

STUDY PROTOCOL

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# Preoperative treatment with mFOLFIRINOX or Gemcitabine/Nab-paclitaxel +/- isotoxic high-dose stereotactic body Radiation Therapy (iHD-SBRT) for borderline resectable pancreatic adenocarcinoma (the STEREO PAC trial): study protocol for a randomised comparative multicenter phase II trial

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## Abstract

**Background** For patients with pancreatic ductal adenocarcinoma (PDAC), surgical resection remains the only potentially curative treatment. Surgery is generally followed by postoperative chemotherapy associated with improved survival, yet neoadjuvant therapy is a rapidly emerging concept requiring to be explored and validated in terms of treatment options and oncological outcomes. In this context, stereotactic body radiation (SBRT) appears feasible and can be safely integrated into a neoadjuvant chemotherapy regimen of modified FOLFIRINOX (mFFX) with promising benefits in terms of R0 resection, local control and survival. However, the optimal therapeutic sequence is still not known, especially for borderline resectable PDAC, and the role of adding SBRT to chemotherapy in the neoadjuvant setting needs to be evaluated in randomised controlled trials. The aim of the STEREO PAC trial is to assess the impact and efficacy of adding isotoxic high-dose SBRT (iHD-SBRT) to neoadjuvant mFFX or Gemcitabine/Nab-Paclitaxel (Gem/Nab-P) in patients with borderline resectable PDAC.

**Methods** This is a randomised comparative multicentre phase II trial, planning to enrol patients (n = 256) diagnosed with a borderline resectable biopsy-confirmed PDAC. Patients will receive 4 cycles of mFFX (or 6 doses of Gem/Nab-P). After full disease restaging, non-progressive patients will be randomised for receiving either 4 additional mFFX cycles (or 6 doses of Gem/Nab-P) (Arm A), or 2 mFFX cycles (or 3 doses of Gem/Nab-P) + iHD-SBRT (35 to

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55 Gy in 5 fractions) + 2 mFFX cycles (or 3 doses of Gem/Nab-P) (Arm B). Then curative surgery will be performed followed by adjuvant chemotherapy according to patient's condition. The co-primary endpoints are R0 resection and disease-free survival after the complete sequence strategy. The secondary endpoints include resection rate, overall survival, locoregional failure / distant metastasis free interval, pathologic complete response, toxicity, postoperative complications and quality of life assessment.

**Discussion** This trial will help define the best neoadjuvant treatment sequence for borderline resectable PDAC and aims to evaluate if a total neoadjuvant treatment integrating iHD-SBRT improves the patients' oncological outcomes.

**Trial registration** The study was registered at ClinicalTrials.gov (NCT05083247) on October 19th, 2021, and in the Clinical Trials Information System (CTIS) EU CT database (2022-501181-22-01) on July 2022.

**Keywords** Pancreatic adenocarcinoma, FOLFIRINOX, Stereotactic body radiation, Borderline resectable, Chemotherapy, Neoadjuvant therapy, Clinical trial

### Introduction- background and rationale

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive cancer with a poor prognosis mainly due to the high frequency of distant metastases or the locally advanced stage of the tumour excluding a surgical procedure from the outset [1]. In Belgium, with nearly 1,700 deaths a year, PDAC ranks fourth in the cancer mortality classification. According to some estimations, PDAC will reach the second place by 2030, especially in the western world [2]. This type of cancer has often few and late symptoms making the diagnosis more delayed. One-third of the patients are metastatic at diagnosis, less than 20% of the cases are immediately resectable and about 50% have a potentially resectable cancer called "borderline resectable" (BR) or locally advanced and unresectable (LAPC); the classification of resectability being determined according to the relationship of the tumour with the neighboring vascular structures [3]. All stages combined, the overall survival (OS) rate at 5 years is only 7%. Surgical resection is the only treatment modality offering a chance of cure. However, even operated patients have a poor prognosis with an OS at 5 years of 20%. Complete microscopic (R0) resection represents a requisite component of curative therapy for patients with PDAC [2, 4].

As a standard, surgery is usually followed by adjuvant therapy that significantly improves survival; this concept was proven by several trials (PRODIGE-24, CONKO-001 and ESPAC-4): usually 6 months of modified FOLFIRINOX (mFFX) regimen is administered in fit patients (improved disease-free survival [DFS] by 40% from 12 to 18 months) and in more frail or older patients, gemcitabine monotherapy or in combination with capecitabine is given (improved DFS by 20%) [5–7]. However, only around 50% of the patients are able to complete full adjuvant therapy sequence [5–7]. Neoadjuvant therapy (NAT) is recommended in international guidelines, although this rapidly emerging concept still needs to be further explored and validated in BR PDAC [8–11]. Neoadjuvant regimen designed to both select patients for surgery and optimize surgical outcomes are

needed. Yet the exact sequence and regimens remain to be determined, particularly regarding the potential additional benefit of a total neoadjuvant treatment (TNT) including stereotactic body radiation therapy (SBRT).

In recent randomised phase III trials, neoadjuvant chemotherapy (gemcitabine+S1) was shown to be efficacious in resectable tumours in Asian patients while in the PREOPANC trial, gemcitabine-based chemoradiation (CRT) reported, after a median follow-up of 59 months, a limited improvement in survival for resectable/BR PDAC (15.7 vs. 14.3 months,  $p=.025$ ) [12, 13]. Recently, the results of the phase III CONKO-007 trial including 525 LAPC patients in which an induction mainly by mFFX was followed or not by CRT were presented. The primary endpoint, the R0 resection rate (RR), was not associated with a significant improvement (30 vs. 42% for CRT,  $p=.143$ ) as well as for the OS and PFS, with the exception of the circumferential resection margin (CRM)-R0 RR (15 vs. 33% for CRT,  $p=.001$ ) [14]. As reported in several prospective observational/phase II trials, pre-operative mFFX prolonged by SBRT appears feasible and associated with promising outcomes in terms of R0 resection and prolonged survival [15, 16]. When compared with conventional long course CRT, SBRT offers several advantages such as the shorter duration of treatment (1 week vs. 4 to 6 weeks). Therefore, patients receiving SBRT can resume systemic therapy more quickly, reducing long interruptions of full-dose chemotherapy. Another advantage of SBRT is the improvement of local control with the possibility of delivering safely higher biologically effective doses (BED) to the tumour and the tumour/vessel interfaces (TVIs) [15, 16]. It is therefore an attractive option to propose both local control and a downstaging/shrinking of tumours with vascular contacts/invasion that preclude R0 resection. As the exact and best therapeutic sequence is not yet known, the role of adding SBRT to chemotherapy for BR PDAC requires validation in randomised trials. However, the type of pancreatic SBRT seems pivotal to yield the expected benefits as illustrated in the randomised phase II Alliance

