

STUDY PROTOCOL

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Efficacy of neoadjuvant FOLFIRINOX in resectable pancreatic cancer (NeoFOL-R): study protocol for an international, multicenter, prospective, randomized controlled trial

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Abstract

Background Recent randomized controlled trials (RCTs) regarding the outcomes of neoadjuvant chemotherapy for patients with resectable pancreatic cancer (PC) reported inconsistent results. As the survival rate of FOLFIRINOX was found to be superior to that of gemcitabine, interest in the efficacy of neoadjuvant chemotherapy with FOLFIRINOX for resectable PC is growing. In this study, we aimed to investigate the efficacy of neoadjuvant FOLFIRINOX in patients with resectable PC.

Methods This international (South Korea, Australia, and Taiwan), multicenter, phase 3, RCT will include 609 patients with resectable pancreatic ductal adenocarcinoma and ECOG performance 0–1. Resectable PC is defined as no arterial contact and no tumour contact with the superior mesenteric vein/portal vein or $\leq 180^\circ$ contact without vein contour irregularity. Neoadjuvant FOLFIRINOX consisted of oxaliplatin (85 mg/m²), administered intravenously over 2 h, followed by leucovorin (400 mg/m²) over 2 h and irinotecan (180 mg/m²) over 90 min, administered

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concurrently. Subsequently, an intravenous bolus infusion of 5-FU (400 mg/m²) and a continuous infusion of 5-FU (2400 mg/m²) over 46 h, repeated every 2 weeks for 6 cycles. Adjuvant therapy with modified FOLFIRINOX (mFOLFIRINOX) included oxaliplatin (85 mg/m²), irinotecan (150 mg/m²), leucovorin (400 mg/m²), and fluorouracil (2400 mg/m²) over 46 h and repeated every 2 weeks, with six cycles in the neoadjuvant group and 12 cycles in the upfront surgery group. The primary endpoint is a two-year survival rate by intention-to-treat. Secondary outcomes are overall survival, disease-free survival, resection rate, R0 resection rate, lymph node negative rate, recurrence rate, response rate. When calculating with a significance level of 5% and a statistical power of 80%, 171 events (deaths) are needed. Considering the 5-year participant enrollment period and a minimum of a 2-year follow-up period, 518 patients were required to observe 171 events. A total of 609 patients were required when the dropout rate was calculated as 15%.

Discussion The NeoFOL-R trial investigates the efficacy of perioperative versus adjuvant FOLFIRINOX for patients with resectable PC. The study is ongoing, starting in February 2024 in South Korea, Australia, and Taiwan.

Trial registration NCT 05529940. Registered in September 2022. KCT0008360 (Korean Clinical Trial Database). Registered in April 2022.

Keywords FOLFIRINOX, Neoadjuvant, Perioperative, Pancreatic cancer, Resectable

Introduction

The standard treatment for resectable pancreatic cancer (PC) is surgical resection followed by adjuvant chemotherapy. Adjuvant chemotherapy after surgery significantly improved the survival of PC patients, but there is a problem in that only about 50% of patients start adjuvant chemotherapy after pancreatectomy [1, 2].

Gemcitabine was previously the main anticancer drug used for adjuvant chemotherapy in PC, but modified FOLFIRINOX (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) showed a superior patient survival (54 months vs. 35 months) compared to gemcitabine (PRODIGE-24/CCTG PA-6 clinical study) [3]. Accordingly, FOLFIRINOX is being established as the standard regimen for adjuvant chemotherapy for resected PC patients with favourable performance status in many countries.

Neoadjuvant chemotherapy might control potential metastatic lesions that are not detected in early disease status and improve the R0 resection rate. Additionally, it prevents unnecessary surgeries by selecting patients with rapid disease progression. Furthermore, compared with chemotherapy administered after surgery, more patients can complete the planned chemotherapy schedule with full dosages in the neoadjuvant setting.

