400 mg/m² every 14 days) within 7 days of randomisation. Dose modification according to DPYD and UGT polymorphisms followed recommendations reported in the trial protocol. Each treatment administration was preceded by a blood testing and a physical examination including adverse events assessment by the attending oncologist.

Resection was planned between 4 and 8 weeks after final intravenous chemotherapy administration and was performed according to standard clinical practice. After discontinuation of the trial intervention, a physical examination, blood samples, and tumour markers assessment, alongside a chest and abdomen imaging with contrast enhanced CT or MRI, was repeated every 3 months during the first year after randomisation, every 4 months during the second year, and every 6 months

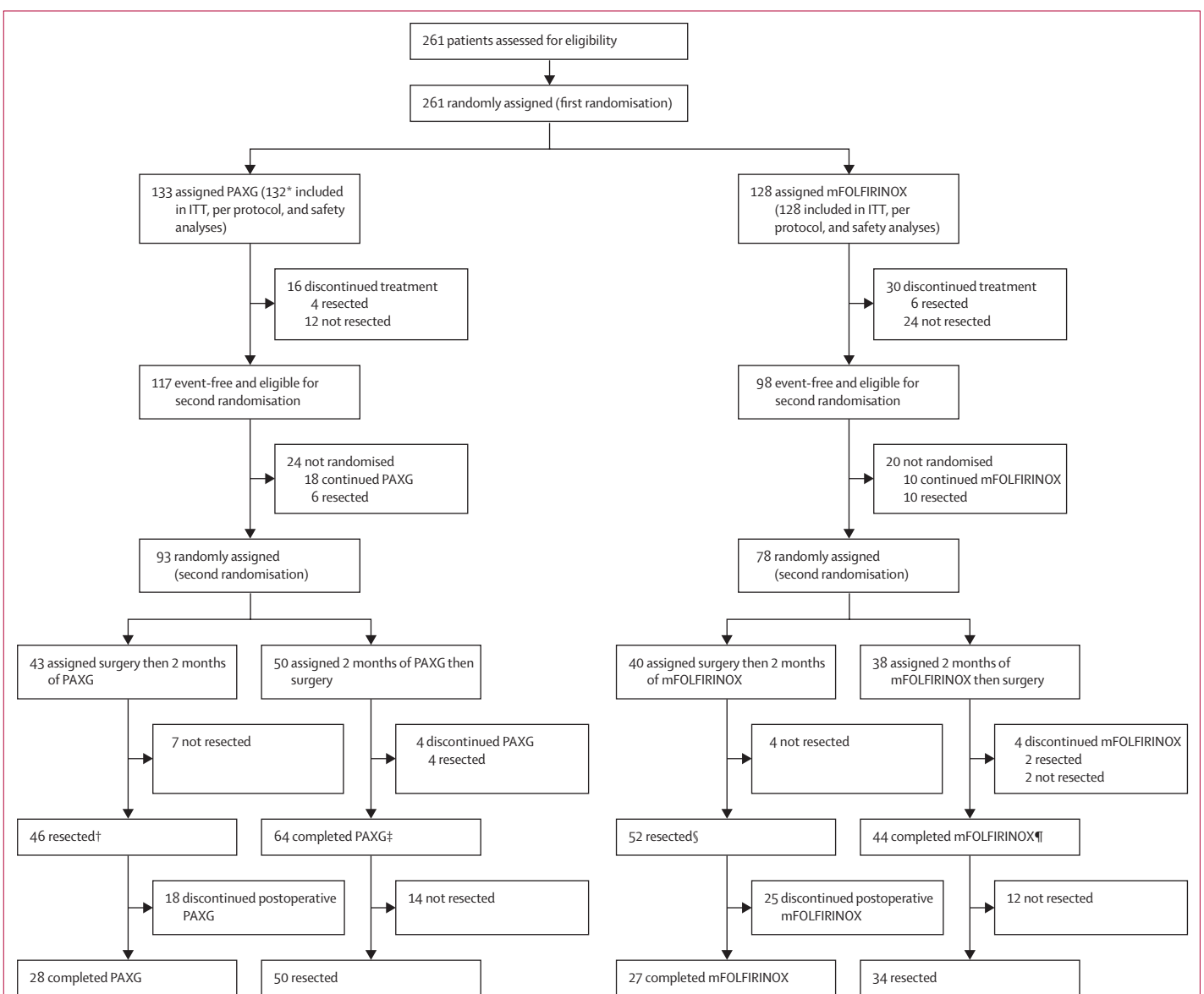

Figure 1: **Trial profile**
ITT=intention-to-treat. *One patient in the PAXG group had a pathological diagnosis of ampullary carcinoma at final histology after surgery, thus was excluded from the analyses. †Includes four resected before completion of first stage and six resected at second randomisation. ‡Includes 18 patients who did not undergo second randomisation and completed 6 months of PAXG. §Includes six resected before completion of first stage and ten resected at second randomisation. ¶Includes ten patients that did not undergo second randomisation and completed 6 months of mFOLFIRINOX.

from the third year onwards or whenever clinically indicated until disease recurrence.