A021501 trial designed to compare the outcomes of BR patients treated with induction with FOLFIRINOX alone or followed by low-dose SBRT (33 Gy in 5 fractions with simultaneous integrated boost (SIB) up to 40 Gy at TVI or 25 Gy in 5 fractions) [17]. The results regarding the patients enrolled prior to closure for futility (70 patients enrolled in ARM A (FFX) and 56 in arm B (FFX+SBRT - underpowered) were recently published and the primary objective was not met (18-months OS rate: 67.9 vs. 47.3% in disfavor of the SBRT arm) [17]. In addition to several design shortcomings, reducing the delivered RT dose to or close to palliative dose range for safety purpose, as done in the Alliance trial, is not a solution as the maximal BED obtained (55 Gy) is well below the ablative doses sought with SBRT [15, 18]. It is essential to continue to improve the pancreatic SBRT technique, in particular by trying to deliver very high BED ≥ 70 Gy, as this seems correlated with improved OS and PFS on multivariate analysis [15, 19–22]. One safe method to achieve high-BED SBRT is to use an isotoxic dose prescription (IDP), based on organ at risk (OAR) tolerance levels and not on the tumour volume as usually done [16, 23]. Whilst protecting the OARs, the iHD-SBRT technique permits to reach the highest achievable dose level to increase the local tumour control probability and to safely obtain a BED<sub>10</sub> ≥ 70 Gy [16, 24]. We recently reported feasibility and preliminary efficacy data of the TNT sequence combining preoperative FFX x 6 cycles (or Gemcitabine/Nab-Paclitaxel [Gem/Nab-P] in case of intolerance or no response) prolonged by iHD-SBRT (SIB up to 53 Gy at the TVI in 5 fractions) with promising results [16].

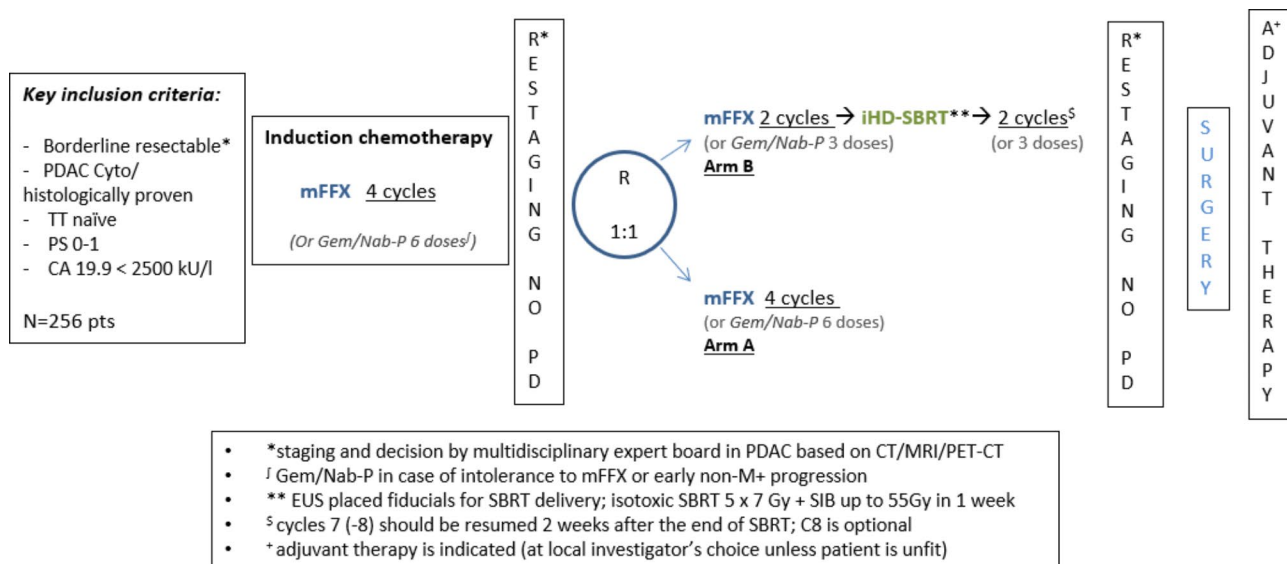
The present study proposes now to evaluate the impact and efficacy of incorporating iHD-SBRT to preoperative neoadjuvant mFFX or Gem/Nab-P in patients with BR PDAC in a TNT sequence. We hypothesize that this full sequence strategy of pre-operative treatment is safe and feasible and will improve both the surgical management (R0 resection) and the prognosis of PDAC patients as evaluated by the DFS, as co-primary end-points.

**Method**

The SPIRIT reporting guidelines were used for this protocol and the completed SPIRIT checklist is available in Supplementary Table 1 [25].

**Trial design**

This study is a multicenter randomised open-label comparative phase II trial. Patients who have been diagnosed with borderline resectable PDAC (according to the NCCN definition [8]) will be enrolled. Patients are initially planned to be recruited at 10 centers in Belgium with expertise in pancreatic surgery, including collaborative centers within the Belgian healthcare convention. Patients will receive 4 cycles of mFFX (or 6 doses of Gem/Nab-P) (Fig. 1). After full disease restaging, non-progressive patients will be randomised for receiving either 4 mFFX cycles (or 6 doses of Gem/Nab-P) (Arm A), or 2 mFFX cycles (or 6 doses of Gem/Nab-P)+iHD-SBRT followed by 2 additional mFFX cycles (or 6 doses of Gem/Nab-P) (Arm B). After full disease restaging, a curative surgery will be performed consisting of oncological pancreatotomy, followed by adjuvant chemotherapy according to patient’s condition. In case of contraindication to



Co-Primary endpoints : R0 and DFS (HR:0,61) / Secondary : LC, OS, RR, pCR, toxicity, QoL, EUS

**Fig. 1** Overview of treatment sequences of the trial

mFFX, early intolerance or loco-regional progression, Gem/Nab-P regimen can be chosen for 12 doses (6 doses followed by restaging, then either 6 doses in arm A, or 3 doses / iHD-SBRT / 3 doses in arm B), before surgery. Surgery is planned to be performed ideally 6–8 weeks (maximum 10 weeks) after iHD-SBRT delivery for Arm B and ideally 3–4 weeks (maximum 6 weeks) after the last cycle of chemotherapy for Arm A.

### Randomization and minimization of bias

The randomisation will be performed in subjects after receiving the first 4 cycles doses of FFX (or 6 doses Gem/Nab-P), showing a manageable tolerance and no progressive disease at restaging. Subjects will be centrally and automatically randomised electronically by the RedCap® system.

To minimize the imbalance in the distribution of treatment numbers within the levels of each individual prognostic factor, a minimization technique will be used for random treatment allocation stratifying by centers and CA 19.9 levels.