The efficacy of preoperative chemotherapy in resectable pancreatic cancer remains controversial due to the inconsistent results from small study population and different chemotherapy regimens. A Dutch group recently reported that neoadjuvant chemoradiation with gemcitabine in resectable/borderline resectable PC was associated with better survival compared to upfront surgery (5-year survival rate; 16.5% vs 6.5%, hazard ratio; 0.73, 95% CI 0.56–0.96, $P=0.025$) (PREOPANC trial) [4]. However, this trial did not show a significant survival difference between neoadjuvant treatment and upfront

surgery in the resectable patients only (HR 0.79, 95% CI 0.54–1.16, $P=0.23$). A recent NORPACT trial including 140 patients with resectable pancreatic cancer reported neoadjuvant FOLFIRINOX did not improve overall survival (median overall survival; NAT vs. upfront surgery, 25.1 vs. 34.9 months, $P=0.096$) [5]. The NEONAX trial conducted by Germany reported that the disease-free survival rate, the primary endpoint of the trial examining perioperative gemcitabine plus nab-paclitaxel in resectable PDAC, was not reached in either arm of neoadjuvant or upfront surgery [6]. In the Prep-02/JSAP-05 clinical trial, there was a significant difference in median survival (upfront surgery; 26.6 months vs. neoadjuvant treatment; 36.7 months) [7]. However, in this study, only patients without arterial contact were included in the inclusion criteria, therefore, many borderline resectable patients might be included. The systematic and prospective clinical trials are essential to standardize the treatment protocols for resectable PC. Therefore, we aimed to investigate the efficacy of neoadjuvant chemotherapy in patients with resectable PC using FOLFIRINOX.

Methods

Study design

The NeoFOL-R trial is an international, open-label, multicenter, prospective, randomized phase 3 clinical trial. Australia, Taiwan, and Republic of Korea participate in this trial. Patients with histologically diagnosed of pancreatic adenocarcinoma with resectable clinical stage are randomly assigned either to upfront surgery followed by twelve cycles of adjuvant FOLFIRINOX (comparator group; arm A) or six cycles of neoadjuvant FOLFIRINOX followed by surgery and adjuvant FOLFIRINOX (intervention group; arm B) (Fig. 1).

Randomization is conducted by a web-based randomization program under the supervision of the Medical

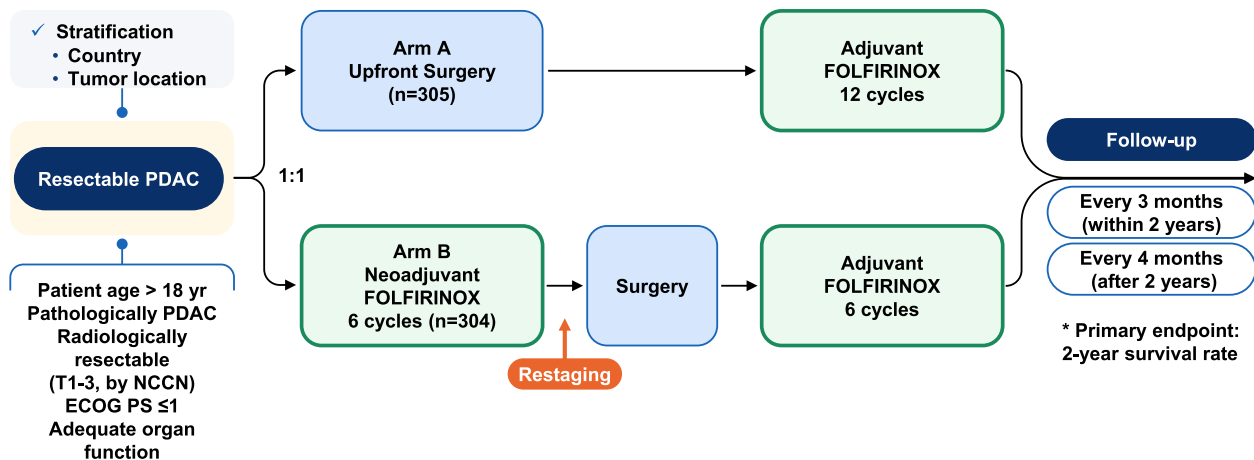


Fig. 1 Trial design

Research Collaborating Center at Seoul National University College of Medicine. Randomization is stratified by countries (Australia, Singapore, Taiwan, Korea) and tumor locations (pancreatic head, pancreatic body/tail).