Outcomes

The primary efficacy endpoint was EFS, calculated from the date of randomisation to the date when the local investigator reported the first qualifying event. Any of the following was considered as an event: (1) radiological progression; (2) disease recurrence; (3) two consecutive CA19-9 increases, each of 20% or more, separated by 4 weeks or more (limited to patients with basal level over the superior normal laboratory limit); (4) unresectability; (5) intra-operative metastasis; and (6) death. Patients without events at the time of analysis (July 31, 2025) were censored on the date of the latest informative follow-up.

The secondary endpoints were rates of radiological response, CA19-9 response, resection, complete pathological response, absence of pathological lymph-node involvement, absence of pathological resection margins infiltration, detection of metastases during or within 3 months of surgery, surgical morbidity, chemotherapy toxicity, quality of life, and overall survival. The objective response rate was assessed every 8 weeks by the local investigator based on the revised RECIST criteria.[21] Due to insufficient funding, the radiological response assessment deviated from the per-protocol plan of a central radiology review. Sequential measurements of CA19-9 serum level were repeated at baseline and every 4 weeks during treatment. CA19-9 response was measured in patients with basal level over the superior normal laboratory limit.[22] Namely, patients were classified as non-responders if the percentage reduction at nadir (lowest value assessed while on treatment) with respect to the basal value was inferior to 50%, as minor responders if it was between 50 and 89%, and as major responders if it was 90% of more.[22] The local investigator graded treatment-related adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.[23] Quality-of-life was assessed using the European Organization for Research and Treatment of Cancer (EORTC) 30-item Quality-of-Life Questionnaire (EORTC QLQ-C30) and the 26-item EORTC questionnaire for patients with PDAC (EORTC QLQ-PAN26), both completed by the patients at baseline and after 4 months of chemotherapy. The scores of each EORTC QLQ-C30 and EORTC QLQ-PAN26 scale were calculated according to the EORTC scoring manual.[24] Between-group comparison of treatment-baseline changes in each scale score were assessed by means of analysis of variance. The best health response (improvement, no change, or deterioration) considered the proportion of patients with a clinically meaningful change (defined as a ≥10-point change from baseline). Overall survival was calculated from the date of randomisation until death. Participants who were alive at the time of analysis were censored at the date of the latest time seen alive.

Trial pertinent data wer3 collected in electronic case-report forms by the investigators and analysed by a statistician who vouches with all the authors for their accuracy and completeness. A clinical research organisation collected the electronic case-report forms and monitored the study. An expert radiologist, who was masked to treatment group, centrally reviewed baseline

	PAXG (n=132)	mFOLFIRINOX (n=128)
Age, years	65 (60–70)	63 (57–69)
<65	66 (50%)	76 (59%)
≥65	66 (50%)	52 (41%)
Sex		
Male	64 (48%)	66 (52%)
Female	68 (52%)	62 (48%)
Race		
White	132 (100%)	128 (100%)
Karnofsky performance status		
≤80	9 (7%)	11 (9%)
90–100	123 (93%)	117 (91%)
Anatomical classification		
Resectable	63 (48%)	63 (49%)
Borderline resectable*	69 (52%)	65 (51%)
CA19-9		
Positive	100 (76%)	85 (66%)
Negative	32 (24%)	43 (34%)
Median (95% CI)†	261 (85–940)	226 (116–940)
≤5 × ULN	71 (54%)	79 (62%)
>5 × ULN	61 (46%)	49 (38%)
Clinical tumour staging		
I	71 (54%)	57 (45%)
II	50 (38%)	58 (45%)
III	11 (8%)	13 (10%)
Tumour location		
Head	93 (70%)	96 (75%)
Uncinate process	11 (8%)	9 (7%)
Body	17 (13%)	16 (13%)
Tail	10 (8%)	6 (5%)
Diffuse	1 (1%)	1 (1%)
Genetic variants‡		
Not available	36 (27%)	36 (28%)
Pathogenic	16/96 (17%)	12/92 (13%)
BRCA1 or *BRCA2* gPV	11/96 (11%)	4/92 (4%)
Other gPVs§	5/96 (5%)	8/92 (9%)
None	80/96 (83%)	80/92 (87%)

Data are as median (range), n (%), or n/N (%), unless otherwise stated. CA19-9=carbohydrate antigen 19-9. ULN=upper limit of normal. gPV=germline pathogenic variant. *Patients were included in the borderline resectable population based on both surgical and biological criteria (CA19–9 of 500 IU/mL or greater). †Median values and 95% CIs are calculated for the group of patients with positive CA19-9 values. ‡Genetic testing results refer to germline variants only. §Includes germline pathogenic variants in *ATM*, *MLH1*, *MSH3*, *MSH6*, *MUTYH*, *NBN*, *PALB2*, and *SDHB*.

Table 1: **Baseline characteristics in the intention-to-treat population by treatment regimen**

CT scans at the end of the study to confirm both the anatomical resectability and the AJCC classification.