### Objectives and end-points

The co-primary objectives are to compare both the R0 resection rate (a R0 resection is considered if the distance between the inked margins and the tumour cells is > 1 mm, with a central pathology review) and the disease-free survival (DFS) in arm A ('standard'-chemotherapy) to arm B ('experimental'- chemotherapy+iHD-SBRT) in an intention-to-treat analysis. DFS is defined as time from randomization to the first documentation of one of the following events: radiological disease progression (defined according to the RECIST criteria version 1.1 [26]), discovery of hepatic metastasis or peritoneal carcinomatosis during surgery, recurrent disease following curative surgery or death due to any cause. Secondary objectives include: resection rate, OS (by intention-to-treat), locoregional failure free interval (LFFI), distant metastases free interval (DMFI), complete feasibility of the therapeutic sequence, pathologic complete response rate (pCR), toxicity (early and late), postoperative complications rate, quality of life (QoL) assessment at different timepoints and technical/quality success rate of endoscopic ultrasound (EUS)-delivered fiducials. LFFI is defined as the time interval between the randomisation and the date of locoregional failure, and DMFI as the period of time without distant metastasis after randomization. The complete feasibility of the therapeutic sequence is defined as the proportion of patient who performed completely the allocated neoadjuvant sequence until surgery. pCR is defined as the proportion of patients in whom a complete or a major response (<10% of residual tumour cells) is confirmed by histopathologic review of the surgical specimen. The toxicity is assessed

per Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [27]. Postoperative complications are graded according to the Clavien-Dindo classification and the Comprehensive Complication Index (CCI, calculated on <https://www.cci-calculator.com/cciCalculator>) and quality of life is assessed per EORTC QLQ-C30 version 3.0, QLQ-PAN26 questionnaires and PHQ-9 scale [28–32]. The technical success of EUS-delivered fiducials is defined as at least one marker presumed to be inside at the end of the EUS procedure. The quality success is defined as a score equal or higher than 6/12 points based on the quality score defined in Figueiredo et al. 2021 [33].

### Inclusion and exclusion criteria

Patients will be first included in the study on the basis of the following criteria.

#### *Inclusion criteria.*

- Cytologic or histologic proof of adenocarcinoma of the pancreatic head or uncinated process or body or tail. Diagnosis should be verified by local pathologist.
- TNM stage: T1-4N0-2M0.
- Confirmation of *clinical and radiographic stage* as borderline resectable determined by review of a high-quality diagnostic multisliced triphasic computed tomography (CT) and/or magnetic resonance (MRI) with contrast by a multidisciplinary board composed by a dedicated oncological pancreatic surgeon, radiologist and oncologist; according to the NCCN criteria (v1.2022 [8]).
- Age ≥ 18 years old.
- No prior chemotherapy or radiation for pancreatic cancer unless the neoadjuvant regimen as described.
- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
- No grade ≥ 2 neuropathies.
- Laboratory parameters as follows: absolute neutrophil count (ANC) ≥ 1,500/mm<sup>3</sup>, platelet count ≥ 100,000/mm<sup>3</sup>, hemoglobin ≥ 9 g/dL, creatinine ≤ 1.5 x upper limit of normal (ULN) or estimated glomerular filtration rate (GFR) > 45 mL/min, bilirubin ≤ 1.5 x ULN (including after adequate biliary stenting with metal stent), aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ≤ 2.5x ULN, CA 19.9 < 2500 kU/l (baseline and absence of cholestasis).

#### *Exclusion criteria.*

- Evidence of extrapancreatic disease on diagnostic imaging or laparoscopy, including distal nodal involvement beyond the peripancreatic tissue and/or distant metastases.
- Unresectable disease as defined by the NCCN criteria, i.e. > 180° arterial encasement (superior mesenteric and coeliac arteries), unreconstructible or



fully thrombosed venous invasion and/or occlusion of a long segment [8].

- CA 19.9 > 2500 kU/l (baseline and in absence of cholestasis).
- Contraindication to surgery.
- Contraindications to receive mFFX or Gem/Nab-P.
- History of radiotherapy of the upper abdomen.
- Prior treatment with oxaliplatin, irinotecan, fluorouracil or capecitabine.
- Age < 18 years old.
- Major surgery within 4 weeks of study entry.
- Pre-existing uncontrolled disease including, but not limited to: active infection, symptomatic congestive heart failure, unstable angina, social/psychiatric disorder that would limit adherence to treatment and understanding of the informed consent form.
- Other concurrent anticancer therapies.
- Existence of another active neoplasia other than basal cell carcinoma of the skin, carcinoma in situ or non-metastatic prostate cancer. Patients with an history of neoplasia must be in remission for more than 5 years to be included in the protocol.
- Pregnant or breastfeeding women; for women of childbearing potential only, a negative pregnancy test taken < 7 days prior to enrollment is required. Use of reliable contraception for at least 1 month prior to treatment is mandatory.
- Chronic concomitant treatment with strong inhibitors of the cytochrome p450, family 3, subfamily a, polypeptide 4 gene (CYP3A4) is not authorized in this study; patients on potent CYP3A4 inhibitors must discontinue medication for 14 days prior to study enrollment.

*Specific and additional exclusion criteria before randomization and after initial chemotherapy.*

- Progressive disease (RECIST or PET-CT, including non-locoregional nodal involvement and increase of CA 19.9 by 20%) after receiving 4 cycles of FFX (or 6 doses Gem/Nab-P), including after a shift of chemotherapy in case of early progression/intolerance.
- CA19.9 level > 1000 kU/l after 4 cycles of FFX (or 6 doses Gem/Nab-p).
- Presence of unmanageable toxicity during the first part of neoadjuvant chemotherapy (first 4 cycles or 6 doses of FFX or Gem/Nab-P, respectively).
- Pancreatic tumour > 7.0 cm in greatest axial dimension at the time of randomization.
- Massive invasion of the stomach or intestines and/or direct intestinal invasion of the mucosae visible at ultrasound endoscopy.
- Active gastric or duodenal ulcer disease at the time of randomization; tolerated in case of antecedent

without active ulcer (confirmation by endoscopy before iHD-SBRT).

**Therapeutic schedules (Fig. 2)**

**Neoadjuvant chemotherapy regimens**

Chemotherapy will be administrated at oncologist's discretion and includes mFFX or Gem/Nab-P. mFFX consists of oxaliplatin (85 mg/m<sup>2</sup>), irinotecan (165–180 mg/m<sup>2</sup>), folinic acid (400 mg/m<sup>2</sup>) and 5-fluorouracil (2000–2400 mg/m<sup>2</sup>/46 h) regimen for 6 cycles every 2 weeks. Gem/Nab-P consists of gemcitabine (1000 mg/m<sup>2</sup> weekly, 3 weeks/4) and nab-paclitaxel (125 mg/m<sup>2</sup>, weekly 3 weeks/4).