Study population

Patients are eligible when they meet all of the following criteria; age of 19–80 years, patients with an Eastern Cooperative Oncology Group (ECOG) score of 0–1, no distant metastases on preoperative imaging, patients with adequate organ function (bone marrow function: $WBC \geq 3,000/mm^3$ or absolute neutrophil count $\geq 1,500/mm^3$, platelet $\geq 100 K/mm^3$; liver function: bilirubin $\leq 3 \times$ the upper normal limit (≤ 5.0 mg/dL), AST/ALT ≤ 5 the upper normal limit (< 200 IU/L); renal function: creatinine clearance (Cr) ≥ 60 mL/min or $Cr < 1.5 \times$ upper normal limit), patients physically capable of undergoing surgery, written informed consent, and patients with pancreatic ductal adenocarcinoma diagnosed by histological examination (histologic or cytopathological) evaluated as resectable PC on preoperative imaging according to the NCCN guidelines for pancreatic adenocarcinoma version 2.2021 as follows: no arterial tumour contact (celiac artery, superior mesenteric artery, or common hepatic artery) and no tumour contact with the superior mesenteric vein or portal vein or $\leq 180^\circ$ contact without vein contour irregularity [8].

Exclusion criteria are borderline resectable or locally advanced PC, previous pancreatic surgery, previous chemotherapy or radiation therapy for pancreatic cancer, distant metastases or recurrent pancreatic cancer, body or tail cancer requiring combined resection of adjacent organs (stomach or kidney) except for the adrenal gland, patients within five years of diagnosis of other organ malignancies with the exception of adequately treated non-melanoma skin cancer and carcinoma in situ without evidence of disease, pregnant or lactating women,

serious concomitant systemic disorders that would compromise the safety of the patient or patient's ability to complete the study.

Treatment

Dosage of FOLFIRINOX

Neoadjuvant FOLFIRINOX consisted of oxaliplatin ($85 \text{ mg}/m^2$), administered intravenously over 2 h, followed by leucovorin ($400 \text{ mg}/m^2$) over 2 h and irinotecan ($180 \text{ mg}/m^2$) over 90 min, administered concurrently. Subsequently, an intravenous bolus infusion of 5-FU ($400 \text{ mg}/m^2$) and a continuous infusion of 5-FU ($2400 \text{ mg}/m^2$) over 46 h, repeated every 2 weeks for 6 cycles. Irinotecan dosing was adjusted to either 150 or $180 \text{ mg}/m^2$ based on the investigator's discretion. Adjuvant therapy with modified FOLFIRINOX (mFOLFIRINOX) included oxaliplatin ($85 \text{ mg}/m^2$), irinotecan ($150 \text{ mg}/m^2$), leucovorin ($400 \text{ mg}/m^2$), and fluorouracil ($2400 \text{ mg}/m^2$) over 46 h and repeated every 2 weeks, with six cycles in the neoadjuvant group and 12 cycles in the upfront surgery group.

The initial dose of study medication (i.e., cycle 1) will be in accordance with the recommended dose as per protocol. Dose adjustments may be based on the maximum graded toxicity within the previous cycle, using the Common Terminology Criteria for Adverse Events (CTCAE ver 5.0). If the dose of Leucovorin is the same in the Arm A and Arm B, it may vary by country to account for country-specific insurance circumference.