Statistical analysis

A superiority comparison was planned. Based on a proportion of patients alive without an event at 3 years from randomisation of 20% in the mFOLFIRINOX group (null hypothesis),[11] we anticipated that the EFS rate would be 15% higher in the PAXG group (alternative hypothesis), which would correspond to a hazard ratio (HR) estimated by Cox proportional hazards model of 0·65. We calculated that, under exponential distribution and with a dropout rate of 4%, the inclusion of 260 patients with 173 events would provide the study with 80% power to show a statistically significant difference of 15% in EFS between groups at two-sided 5% log-rank test. There was no plan to test overall survival at this timepoint. Overall survival analysis will be conducted when 173 deaths have occurred.

Data were analysed in the intention-to-treat population (all randomised patients), except for surgical mortality and morbidity, which was assessed in the resected population, and the EORTC-QLQ questionnaire, which was evaluated in patients who had a completed form both at baseline and at second assessment. Qualitative variables were compared by the χ^2 test or Fisher's exact test, and quantitative variables by parametric or non-parametric equivalent test. Survival rate estimates were calculated with the Kaplan–Meier method.

Multivariable analysis of EFS was conducted with a Cox proportional hazards model. The treatment heterogeneity effects in subgroups defined by prognostic factors were displayed in a forest plot,[25] reporting the within-level effect estimates and interaction test.[26] The statistical analysis plan is available in the appendix (pp 94–107).

Role of the funding source

All the trial costs were covered by donations from patients' associations MyEverest and Codice Viola. The study drugs were provided at no charge by the Italian National Health System (DL Dec 23, 1996, N 648, Gazzetta Ufficiale n° 43, Feb 2, 2005). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 3, 2020, and April 24, 2024, 261 patients were randomly assigned to receive PAXG (133 patients) or mFOLFIRINOX (128 patients; figure 1). One patient in the PAXG group had a pathological diagnosis of ampullary adenocarcinoma at final histology after surgery, thus was excluded from all analyses. All the other patients received at least one administration of the assigned treatment. No protocol deviations were observed. Intention-to-treat, per-protocol, and safety populations overlapped (figure 1). Baseline characteristics were similar between groups (table 1). In 132 patients in the PAXG group, the median age was 65 years (IQR 60–70), 64 (48%) were male, and 68 (52%) were female. In 128 patients in the mFOLFIRNOX group, the median age was 63 years (IQR 57–69), 66 (52%) were male, and 62 (48%) were female. All participants were White.

EFS analysis was performed after a median follow-up of 28·5 months (IQR 20·2–38·2), after events occurred in 183 (70%) of 260 participants (83 [63%] of 132 patients in the PAXG group and 100 [78%] of 128 patients in the

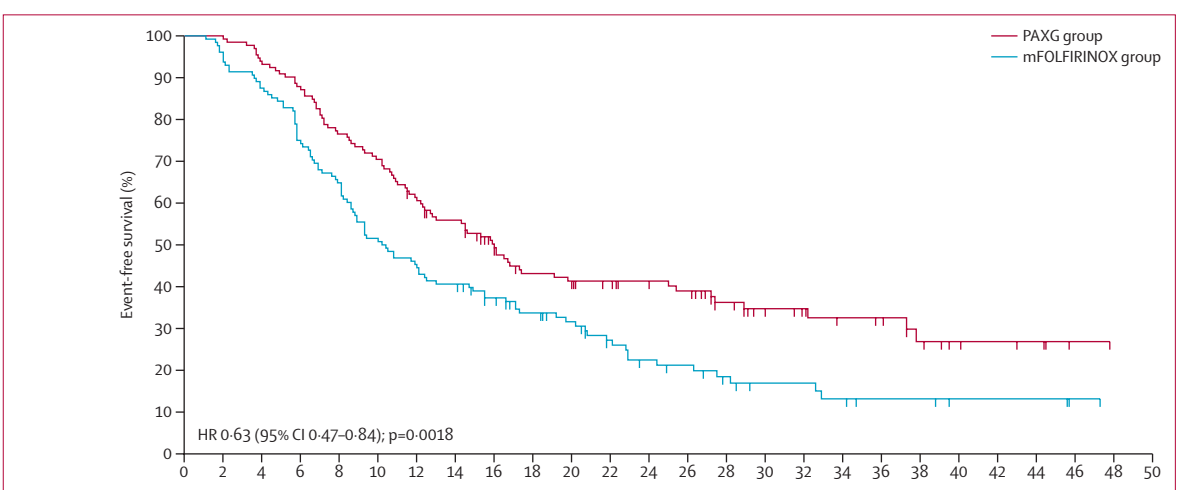

Figure 2: **Kaplan–Meier plot of event-free survival in the intention-to-treat population**
Median event-free survival in PAXG group was 16·0 months (95% CI 12·4–19·8) and in mFOLFIRINOX group was 10·2 months (8·6–13·5). HR=hazard ratio.

mFOLFIRINOX group). Median EFS was significantly longer in the PAXG group than in the mFOLFIRINOX group (16·0 months [95% CI 12·4–19·8] *vs* 10·2 months [8·6–13·5]; HR 0·63 [0·47–0·84]; p=0·0018; figure 2). 1-year EFS rate was 61% (95% CI 57–65) and 3-year EFS rate was 33% (28–37) in the PAXG group, compared with 45% (41–50) at 1 year and 13% (10–17) at 3 years in the mFOLFIRINOX group. Pattern of recurrence was similar in the two groups (table 2). Event type is summarised in table 2.