**Isotoxic high-dose SBRT**

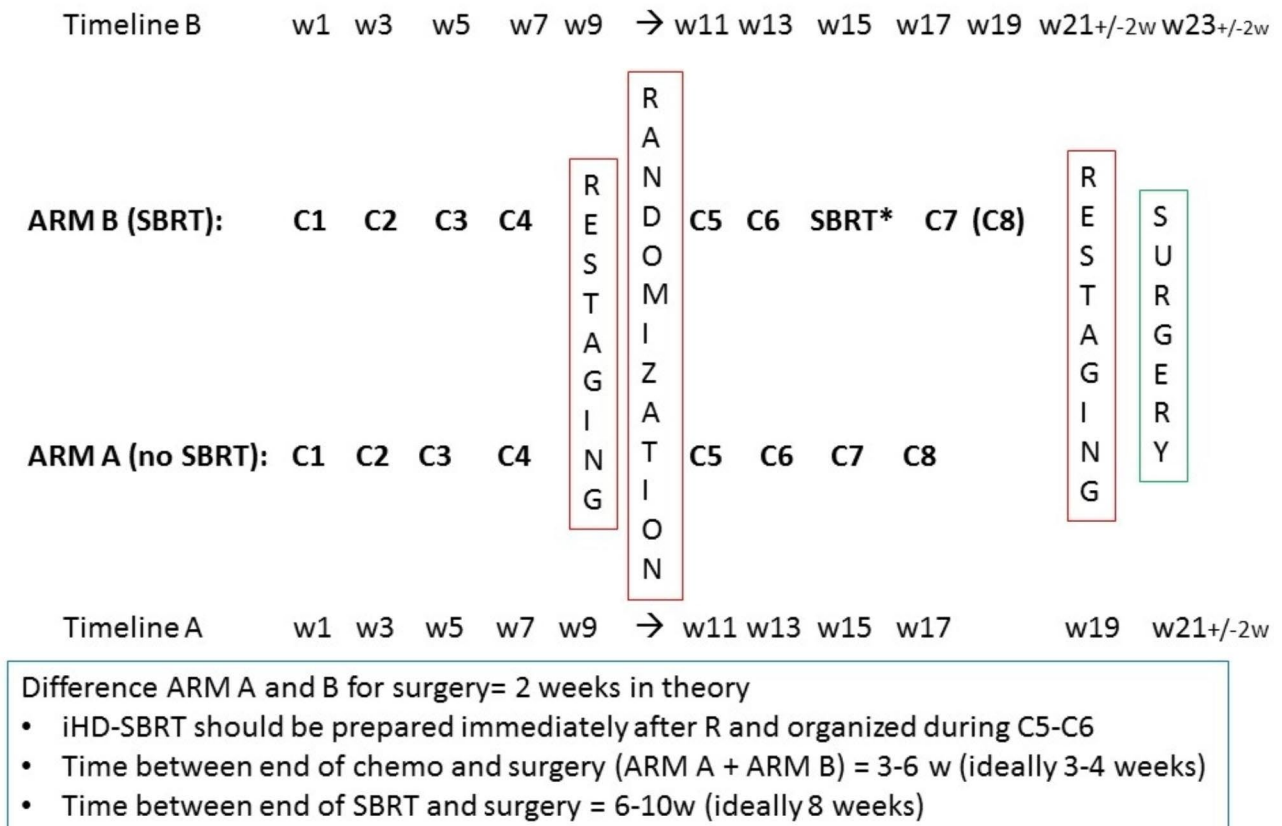
For patients randomized to the iHD-SBRT arm, the iHD-SBRT will be started minimum 1 week and maximum 4 weeks after the end of chemotherapy (6th cycle of FFX or 9th dose of Gem/NabP). Fiducial markers placement (pre-loaded Cook ECHO-TIP F 22G™, Polymarks™ [RT-Idea] or LumiCoil™ platinum fiducial markers [Boston Scientific] charged 19G needle) in the pancreatic tumour under endo-ultrasonography (EUS) guidance is required for all patients receiving SBRT minimum 5 days before the SBRT simulation, as previously described, with the exception of MR-Linac treatments [16, 32]. A minimum of 4-h fasting is required before CT simulation with adequate immobilization device and respiratory motion assessment. iHD-SBRT will be delivered in five consecutive daily fractions according to an IDP [16]. The target dose will be individually maximized to the highest achievable level with simultaneous integrated boost to the tumour and TVIs up to  $D_{\max(0.5 \text{ cc})} < 55 \text{ Gy}$  and until at least one of the mandatory dose constraint levels for OARs is reached. The following OARs dose constraints must be respected: for planning organ at risk volume (PRV) stomach, duodenum, colon and small bowel,  $D_{\max(0.5 \text{ cc})} < 40 \text{ Gy}$ ; for PRV spinal cord,  $D_{\max(0.5 \text{ cc})} < 25 \text{ Gy}$ ; for kidneys,  $D_{\text{mean}} < 14 \text{ Gy}$  and  $V_{12\text{Gy}} < 25\%$ ; and for liver;  $D_{\text{mean}} < 15 \text{ Gy}$  and  $D_{700\text{cc}} < 21 \text{ Gy}$ . A RT quality assurance (QART) manual has been developed and is available to all the participating centres. Pre- and post-treatment QA technical review (including dummy run) and audits will be conducted in order to ensure the protocol compliance and the adequate iHD-SBRT delivery.

**Surgery**

Intra-abdominal exploration with or without pancreatectomy (with minimum multiple biopsies if complete surgery not feasible) ideally within 6 to 8 weeks and maximum 10 weeks after iHD-SBRT completion (Arm B) and ideally 3–4 weeks (maximum 6 weeks) after the last cycle of chemotherapy for Arm A. The final decision to perform a pancreatectomy or not is left to the final judgment

### Treatment flow chart in each arm for mFFX

(NB. For timeline G/NabP: 4 cycles FFX= 6 doses G/NabP; 2cycles=3doses- C8 optional)



**Fig. 2** Treatment flow chart in each arm for FOLFIRINOX (NB. For timeline Gem/Nab-P: 4 cycles FFX=6 doses Gem/Nab-P; 2 cycles FFX=3 doses Gem/Nab-P; C8 optional)

of the specialist surgeon at the time of surgery. Surgery will be performed only in expert centers as defined by the Belgian healthcare convention. Procedures will be performed by laparotomy or laparoscopy according to surgeon’s preference, under general anesthesia, and include either pancreatoduodenectomy, distal pancreatectomy or total pancreatectomy. Vascular resection and reconstruction will be performed in case of suspicion of vascular involvement.