Surgery (both arms)

The type of surgery performed varies depending on the location of the lesion. Pancreaticoduodenectomy is performed if the lesion is located in the pancreatic head, and distal pancreatectomy is performed if the lesion was located in the body or tail of the pancreas. Splenectomy was performed during distal pancreatectomy. If

the frozen section during the operation shows a positive resection margin, a total pancreatectomy can be performed in the two surgeries described above. The criterion for the length of the safety margin for the judgment of negative margins in the surgical specimen is 0 mm.

Arm A: Adjuvant FOLFIRINOX

Surgery will be performed within 4 weeks of randomization in Arm A. Patients who undergo surgical resection and obtain R0 (microscopic negative margin) or R1 (microscopic positive margin) margin status receive twelve cycles of postoperative mFOLFIRINOX chemotherapy within 12 weeks from the day of surgery. Failure to start post-operative chemotherapy within a maximum of 12 weeks from the date of surgery will be treated as a withdrawal due to failure to meet the study conduct schedule. All participants are evaluated periodically for disease status and safety during postoperative chemotherapy. At the end of every 3 cycles, disease status is assessed by tumour markers (CA 19–9 and CEA), abdominal, and chest CT scan.

Arm B: Neoadjuvant and adjuvant FOLFIRINOX

Patients in Arm B start with six cycles of FOLFIRINOX within 4 weeks after the randomization. Each cycle would be performed every two weeks. After cycles 3 and 6 (or in cases of early discontinuation of chemotherapy), treatment response is evaluated using CT scan of chest and abdomen according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria [9] and tumour markers are also assessed. Clinical staging is reassessed after the completion of six cycles of FOLFIRINOX or early discontinuation of prior chemotherapy.

Surgery will be performed within 4–6 weeks from the date of completion of 6 cycles of neoadjuvant chemotherapy in Arm B in case the patients in Arm B do not show any sign of progressive disease.

Outcomes

The primary endpoint is a 2-year overall survival rate by intention-to-treat. Survival is summarized by median and confidence intervals. Secondary endpoints are overall survival, disease-free survival, resection rate, R0 resection rate, lymph node negative rate, the rate of local recurrence and distant metastasis, and response rate.

The overall survival is defined as the time from study start date (study consent date) to the date of death from any cause. Patients who were not reported dead at the time of analysis were censored on the last day they were known to be alive. Disease-free survival is defined as the time between the date of operation and the occurrence of distant metastases, locoregional progression, or death from any cause. Patients who were alive and free of these events at the last follow-up would be censored. Local

recurrence is defined as recurrence in the pancreatic resection margin, residual pancreas, and regional lymph nodes. Response rate after preoperative chemotherapy is defined as the percentage of patients who showed complete response, partial response, and stable disease after three or six cycles of scheduled chemotherapy. The evaluation is based on RECIST v.1.1 [9].

Follow-up

All patients are evaluated for disease status by chest and abdominal CT scan and tumor markers (CA 19–9, CEA) every 3 months up to 2 years after the treatment ends and every 4 months until 5 years. The end date of treatment is defined as the start date of the last chemotherapy.

Data collection and management

Clinical data will be collected and managed by web-based software. Data management is coordinated by a specialized coordinator trained for collecting and managing of clinical trial data in main investigation institutions (Seoul National University, Catholic University). The coordinators are trained in using the electronic case report form system prior to data entry.

The personally identifiable information of all research subjects enrolled in the study is coded and cannot be viewed except by the principal investigator and co-investigators. There is no possibility of identifying specific individuals and families from genetic information, and no possibility of violation of the privacy of research participants.

Safety reporting and monitoring

All adverse events classified as grade 3 or higher according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [10] will be recorded from the first administration of the study chemotherapy until 30 days after the last dose. A serious adverse event (SAE), including death, life-threatening, requiring hospitalization or prolongation of existing inpatients' hospitalization, will be reported by the local investigator in each participating institution. Suspected unexpected serious adverse reactions (SUSARs) are reported to the Medical Ethics Committee and competent authority. Local investigators are responsible for reporting all SUSARs to the clinical trial center within 24 h after obtaining knowledge of the event. An independent Data Safety Monitoring Board (DSMB) will be established to evaluate safety data during the trial period.