The results of a multivariable Cox regression analysis and of univariate analyses, including patient and disease-related prognostic factors, confirmed the treatment effect, and the AJCC classification had a more relevant outcome impact than the anatomical classification variables included in the multivariable analysis (appendix p 4). In the subgroup analysis, the treatment effect was also consistently in favour of the PAXG regimen across all subgroups (appendix p 5).

In the resectable population, the median EFS was 19·1 months (95% CI 14·5–37·3) in the PAXG group and 10·4 months (8·7–14·9) in the mFOLFIRINOX group. 1-year EFS rate was 71% (66–77) and the 3-year EFS rate was 40% (33–47) in the PAXG group, compared with a 1-year EFS rate of 46% (40–52) and a 3-year EFS rate of 15% (9–21) in the mFOLFIRINOX group. In the borderline resectable population, the median EFS was 12·4 months (10·7–17·4) in the PAXG group and 10·2 months (6·9–15·5) in the mFOLFIRINOX group. 1-year EFS rate was 52% (46–58) and the 3-year EFS rate was 26% (19–32) in the PAXG group, compared with a 1-year EFS rate of 45% (38–51) and a 3-year EFS rate of 12% (6–17) in the mFOLFIRINOX group.

The rates of disease control (radiological response or stable disease), CA19-9 reduction, early pathological stage, resections without nodal infiltration at pathological report, intraoperative or early postoperative metastases were significantly better in the PAXG group than in the mFOLFIRINOX group (table 2). No significant difference was detected in rates of resection, resections without margin infiltration at pathological report, and surgical morbidity (Clavien–Dindo classification; table 2).

Quality-of-life questionnaires were fulfilled at baseline and month 4 by 110 (83%) of 132 patients in the PAXG group and 82 (64%) of 128 patients in the mFOLFIRINOX group (appendix p 6). A significantly higher rate of patients not fulfilling the questionnaires due to disease progression or treatment withdrawal due to toxicity was observed in the mFOLFIRINOX (20 [16%] of 128 patients) compared with the PAXG group (seven [5%] of 132 patients; p=0·0064; appendix pp 6–10). No statistically significant difference was observed in quality-of-life domains between treatment groups at baseline and at month 4, apart from a trend towards a worse score in the symptoms scale for nausea and vomiting in the mFOLFIRINOX group (p=0·057). Clinically and statistically significant deterioration of fatigue, taste, weight loss concern, and hepatic symptoms

	PAXG (n=132)	mFOLFIRINOX (n=128)	Relative response increase (95% CI)	p value
RECIST best response	..	..	..	..
Partial response	61 (46%)	50 (39%)	..	..
Stable disease	69 (52%)	67 (52%)	..	..
Progression of disease	2 (2%)	11 (9%)	..	..
Objective response rate	..	..	1·18 (0·89–1·57)	0·25
No	71 (54%)	78 (61%)	..	..
Yes	61 (46%)	50 (39%)	..	..
Disease control rate	..	..	1·08 (1·02–1·14)	0·0088
No	2 (2%)	11 (9%)	..	..
Yes	130 (98%)	117 (91%)	..	..
CA19-9 response	..	..	1·38 (1·15–1·65)	<0·0001
Not applicable	32 (24%)	43 (34%)	..	..
Missing	3 (2%)	0	..	..
No	12/97 (12%)	31/85 (36%)	..	..
Yes	85/97 (88%)	54/85 (64%)	..	..
Pathological stage	..	..	..	..
IA*	31 (23%)	17 (13%)	..	..
IB	15 (11%)	12 (9%)	..	..
IIA	0	0	..	..
IIB	39 (30%)	32 (25%)	..	..
III	13 (10%)	22 (17%)	..	..
IV	1 (1%)	5 (4%)	..	..
Not resected	33 (25%)	40 (31%)	..	..
Pathological stage <II	..	..	1·54 (1·04–1·29)	0·030
No	86 (65%)	99 (77%)	..	..
Yes	46 (35%)	29 (23%)	..	..
Resection	..	..	1·12 (0·96–1·30)	0·17
No	33 (25%)	42 (33%)	..	..
Yes	99 (75%)	86 (67%)	..	..
Lymph-node infiltration	..	..	1·57 (1·06–2·33)	0·022
Yes or unresected	85 (64%)	99 (77%)	..	..
No	47 (36%)	29 (23%)	..	..
Resection margin infiltration	..	..	1·06 (0·83–1·35)	0·63
Yes or unresected	65 (49%)	62 (48%)	..	..
No	67 (51%)	66 (52%)	..	..
Intraoperative or early postoperative metastases	..	..	1·07 (1·01–1·14)	0·034
Yes	6 (5%)	15 (12%)	..	..
No	126 (95%)	113 (88%)	..	..
Clavien–Dindo classification†	..	..	..	..
Missing	2/99 (2%)	2/86 (2%)	..	..
0	7/97 (7%)	5/84 (6%)	..	..
I	48/97 (49%)	29/84 (35%)	..	..
II	25/97 (26%)	34/84 (40%)	..	..
IIIa	12/97 (12%)	12/84 (14%)	..	..
IIIb	2/97 (2%)	1/84 (1%)	..	..
IVa	0	0	..	..
IVb	2/97 (2%)	3/84 (4%)	..	..
V	1/97 (1%)	0	..	..