**Adjuvant chemotherapy**

Adjuvant chemotherapy is indicated for a 4 months period unless patient’s condition after surgery precludes it (regimen left to investigator’s choice) and should be started within 3 months after surgery.

**Assessment and follow-up**

All patients included in the study will be followed up through monitoring visits every 3 months for the first 2 years, then every 6 months for the next 3 years. They

will perform clinical examination with evaluation of late toxicity, laboratory tests including CA 19–9 levels and CT of the chest and the abdomen. In case of recurrence, additional treatment will be proposed at the discretion of the local oncologist. The Table 1 resumes the schedule of enrolment, interventions and assessments of the STEREO-PAC trial.

**Sample size and statistics**

The co-primary endpoints of the study are both R0 resection and DFS after randomisation in the two treatment groups. R0 resection rate is expected to be 40% in the control arm and the difference worth to detect was an absolute increase of 20% (from 40 to 60%) [34]. Based on the current literature, a median DFS of 11 months post-randomisation was chosen for statistical design, and is expected to be prolonged up to 18 months (which translates into HR:0.61 with the assumption of exponential distributions) [35]. To adjust for two primary comparisons, a two sided  $\alpha$ -error of 0.025 and  $\beta$ -error of 0.20,

**Table 1** Flow chart of the schedule of enrolment, interventions and assessments of the STEREO-PAC trial

	Screening -28- D1		Pre-treat- ment-14 -D1 Treat- ment period		Treatment period				1st FU = 15 (+/-7) days after sur- gery (EOT)	FU every 3 mo. for the first 2 y, then every 6 months for the next 3 y
	D1 (cycle 1)	Before C2 and C4	Before C4	15 days after C4	After rando, before C5	Before C6	Before SBRT (Arm B) Radiotherapy	Before C7-C8 surgery		
Informed consent	X									
Demographic data	X									
Eligibility criteria	X <sup>e</sup>			X <sup>g</sup>						
Medical history	X					X <sup>d</sup>				
Echo-endoscopy	X									X <sup>a</sup>
Residual tumoural block or 10 unstained slides of tumour block (FFPE)	X <sup>a</sup>									
Plasma samples	X <sup>a</sup>									X <sup>a</sup>
Concomitant medication	X	X	X	X	X	X	X	X	X	X <sup>b</sup>
Physical exam	X <sup>e</sup>	X	X	X	X	X	X	X	X	X <sup>b</sup>
Urine dipstick	X									
Thoraco-abdominal CT and/or abdominal MRI	X			X		X <sup>d,h</sup>		X		X <sup>b,f</sup>
Restaging				X				X		
FDG-PET (optional)	X <sup>c</sup>		X					X		
CA19-9 and CEA	X <sup>e</sup>			X	X			X	X	X <sup>b</sup>
ECOG PS	X <sup>e</sup>	X	X	X	X			X	X	X <sup>b</sup>
Cardiac assessment (ECG)	X <sup>e</sup>							X		
Lab assessment	X <sup>e</sup>	X	X	X	X	X	X	X	X	X <sup>b</sup>
(S)AE reporting (CTCAE)	X									
Pregnancy test	X <sup>e</sup>									
QoL scales	X <sup>e</sup>			X						X <sup>l</sup>
Prescription of proton- pump inhibitor	X <sup>l</sup>				X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>	X <sup>d</sup>

RESTAGING & RANDOMISATION

**Table 1** (continued)

Screening -28 - D1	Pre-treatment- 14 -D1 Treatment period	Treatment period				1st FU= 15 (+/-7) days after surgery (EOT)	FU every 3 mo. for the first 2 y, then every 6 months for the next 3 y			
		D1 (cycle 1)	Before C2 and C4	Before cycle 3 after C4	15 days after C4	After rando, before C5	Before C6	Before SBRT (Arm B) Radiotherapy	Before C7-C8 surgery	Before Surgery
Decision of adjuvant chemotherapy										X <sup>k</sup>
Survival and cause of death										X <sup>b</sup>

a: only for patients participating in the ancillary translational study of the trial. After surgery, samples will be collected at the 3 months FU then every 6 months for the 2 first years

b: every 3 months for 2 years after the "First Follow-Up Visit (15 days after surgery (EOT)). Thereafter every 6 months during 3 years

c: assessment only needed if older than 28 days before start treatment

d: only for patients randomized in arm B with radiotherapy

e: if screening/eligibility check and pre-treatment visits are on the same day as D1, no double study related tasks need to be performed

f: no CT/MRI to be done anymore after progression

g: Additional exclusion criteria before randomization to be checked

h: CT / MRI simulation in RT treatment position, at Follow-up visit at 3 months (+/-1 month) after surgery

i: Subjects whose tumor is staged as resectable at the initial restaging will continue the planned treatment cycles until planned surgery

FU: Follow-up; EOT: end of treatment

j: only in case of active gastrointestinal ulcer at the diagnosis echo-endoscopy

k: at Follow-up visit at 3 months (+/-1 month) after surgery

l: At the clinical FU 3 months after surgery, then every 6 months for the 2 first years



yielding a power of 80%, we assessed sample size separately for both objectives and chose the largest sample size.

For R0 resection, we need a sample size of 230 evaluable patients. Taking into account a 10% inevaluability rate, 256 patients need to be included to reach the objective related to R0 resection rate.

For DFS, 160 events will be required; with 5 patients included/ month, this number of events could be reached with the randomisation of 206 patients (both arms). An interim analysis (IA) for futility will be performed after 80 events and is expected to be feasible after the inclusion of 160 patients. Béta spending Lan-Demets functions will be used to control for multiplicity. The study could be stopped for futility if, at the IA, the HR estimate is in the interval [0.90; 1.12]).

The study duration is then estimated to be 111 months (51 months for accrual + up to 5 years of follow-up).

Safety will be assessed after the first 20 patients having received the TNT sequence and surgery. Safety analysis will then be planned every six months. The final decision to terminate the trial in case the criteria for stopping rules and futility are encountered will be done by the sponsor of the study.

The statistical analysis of efficacy will consist for DFS on HR testing and for R0 resection on the testing of the difference between R0 resection rates. Analysis will also make use of Kaplan-Meier analysis of DFS, OS and duration of response, in the intention-to-treat population. Multivariable analysis of DFS and OS by means of Cox proportional hazards.

#### Quality assessment of the trial

Chemotherapy will be administered as standard regimens for both mFFX or Gem/Nab-P.

iHD-SBRT will be delivered under a prespecified protocol supervised by the coordinating RT (CB) including QART as followed: each RT site must be credentialed for pancreatic SBRT prior to enrollment (facility questionnaire and dummy run procedure), the first 3 cases treated by iHD-SBRT must be centrally reviewed and approved before the beginning of the treatment (contouring and RT plan) and all the following RT treatments will be centrally reviewed retrospectively.