Statistical analysis

Based on the retrospective data at Seoul National University Hospital, the two-year overall survival rates of upfront surgery and neoadjuvant group in resectable pancreatic cancer were 72% and 81%, respectively, as a

result of matching the propensity score for the initial tumour size, lymph node enlargement, and degree of contact with the portal vein/superior mesenteric vein.

Assuming that the survival rate follows an exponential distribution, 171 events (deaths) were required when calculated with a significance level of 5% and a statistical power of 80%. Considering the 5-year participant enrollment period and a minimum of a 2-year follow-up period, 518 patients were required to observe 171 events. A total of 609 patients were required when the dropout rate was calculated as 15%.

For overall survival and disease-free survival, intention-to-treat analysis will be performed on all randomized patients. Per-protocol analysis is performed for prespecified groups (per protocol 1; those who underwent surgery (with or without tumor resection) or at least one course of chemotherapy, per protocol 2: those who underwent surgery and chemotherapy (neoadjuvant or adjuvant chemotherapy) for at least six cycles, per protocol 3; those who underwent scheduled treatment of surgery and twelve cycles of chemotherapy (neoadjuvant or adjuvant)). A p value < 0.05 is considered to indicate statistical significance.

Discussion

Treatment for pancreatic cancer has undergone a paradigm shift with the success of neoadjuvant approach, especially for borderline resectable or locally advanced disease. However, there has been no improvement in treatment methods and outcomes over the past 20 years for resectable PC. With the recent validation of the efficacy of FOLFIRINOX in pancreatic cancer, there is a need to validate a new treatment paradigm in resectable PC using FOLFIRINOX as a neoadjuvant chemotherapy.

Recent randomized controlled trials regarding the impact of neoadjuvant chemotherapy for resectable PC did not support the neoadjuvant chemotherapy as an applicable therapeutic option. Limitations of the previous studies include the small number of patients enrolled (PREOPANC; 133, NEONAX; 127, NORPACT; 140) which makes it difficult to draw conclusions, the lack of use of FOLFIRINOX, and the short neoadjuvant cycles (PREOPANC; gemcitabine, 3 cycles, NEONAX; gemcitabine plus nab-paclitaxel, 2 cycles, NORPACT; FOLFIRINOX, 4 cycles), which is currently the most effective treatment for pancreatic cancer [4–6]. In addition, the planned treatment was given in less than 40% of the patients, which does not fully validate the effectiveness of neoadjuvant chemotherapy. Moreover, the studies were conducted in the West, which limits the assessment of drug toxicity in Asians. Therefore, these three studies were not of sufficient significance to be used as the basis for international standardized guidelines.

The recent meta-analysis including only randomized controlled trials reported that gemcitabine-based neoadjuvant chemotherapy resulted in favorable overall survival compared to upfront surgery in resectable PC (HR 0.73, 95% CI 0.59–0.91) [11].

Meanwhile, most of the clinical trials described above are being conducted in Western countries, and randomized controlled trials in Asians are very limited. There are differences in response to and toxicity of anticancer drugs between individuals and races. In addition, in the PRODIGE-24/CCTG PA-6 study, the toxicity of mFOLFIRINOX also increased significantly compared to gemcitabine monotherapy, and 6-month treatment was not completed in 33.6% of the cases [3]. Asians differ from Westerners not only in terms of racial differences but also in their average size and body surface area. Anticancer drugs show ethnic and racial differences in drug pharmacokinetics or drug sensitivities throughout their development, from early phase clinical trials to real-world applications [12, 13]. Therefore, there is a need for clinical studies on the dose, toxicity, dosing cycle, and efficacy of FOLFIRINOX that reflect actual pharmacodynamic outcomes in Asian countries.