(Table 2 continues on next page)

	PAXG (n=132)	mFOLFIRINOX (n=128)	Relative response increase (95% CI)	p value
(Continued from previous page)				
Clavien–Dindo classification ≤II†	..	..	1·02 (0·89–1·17)	0·79
Missing	2/99 (2%)	2/86 (2%)	..	..
No	17/97 (18%)	16/84 (19%)	..	..
Yes	80/97 (82%)	68/84 (81%)	..	..
Recurrence pattern‡	..	..	..	..
Local	16/83 (19%)	24/100 (24%)	..	..
Liver	27/83 (33%)	31/100 (31%)	..	..
Peritoneum	13/83 (16%)	17/100 (17%)	..	..
Lung	11/83 (13%)	8/100 (8%)	..	..
Not resectable	5/83 (6%)	3/100 (3%)	..	..
CA19-9 increase	12/83 (14%)	21/100 (21%)	..	..
Other sites	13/83 (16%)	11/100 (11%)	..	..
Event distribution‡	..	..	..	..
Unresectable	5/83 (6%)	3/100 (3%)	..	..
Disease progression	25/83 (30%)	34/100 (34%)	..	..
CA19-9§	4/25 (16%)	9/34 (26%)	..	..
Disease recurrence	45/83 (54%)	55/100 (55%)	..	..
CA19-9§	8/45 (18%)	12/55 (22%)	..	..
Intra-operatory metastasis	4/83 (5%)	6/100 (6%)	..	..
Death	4/83 (5%)	2/100 (2%)	..	..

Data are as n (%) or n/N (%), unless otherwise stated. CA19–9=carbohydrate antigen 19-9. *Includes four complete pathological responses. †Percentages are calculated based on the resected population, excluding missing data. ‡Percentages are calculated based on patients who experienced an event at the time of analysis. §Number of patients experiencing disease progression or disease recurrence based on CA19-9 increase. A more detailed description of CA19-9-based events is reported in the appendix (p 17).

Table 2: **Analysis of secondary endpoints in the intention-to-treat population for both treatment groups**

were observed at month 4 versus baseline in both groups. Leg weakness and body image had a clinically meaningful deterioration in the PAXG group. Role functioning, social functioning, nausea and vomiting, dry mouth, and activity planning had a clinically meaningful deterioration in the mFOLFIRINOX group (appendix pp 6–10).

Overall survival data are not mature yet. Preliminary results indicate a median survival of 32·1 in the PAXG group versus 26·4 months in the mFOLFIRINOX group. 2-year overall survival rate was 66% (95% CI 62–71) and 3-year overall survival rate was 48% (42–53) in the PAXG group, compared with a 2-year overall survival rate of 58% (53–63) and a 3-year overall survival rate of 41% (36–47) in the mFOLFIRINOX group.

At least one grade 3 or worse adverse event was observed in 87 (66%) of 132 patients in the PAXG group and 78 (61%) of 128 patients in the mFOLFIRINOX group, including one fatal event. The most frequent adverse events are reported in table 3 and less common adverse events are reported in the appendix (pp 11–15). Grade 3–4 neutropenia was significantly more frequent in the PAXG group. When considering all-grade toxicity, nausea, diarrhoea, peripheral neuropathy, paraesthesia, oral mucositis, increased aspartate aminotransferase and alanine aminotransferase, and increased gamma glutamyl transpeptidase were significantly worse in the mFOLFIRINOX group, while hand–foot syndrome, nail toxicity, and rash were significantly worse in the PAXG group.

The median duration of presurgical treatment was 162 days (IQR 123–183) and postsurgical treatment was 58 days (54–64) in the PAXG group, and in the mFOLFIRINOX group, median duration of presurgical treatment was 132 days (114–176) and postsurgical treatment was 56 days (35–59). 100 (76%) of 132 patients in the PAXG group and 83 (65%) of 128 patients in mFOLFIRINOX group received treatment for at least 4 months.

The median relative dose-intensity (the proportion of the administered cumulative dose relative to the planned cumulative dose) of presurgical and postsurgical chemotherapy, respectively, was 83% (IQR 80–93) and 73% (59–96) for cisplatin, 70% (62–81) and 75% (67–92) for nab-paclitaxel, 64% (51–79) and 52% (40–73) for capecitabine, and 75% (66–88) and 70% (65–75) for gemcitabine in the PAXG group. In the mFOLFIRINOX group, median relative dose-intensity of presurgical and postsurgical chemotherapy, respectively, were 80% (71–92) and 82% (71–98) for fluorouracil, 77% (68–91) and 80% (72–98) for irinotecan, and 77% (68–91) and 75% (67–87) for oxaliplatin.

Among 99 patients who were resected in the PAXG group, 75 (76%) completed the assigned number of preoperative administrations; 38 (84%) of 45 patients who were assigned eight preoperative administrations and 37 (69%) of 54 patients assigned 12 preoperative administrations. Among 86 patients who were resected in the mFOLFIRINOX group, 58 (67%) completed the assigned number of preoperative administrations; 38 (73%) of 52 patients who were assigned eight preoperative administrations and 20 (59%) of 34 patients assigned 12 preoperative administrations. After surgery, 28 (62%) of 45 patients in the PAXG group and 27 (52%) of 52 patients in the mFOLFIRINOX group completed the four planned postoperative administrations. Treatment at the time of event occurrence is summarised in the appendix (p 16).