Surgery will be performed by expert pancreatic surgeons in dedicated expert centers as it is currently requested in Belgium by the healthcare program. The coordinating surgeon (JN) will chair an expert surgical committee that will review the procedures and potential complications after TNT.

Pathological evaluation and full margins assessment will be centrally reviewed by a committee under the supervision of the coordinating pancreatic pathologist

(PD) and reported according to the recommendations from the Pancreatobiliary Pathology Society [36].

#### Monitoring

Throughout the trial, an external independent expert committee will be responsible for monitoring and reviewing the data and make recommendations. Audits will periodically be performed in each participating center in order to randomly check compliance with the protocol, compliance with in- and exclusion criteria, proper implementation, conduct of Informed Consent procedures, data verification (i.e. crosscheck data in RedCap® with patient dossier and vice versa), and adequate reporting of serious adverse events (SAEs). Adverse events are graded using the CTCAE version 5.0 [27]. Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to the Competent Authority and Ethics Committee according to national regulation.

#### Study termination

The termination of the study is at the discretion of the sponsor in any of the following events:

- Medical or ethical reasons affecting the continued execution of the study.
- Difficulties in recruiting patients.
- Occurrence of adverse events unknown to date as to their nature, severity and duration, or unexpected incidence/severity of known adverse events.

Study safety data will be reviewed by the sponsor and investigators on an ongoing basis to ensure that continuation of the study is appropriate.

#### Ethical considerations

The study has been approved by the central Ethical Committee through the Clinical Trials Information System (CTIS) procedure (approval obtained on November 9th, 2022; reference number: 2022-501181-22-01). It has been registered at the ClinicalTrials.gov database (NCT05083247) on October 19th, 2021. The protocol has been designed according to the principles of Good Clinical Practice of the International Conference on Harmonization and of the Declaration of Helsinki. All patients will provide a written informed consent before starting treatment. An additional written informed consent will be obtained for the patients participating in the ancillary translational study for the collection of biological specimens. Subjects are free to discontinue the study at any time without giving their reason(s). Model of informed consent is available in Supplementary Material (Additional File 1 & 2). All the data collected during the study will be coded and the data entry will be done through the Red-Cap® software.

## Discussion

Neoadjuvant treatment is a rapidly emerging concept that still needs further investigation and validation in the treatment of BR PDAC. While several chemotherapeutic regimens and radiotherapeutic techniques have recently proven their relative efficacy, the best sequence and regimens remain to be determined [15, 37, 38]. The present study proposes to evaluate the impact of incorporating iHD-SBRT to preoperative neoadjuvant mFFX or Gem/Nab-P in patients with borderline resectable PDAC in a novel neoadjuvant sequence.

The mFFX chemotherapy regimen has been reported as safe, feasible, and active prior to surgery in phase II trials [39, 40]. It has also become one of the first choices in first line for patients with metastatic PDAC with a good performance status without severe co-morbidity since the PRODIGE4/ACCORD11 study. Several other studies confirmed its superiority over gemcitabine alone at the cost of increased toxicity [41–43]. FFX regimen achieves a median survival of only 11 months in metastatic patients [41]. FFX became the preferred chemotherapy regimen of many centers in the neoadjuvant approach. Recent retrospective studies and a meta-analysis showed that this neoadjuvant regimen seems to be the most effective with significantly better secondary resection rate and OS than other chemotherapy regimens [37, 38, 44]. Modifications of FFX regimen (attenuated doses of 5-fluorouracil and/or irinotecan) are widely used to improve tolerability, and decrease adverse events. Both retrospective and recent prospective trials showed comparable efficacy in metastatic disease and in LAPC [45]. FOLFIRINOX regimen in an adapted dose is also currently the standard of care in the adjuvant setting with a significant improvement in DFS and OS [5].

The combination of gemcitabine and nab-paclitaxel was also reported as efficient in the metastatic setting [46–48]; it was also recently reported in the neoadjuvant setting in phase II trials [33, 47]; the SWOG trial reported similar data using either FFX or Gem/Nab-P regimens in a randomised phase II with no true benefit on DFS after surgery but a significant rate of major pathological response [32]. It can be therefore considered as a valuable alternative to FFX in case of contraindications.

SBRT uses the latest technological advances developed over the past two decades in the field of radiotherapy, both in dose delivery and image-guided radiotherapy. SBRT allows the delivery of high ablative equivalent biological doses in few sessions (1 to 5) at the level of the gross tumour volume (GTV) in a highly conformational way, which makes it possible to reduce the dose and therefore the toxicity to nearby OAR [15]. The SBRT technique can be easily integrated into a neoadjuvant approach and the results of available Phase I/II and retrospective studies are promising, showing very high rates of

R0 resection for BR and LAPC patients (84–97.5%) [15]. Therefore, and despite the lack of level I evidence, leading international (radio)oncological societies have already listed SBRT as a treatment option for localized PDAC in their guidelines [8–11]. In order to preliminarily evaluate the feasibility and safety of iHD-SBRT in a total neoadjuvant sequence for the treatment of localized pancreatic adenocarcinoma, we have already performed a prospective analysis in 39 consecutive BR (18/39) and LAPC (16/39) patients [15]. Our results showed that iHD-SBRT displays an excellent toxicity profile, also for potentially high-risk patients with radiological direct gastrointestinal tumoral invasion at diagnosis, and can be easily integrated in a total neoadjuvant strategy. The oncological outcomes were also promising including: median OS and DFS of 24.5 and 15.6 months, respectively, a 1-year local control of 74.1%, a median locoregional DFS not reached and late/early gastrointestinal toxicity <5% [15]. Given the lack of comparative evidence, we also retrospectively compared the outcomes of PDAC patients treated with iHD-SBRT (n=41) or conventional CRT (n=41) in the same tertiary cancer center [24]. The mOS was in favour of the iHD-SBRT group (22.5 vs. 15.9 months,  $p < .001$ ) even after multivariate analysis (HR 0.39 [CI95% 0.18–0.83],  $p = .014$ ) [24]. The iHD-SBRT group also displayed significantly better median PFS and 1y-LC (median PFS: 16.7 vs. 11.5 months,  $p = .011$ ; 1-yLC: 75.8 vs. 39.3%,  $p = .004$ ) [24]. All of these results further support the implementation of SBRT treatments for PDAC patients and highlight the need for well-designed studies in this area, particularly investigating the benefit of adding optimally delivered iHD-SBRT in a total neoadjuvant setting that emerges now in other cancers [49].