Few studies have prospectively explored the efficacy of neoadjuvant treatment in resectable PC. This study will provide high-level evidence on the neoadjuvant FOLFIRINOX for patients with resectable PC.

Abbreviations

CA 19–9	Carbohydrate antigen 19–9
CEA	Carcinoembryonic antigen
CI	Confidence interval
CT	Computed tomography
DSMB	Data Safety Monitoring Board
FOLFIRINOX	5-Fluorouracil with leucovorin, irinotecan, and oxaliplatin
RCT	Randomized controlled trial
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SUSAR	Suspected Unexpected Serious Adverse Reactions
ECOG	Eastern Cooperative Oncology Group

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Trial status

The NeoFOL-R trial is an international multicenter randomized phase III trial, conducted in Australia, Korea, and Taiwan. The trial started accrual on December 19th, 2023. The first participant was registered on January 3rd, 2024. The latest version number of the protocol is 2.4 (Approval date: December 27th, 2024). The recruitment will be completed by Dec 31st, 2028.

Authors' contributions

The original idea of this trial was developed by MAL and JYJ. The original protocol writing for this study was completed by HSJ and SJP. JMC and YSY have overall responsibility for research conducted in Australia and Taiwan, respectively. YH, YJC, JY, DYO, YSY, JWK, CSL, JHP, ISC, THH, HSK, H CJ, KSA,

JK, YDY, JWK, HKH, CKL, HC, YKJ, KP, JHY, IWH, HIS, JDY, SYJ, SJY, HC, WK, JSP participate in patient recruitment and are responsible in their respective institutions. All authors reviewed the final version of the manuscript prior to submission.

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Data availability

Study protocol is available at the website of the Clinicaltrials.gov (<https://clinicaltrials.gov/ct2/show/NCT05529940>). Data generated or analysed during the current study will be available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Ethics Review Board of Seoul National University Hospital (No. H-2211–115-1380) (Latest version 2.3). The ethics approval for this study has been obtained from all participating institutions. In Australia, approval was granted by Epworth Hospital (EH2022-940; IRB approval date: Jan 08, 2024; latest version 1.5). In Taiwan, approvals were obtained from the following institutions: National Taiwan University Hospital (IRB approval date: Aug 14, 2025; version 3.8), Linkou Chang Gung Memorial Hospital and Kaohsiung Chang Gung Memorial Hospital (IRB approval date: May 15, 2025; version 3.6), Taipei Veterans General Hospital (IRB approval date: May 21, 2025; version 3.6), Taichung Veterans General Hospital (IRB approval date: Aug 13, 2025; version 2.0), China Medical University Hospital (IRB approval date: Apr 02, 2025; version 3.1), Kaohsiung Medical University Chung-Ho Memorial Hospital (IRB approval date: Jan 21, 2025; version 2.0), Tri-Service General Hospital (IRB approval date: Aug 08, 2025; version 3.7), and National Cheng Kung University Hospital (coordinating center in Taiwan) (IRB approval date: Feb 25, 2025; version 3.6; B-BR-113–070). This study was conducted in compliance with the Declaration of Helsinki as amended in 2013.

The patients treating physicians, local investigator, or research nurse of the participating centers follow Good Clinical Practice (GCP) and other applicable regulations in informing the patient and obtaining consent. Before informed consent may be obtained, the investigator should provide the patient ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the patient. Patients are well informed that participation is voluntary and that they may withdraw at any point during the study. Informed consent includes consent for collection and use of biological specimens (i.e. blood and tissue). Written informed consent of patients is required before enrollment in the trial or study related procedures take place. All data are handled with strict confidentiality, assuring anonymity of patients. Any proposed amendments to the project including any changes will be submitted to the Ministry of Food and Drug Safety (KFDA) for approval prior to implementation. These changes will be provided to the trial participants immediately by the main research team and re-consent for participation in the research will be collected if required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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