Discussion

The primary analysis of the CASSANDRA trial showed that preoperative treatment with the PAXG regimen led to a significantly longer EFS compared with mFOLFIRINOX in patients with stage I–III, resectable or borderline resectable PDAC. The EFS improvement satisfied the superiority hypothesis used to calculate the sample size, translating into a 37% reduction in the risk of events and in a 20% absolute difference at 3 years, was independent from other variables at the multivariable analysis, and was maintained across all patient subgroups. Such differences would achieve a score of A according to the European Society for Medical Oncology–Magnitude of Clinical Benefit Scoring methodology (corresponding to the highest clinical benefit in the curative setting).

	PAXG (n=132)			mFOLFIRINOX (n=128)			p value
	Grades 1–2	Grade 3	Grade 4	Grades 1–2	Grade 3	Grade 4	
Haematological toxicity							
Anaemia	42 (32%)	3 (2%)	0	30 (23%)	0	0	0·058
Neutrophil count decreased (neutropenia)	37 (28%)	47 (36%)	9 (7%)	34 (27%)	31 (24%)	6 (5%)	0·012
Platelet count decreased	30 (23%)	1 (1%)	0	28 (22%)	1 (1%)	0	0·87
Febrile neutropenia	0	3 (2%)	0	0	1 (1%)	1 (1%)	0·68
Non-haematological toxicity							
Fatigue	86 (65%)	10 (8%)	1 (1%)	81 (63%)	10 (8%)	0	0·67
Nausea	76 (58%)	6 (5%)	0	90 (70%)	8 (6%)	0	0·012
Peripheral neuropathy	54 (41%)	7 (5%)	0	82 (64%)	4 (3%)	0	0·0006
Paraesthesia	30 (23%)	3 (2%)	0	47 (37%)	1 (1%)	0	0·030
Diarrhoea	46 (35%)	3 (2%)	0	76 (59%)	7 (5%)	0	<0·0001
Fever	45 (34%)	0	0	43 (34%)	1 (1%)	0	0·96
Hand–foot syndrome	42 (32%)	4 (3%)	1 (1%)	2 (2%)	0	0	<0·0001
Abdominal pain	32 (24%)	2 (2%)	0	44 (34%)	3 (2%)	0	0·056
Decreased appetite	31 (23%)	3 (2%)	0	29 (23%)	0	0	0·56
Vomiting	30 (23%)	2 (2%)	1 (1%)	38 (30%)	5 (4%)	0	0·13
Constipation	30 (23%)	0	0	24 (19%)	0	0	0·43
Dysgeusia	29 (22%)	0	0	19 (15%)	1 (1%)	0	0·19
Pain	29 (22%)	0	0	32 (25%)	0	0	0·56
Rash	19 (14%)	0	0	4 (3%)	0	0	0·0014
Mucositis oral	14 (11%)	1 (1%)	0	28 (22%)	4 (3%)	0	0·0043
Nail toxicity	11 (8%)	2 (2%)	0	3 (2%)	0	0	0·012
Infusion-related reaction	7 (5%)	1 (1%)	0	4 (3%)	5 (4%)	0	0·75
AST or ALT increased	7 (5%)	4 (3%)	0	21 (16%)	9 (7%)	1 (1%)	0·0005
Cough	6 (5%)	0	0	13 (10%)	0	0	0·082
Infection*	11 (8%)	0	0	5 (4%)	2 (2%)	0	0·36
Biliary tract infection	2 (2%)	4 (3%)	0	2 (2%)	4 (3%)	0	0·96
Sepsis	0	5 (4%)	0	0	3 (2%)	1 (1%)	0·77
Cholecystitis	0	1 (1%)	0	0	2 (2%)	0	0·54
GGT increased	2 (2%)	0	0	9 (7%)	4 (3%)	0	0·0028

Data are as n (%). p value compares all grade toxicities. Grade 1–2 treatment-related adverse events with an incidence of at least 10% in either group and grade 3–4 events with an incidence of at least 1% in either group are shown. All events are listed in the appendix (pp 11–15). Adverse events include those reported from the first dose of the study drug up to 30 days after the last dose. One treatment-related death due to sepsis in the mFOLFIRINOX group was reported with the worst grade before death. AST=aspartate aminotransferase. ALT=alanine aminotransferase. GGT=gamma-glutamyl transferase. *Includes lung, urinary tract, and catheter-related infections.