## Conclusion

The purpose of this prospective randomised phase II is to evaluate the impact and efficacy of incorporating isotoxic high-dose SBRT into a total neoadjuvant treatment sequence including active chemotherapy for borderline resectable pancreatic adenocarcinoma. Therefore, this trial will help to define the best standard neoadjuvant treatment sequence.

## Trial status

Protocol version n°: 1.2 Date: October 18, 2022.

Date of beginning of recruitment: March 15, 2023.

Approximate date of complete accrual: 1/1/2028.

The STEREO-PAC trial is a multicenter randomized phase II trial, conducted in 10 initial centers that provide multidisciplinary treatment for pancreatic cancer throughout Belgium. At the time of submission of this paper, all initial centers were activated. The first patient was included on March 24, 2023.

**Abbreviations**

iHD-SBRT	Isotoxic High Dose Stereotaxic Body Radiation Therapy
PDAC	Pancreatic ductal adenocarcinoma
R0	Complete microscopic resection
SBRT	Stereotaxic Body Radiation Therapy
mFFX	Modified FOFIRINOX
Gem/Nab-P	Gemcitabine/Nab-Paclitaxel
TNT	Total neoadjuvant treatment
BR	Borderline resectable
LAPC	Locally advanced pancreatic cancer
OS	Overall survival
FFX	FOFIRINOX
DFS	Disease-free survival
NAT	Neoadjuvant therapy
RT	Radiation therapy
BED	Biologically effective dose
TVI	Tumour/vessel interface
SIB	Simultaneous integrated boost
IDP	Isotoxic dose prescription
OAR	Organ at risk
mDFS	Median disease-free survival
RECIST	Response evaluation criteria in solid tumours
LFFI	Locoregional failure free interval
DMFI	Distant metastases free interval
pCR	Pathologic complete response rate
QoL	Quality of life
EUS	Endoscopic ultrasound
CTCAE	Common Terminology Criteria for Adverse Events
EORTC	European Organisation for Research and Treatment of Cancer
CT	Computed tomography
MRI	Magnetic resonance imaging
ECOG	Eastern Cooperative Oncology Group
ANC	Absolute neutrophil count
ULN	Upper limit of normal
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GFR	Glomerular filtration rate
NCCN	National Comprehensive Cancer Network
PET	Positron emission tomography
PRV	Planning organ at risk volume
QA	Quality assurance
HR	Hazard ratio
IA	Interim analysis
QART	Quality assurance of radiation therapy
SAE	Serious adverse events
SUSAR	Suspected Unexpected Serious Adverse Reactions

**Supplementary Information**

The online version contains supplementary material available at <https://doi.org/10.1186/s12885-023-11327-x>.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Not applicable.

**Authors' contributions**

Study conception and design: JLV, CB; Drafting of manuscript: JN, CB, JLV; CB is principal investigator of the department of radiation-oncology and national coordinator for radiation-oncology; JN is national coordinator for surgery; JLV is principal investigator and national coordinating investigator of the study. CB, IB, KG, TVD, JLV are local investigators in their institutions. PD is the referent pancreatic pathologist and pathology coordinator for the study. MP is the referent statistician of the study. Critical revisions: all authors. All authors are members of the steering committee of the study. All authors read and approved the final manuscript.

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**Data Availability**

Not applicable.

**Declarations****Competing interests**

The authors declare no competing interests.

**Ethics approval, consent to participate and confidentiality**

The study protocol was approved by the central Ethics Committee through CTIS procedure (Reference N°2022-501181-22-01 - Date: November 9th, 2022). The study is approved by each participating institution's Institutional Review Board. This study will be conducted according to the principles of the Declaration of Helsinki (version October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). 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. Additional informed consent for the biological collateral study includes consent for collection and use of biological specimens (i.e. blood and tissue). Written informed consent of patients is required before enrolment in the trial or study related procedures take place. All data provided to the sponsor will be handled with strict confidentiality, assuring anonymity of patients. To guarantee the security of data, and to ensure compliance with the GDPR and to ensure that the principles of confidentiality, integrity and availability of data are respected, several measures have been put in place, in particular:

- The anonymized participant information will be stored in locked file cabinets in areas with limited access with key or batch control.

- All databases will be secured with encrypted and password-protected access systems and audit trail.

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The sponsor has a liability insurance which will be annually renewed in the event of any indemnity and compensation related to the trial.

**Consent for publication**

Not applicable.

**Sponsor of the study**

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The sponsor has ultimate authority over all the activities related to this study and will have access to the final trial dataset.

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#### References

- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63:11–30.
- Kleeff J, Korc M, Apte M, et al. Pancreatic cancer. *Nat Rev Dis Primers*. 2016;2:16022.
- Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, Version 2.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2017;15:1028–61.
- Balaban EP, Mangu PB, Khorana AA, et al. Locally Advanced, Unresectable Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2016;34:2654–68.
- Conroy T, Hammel P, Hebbar M, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. *N Engl J Med*. 2018;379:2395–406.
- Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. *JAMA*. 2013;310:1473–81.
- Neoptolemos JP, Palmer DH, Ghaneh P, et al. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet*. 2017;389:1011–24.
- National Comprehensive Cancer Network. Pancreatic Adenocarcinoma. (Version 2.2022), [https://www.nccn.org/professionals/physician\\_gls/pdf/pancreatic.pdf](https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf) (accessed 18 January 2023).
- Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2021;19:439–57.
- Khorana AA, McKemin SE, Berlin J, et al. Potentially curable pancreatic adenocarcinoma: ASCO clinical practice guideline update. *J Clin Oncol*. 2019;37:232082–2088.
- Palta M, Godfrey D, Goodman KA, et al. Radiation Therapy for Pancreatic Cancer: executive summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol*. 2019;9:322–32.
- Unno MMF, Matsuyama Y, Satoi S, Matsumoto I, Aosasa S, Shirakawa H, Wada K, Fujii T, Yoshitomi H, Takahashi S, Sho M, Ueno H, Kosuge T. Randomized phase II/III trial of neoadjuvant chemotherapy with gemcitabine and S-1 versus upfront surgery for resectable pancreatic cancer (Prep-02/JSAP05). *J Clin Oncol*. 2019;37:189.
- Versteijne E, Suker M, Groothuis K et al. Preoperative Chemoradiotherapy Versus Immediate surgery for Resectable and Borderline Resectable Pancreatic Cancer: results of the dutch Randomized Phase III PREOPANC Trial. *J Clin Oncol* 2020; JCO1902274.
- Fietkau R, Ghadimi M, Grützmann R, et al. Randomized phase II trial of induction chemotherapy followed by chemoradiotherapy or chemotherapy alone for nonresectable locally advanced pancreatic cancer: first results of the CONKO-007 trial. *JCO*. 2022;40(S16):4008–8. [Abstract].
- Bouchart C, Navez J, Closset J, et al. Novel strategies using modern radiotherapy to improve pancreatic cancer outcomes: toward a new standard? *Ther Adv Med Oncol*. 2020;12:1758835920936093.
- Bouchart C, Engelholm JL, Closset J, et al. Isotoxic high-dose stereotactic body radiotherapy integrated in a total multimodal neoadjuvant strategy for the treatment of localized pancreatic ductal adenocarcinoma. *Ther Adv Med Oncol*. 2021;13:17588359211045860.
- Katz MH, Shi Q, Meyers J et al. Efficacy of preoperative mFOLFIRINOX vs mFOLFIRINOX plus hypofractionated radiotherapy for borderline resectable adenocarcinoma of the pancreas: the A021501 phase 2 randomized clinical trial. *JAMA Oncol* 2022; Jul 14:e222319.
- Grossberg AJ, Jethwa KR, Ellsworth SG. Neoadjuvant mFOLFIRINOX vs mFOLFIRINOX plus radiotherapy in patients with Borderline Resectable Pancreatic Cancer—The A021501 trial. *JAMA Oncol*. 2022. <https://doi.org/10.1001/jamaoncol.2022.6135>.
- Zhu X, Shi D, Li F, et al. Prospective analysis of different combined regimens of stereotactic body radiation therapy and chemotherapy for locally advanced pancreatic cancer. *Cancer Med*. 2018;7:2913–24.
- Rudra S, Jiang N, Rosenberg SA, et al. Using adaptive magnetic resonance image-guided radiation therapy for treatment of inoperable pancreatic cancer. *Cancer Med*. 2019;8:2123–32.
- Zhu X, Cao Y, Su T, et al. Failure patterns and outcomes of dose escalation of stereotactic body radiotherapy for locally advanced pancreatic cancer: a multicenter cohort study. *Ther Adv Med Oncol*. 2020;12:1–11.
- Arcelli A, Guido A, Buwenge M, et al. Higher biologically effective dose predicts survival in SBRT of pancreatic cancer: a multicentric analysis (PAULA-1). *Anti Can Res*. 2020;40:465–72.
- Zindler JD, Thomas CR Jr, Hahn SM, et al. Increasing the therapeutic ratio of stereotactic ablative radiotherapy by individualized isotoxic dose prescription. *J Natl Cancer Inst*. 2015;108:dvj305.
- Manderlier M, Navez J, Hein, et al. Isotoxic high-dose stereotactic body radiotherapy (iHD-SBRT) versus conventional chemoradiotherapy for localized pancreatic cancer: a single cancer center evaluation. *Cancers (Basel)*. 2022;14:5730.
- Chan A-W, Tetzlaff JM, Göttsche PC, et al. SPIRIT 2013 explanation and elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586.
- Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guidelines (version 1.1). *Eur J Cancer*. 2009;45:228–47.
- U.S. department of health and human services. National Institutes of Health NCI. Common Terminology Criteria for Adverse Events (CTCAE), v5.0. November 27, 2017. (Available from: [https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_5.0/](https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/)) (accessed 18 January 2023).
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
- Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258(1):1–7.
- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–76.
- The European Organization for Research and Treatment of Cancer QLQ - PAN. 26; <https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-PAN26-English.pdf> (accessed 18 January 2023).

32. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16:606–13.
33. Figueiredo M, Bouchart C, Moretti L, et al. EUS-guided placement of fiducial markers for stereotactic body radiation therapy in pancreatic cancer: feasibility, security and a new quality score. *Endosc Int Open*. 2021;9:E253–7.
34. Schlitter AM, Esposito I. Definition of microscopic tumor clearance (R0) in pancreatic cancer resections. *Cancers (Basel)*. 2010;2:2001–10.
35. Sohal DPS, Duong M, Ahmad SA, et al. Efficacy of Perioperative Chemotherapy for Resectable pancreatic adenocarcinoma: a phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2021;7:421–7.
36. Wang H, Chetty R, Hosseini M, et al. Pathologic examination of pancreatic specimens resected for treated pancreatic ductal adenocarcinoma: recommendations from the Pancreatobiliary Pathology Society. *Am J Surg Pathol*. 2022;46:754–64.
37. Dhir M, Zenati MS, Hamad A, et al. FOLFIRINOX Versus Gemcitabine/Nab-Paclitaxel for Neoadjuvant Treatment of Resectable and Borderline Resectable Pancreatic Head Adenocarcinoma. *Ann Surg Oncol*. 2018;25:1896–903.
38. Janssen QP, Buettner S, Suker M et al. Neoadjuvant FOLFIRINOX in patients with borderline resectable pancreatic cancer: a systematic review and patient-level meta-analysis. *J Natl Cancer Inst* 2019.
39. Murphy JE, Wo JY, Ryan DP, et al. Total neoadjuvant therapy with FOLFIRINOX followed by Individualized Chemoradiotherapy for Borderline Resectable pancreatic adenocarcinoma: a phase 2 clinical trial. *JAMA Oncol*. 2018;4:963–9.
40. Katz MH, Shi Q, Ahmad SA, et al. Preoperative modified FOLFIRINOX treatment followed by capecitabine-based chemoradiation for Borderline Resectable Pancreatic Cancer: Alliance for clinical trials in Oncology Trial A021101. *JAMA Surg*. 2016;151:e161137.
41. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med*. 2011;364:1817–25.
42. Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol*. 2013;31:23–9.
43. Thibodeau S, Voutsadakis IA. FOLFIRINOX Chemotherapy in metastatic pancreatic Cancer: a systematic review and Meta-analysis of Retrospective and Phase II Studies. *J Clin Med* 2018; 7.
44. Hackert T, Sachsenmaier M, Hinz U, et al. Locally Advanced Pancreatic Cancer: Neoadjuvant Therapy with Folfirinor results in resectability in 60% of the patients. *Ann Surg*. 2016;264:457–63.
45. Stein SM, James ES, Deng Y, et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. *Br J Cancer*. 2016;114:737–43.
46. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013;369:1691–703.
47. Goldstein D, El-Maraghi RH, Hammel P et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: long-term survival from a phase III trial. *J Natl Cancer Inst* 2015; 107.
48. Van Laethem JLB, Borbath Y, Verset G, Demols A, Puleo F, Peeters M, Annet L, Ceratti A, Ghilain A, Komuta M, Demetter P, Maréchal R. Preoperative gemcitabine-nab-paclitaxel (G-NP) for (borderline) resectable (BLR) or locally advanced (LA) pancreatic ductal adenocarcinoma (PDAC): feasibility results and early response monitoring by Diffusion-Weighted (DW) MR. *J Clin Oncol*. 2016;34:4116.
49. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:29–42.

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