Table 3: **Summary of adverse events in the intention-to-treat population**

Several secondary endpoints were also significantly better in the PAXG group than in the mFOLFIRINOX group, showing internal consistency and endorsing the primary endpoint validity. A significantly higher percentage of patients in the PAXG group than those in the mFOLFIRINOX group had a CA19-9 reduction of at least 90% and obtained radiological disease control, both of which were reported to be associated with a survival improvement.[22,27] Consistently, the rate of patients who obtained a complete pathological response, who had a pathological stage IA or IB, and who had intraoperative or early postoperative metastases detection was significantly improved with the PAXG regimen. No significant difference was observed between groups in grade 3–4 toxicity, except for neutropenia, which was significantly more frequent in the PAXG group. Nevertheless, this higher rate of neutropenia was not accompanied by an increase in septic events. Conversely, in terms of all-grade toxicities, the safety profile was better in the PAXG group than in the mFOLFIRINOX group. Both regimens negatively affected fatigue, taste, weight loss, and hepatic symptoms; PAXG caused clinically meaningful deterioration in limb weakness and body image, while mFOLFIRINOX led to clinically meaningful impairment in role functioning, social functioning, nausea and vomiting, dry mouth, and activity planning. Notably, a larger proportion of patients in the mFOLFIRINOX group than in the PAXG group did not fulfil the quality-of-life questionnaires due to disease progression or treatment toxicity. Intuitively, these circumstances are probably related to a worse quality of life and the

absence of data from these patients could have masked a larger difference between groups. The longer treatment duration and the higher rate of assigned treatment completion before and after surgery in the PAXG compared with the mFOLFIRINOX group attests to the tolerability and effective delivery of this combination.

The CASSANDRA trial had well balanced groups, a negligible rate of patients with inadequate histology (1 [<1%] of 261 randomly assigned participants; pathological diagnosis of ampullary adenocarcinoma), excellent surgical mortality and morbidity outcomes, and a resection rate that was consistent with previous trials, despite the higher rate of borderline resectable disease.[11,15] Moreover, the 100% compliance with the assigned chemotherapy and the performance of both regimens in terms of response rate, dose-intensity, and toxicity, which fell within the previously reported ranges,[6,12–14] further endorse data robustness.

The PAXG regimen was compared with the mFOLFIRINOX regimen, which in previous phase 2 and 3 randomised trials yielded results similar to chemoradiation with either gemcitabine or capecitabine in the resectable or borderline resectable population,[8,15] to gemcitabine plus capecitabine in the borderline resectable setting,[8] and to nab-paclitaxel plus gemcitabine in patients with resectable disease.[28] Accordingly, the superiority of PAXG, directly compared with mFOLFIRINOX in the context of a phase 3 trial, qualifies this regimen as the most suitable standard option in the resectable or borderline resectable setting.

The choice and the definition of the primary endpoint could be considered a trial limitation. Although EFS is not routinely used, disease-free survival, a conceptually overlapping measure, was previously used as the primary endpoint in phase 3 trials in the adjuvant setting of PDAC and was considered a sufficiently reliable overall survival surrogate endpoint by the scientific community to justify changes in the standard of care.[3,6] Moreover, in trials that used overall survival as the primary endpoint in the resected, resectable, or borderline resectable population and reported disease-free survival analysis, the two HRs coincided,[11,12] suggesting that disease-free survival might be considered an adequate proxy for overall survival in early stage PDAC. Although the importance of overall survival is indisputable and determining whether EFS improvement translates into an overall survival advantage remains a relevant secondary endpoint, EFS allows timely detection of meaningful differences while minimising confounding by post-progression therapies. Also, EFS is a commonly used primary endpoint in other solid tumour and haematological neoadjuvant trials and has been listed by the US Food and Drug Administration in the table of surrogate endpoints that were used for drug approval or licensure as a suitable measure for pivotal trials of investigational drugs for different tumours.[29]

The use of CA19-9 increases as an event was a choice not based on available evidence and might be disputable. Nevertheless, CA19-9 failure without a correlation with imaging was detected in 33 (18%) of 183 patients with an event in the CASSANDRA trial, without significant differences between groups. This definition was applied uniformly across both groups, eliminating potential bias. If any difference was to occur, it would theoretically favour the mFOLFIRINOX group due to the 10% higher proportion of patients with normal baseline CA19-9 serum levels who were not exposed to this possible event. Furthermore, many trials showed that CA19-9 response is superior to RECIST criteria as a surrogate measure of survival,[9,27,30] CA19-9 elevation is an early and reliable sign for PDAC recurrence,[31] and chemotherapy changes based on CA19-9 modification kinetics have a positive effect on patients' outcome,[32] suggesting that this cheap and easy-to-use tool might be more reliable and informative than traditional radiological assessments in this disease. Finally, as CA19-9 is more sensitive to disease progression than CT scans, we would expect EFS to be shorter in our trial compared with other trials that do not use CA19-9. But, despite the use of this more stringent criterium for event definition, the median EFS in the mFOLFIRINOX group was 2 months longer in the CASSANDRA trial compared with the PREOPANC-1 trial.[11] Accordingly, consistency with contemporary studies' outcomes is reassuring for the quality of the control group in CASSANDRA.

Another area of potential criticism is the decision to include both resectable and borderline resectable patients in the CASSANDRA trial. However, this strategy is supported and substantiated by univariate and multivariable analysis results that support the absence of an independent prognostic role of the anatomical resectability classification and further suggests that AJCC classification could be preferred for future trials in PDAC, as per any other solid tumour.

Evidence supports neoadjuvant therapy as a standard option for resectable or borderline resectable PDAC based on PREOPANC-1 results and supporting phase 2 randomised trials.[4,7,8,11] Further evidence favouring the use of neoadjuvant therapy in resectable disease was also provided by the phase 3 JSAP-05 trial.[33] Moreover, the use of mFOLFIRINOX in this setting was prospectively validated in the PREOPANC-2 trial.[15] Accordingly, the hypothesis that the subgroup of patients with resectable PDAC should be treated with upfront surgery has to be prospectively proven. Importantly, our conclusion regarding PAXG superiority over mFOLFIRINOX is valid, regardless of the broader debate on neoadjuvant versus adjuvant strategies and our study provides clinicians with evidence-based guidance for optimal regimen selection within the neoadjuvant framework.

The absence of a central pathological and radiological response review could be perceived as a trial limitation as well. However, pathological and radiological assessments were performed by uninvolved physicians in academic, high-volume institutions, reflecting real-word practice and enhancing generalisability, with centre stratification balancing potential quality variations.

The results were achieved in view of the high-volume, academic, referral centres that were selected for the CASSANDRA trial. This scenario could limit the external validity of the reported results. However, the multidisciplinary management of PDAC is particularly challenging and should be confined to institutions with adequate expertise. The generalisability of CASSANDRA data might be also limited by the upper age limit. However, both the PAXG and the FOLFIRINOX regimens were tested only in patients younger than 75 years.[12–14] The mFOLFIRINOX regimen was tested as adjuvant treatment for patients aged up to 79 years.[6] However, data on this population were not separately reported, only 47 patients were aged 70 years or older, and no information was reported for those older than 75 years. Therefore, no sufficient information about the safety of the two regimens is available and separate trials should be performed in this population to address chemotherapy risk–benefit ratio.

In conclusion, the CASSANDRA trial showed that preoperative PAXG is superior to mFOLFIRINOX, providing a significant EFS, disease control, CA19-9 response, and pathological response benefit to patients with stage resectable or borderline resectable PDAC. Accordingly, preoperative PAXG should be considered as the standard comparator group for future trials in this setting. Preoperative PAXG could be considered a standard option for resectable or borderline resectable PDAC. Exploring the underlying biological mechanisms that guide the identification of the patients' subgroups benefiting or not from preoperative therapy is a paramount important challenge.

Contributors

MR designed and conceptualised the study. MR, MMac, GO, LP, GM, CC, IGR, KB, MS, GBa, DT, BM, ES, GBe, NL, SB, MDM, ET, MMi, SL, GE, MMaz, and DP were involved in acquisition of data. MR and VT performed the data analysis. MR, MMac, GO, CC, VT, and MF contributed to data interpretation. MR drafted the manuscript. MMac, GO, CC, and MF contributed to critical review and revision of this manuscript. MR, CC, and VT had full access to and verified all the data in the study. MR guarantees integrity, accuracy, completeness of data analyses, and adherence to the protocol. All authors have reviewed the manuscript and approved the submission for publication. The corresponding author had full access to all the data and had final responsibility for submitting them for publication. All authors had access to the study data if they wished.

Declaration of interests

MR: personal honoraria for consulting and advisory role from LeoPharma, Viatris, and BMS; research funding to institution from AstraZeneca; and travel expenses from Daiichi Sankyo. LP: travel expenses from AstraZeneca. MS: personal honoraria from MSD, Merck, Servier, AstraZeneca, and Daiichi Sankyo; travel expenses from Servier and Merck; and participation in advisory boards for Rottapharm Biotech. ES: personal honoraria for consulting role from AstraZeneca; advisory role for Merck Serono; and travel expenses from Merck Serono. MDM: participation in advisory boards for OncoSil Medical and travel expenses from Viatris. MMi: personal honoraria from Servier; Viatris; and OncoSil Medical for consulting role; and travel expenses from AstraZeneca. SL: research funding to institution from Amgen, Merck Serono, Bayer, Roche, Lilly, AstraZeneca, and Bristol Myers Squibb; personal honoraria from Amgen, Merck Serno, Lilly, Servier, AstraZeneca, Incyte, Daiichi Sankyo, Bristol-Myers Squibb, MSD, Astellas, Bayer, Takeda, Rottapharm Biotech, Beigene, Helion, Nimbus Therapeutics, and Fosum Pharma for consulting role; personal honoraria from Roche, Lilly, Bristol Myers Squibb, Servier, Merck Serono, Pierre Fabre, GlaxoSmithKline, Amgen, MSD Oncology, and Incyte for presentations, speakers bureaus, and educational events; participation in advisory boards for Amgen, Merck Serno, Lilly, Servier, AstraZeneca, Incyte, Daiichi Sankyo, Bristol Myers Squibb, MSD, Astellas, Bayer, Takeda, Rottapharm Biotech, Beigene, Helion, Nimbus Therapeutics, and Fosum Pharma. All other authors declare no competing interests.

Data sharing

De-identified data that support the findings of this study will not be made publicly available for secondary use because they contain information that could compromise research participant consent. According to European and Italian regulations, any re-use of the data must be approved by the ethical committee. Access to the data will be considered upon reasonable request sent to the corresponding author and Associazione Italiana Studio Pancreas.

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