

SYNOPSIS PANACHE	
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Title	PANACHE-01 – resectable Pancreatic Adenocarcinoma Neo-Adjuvant FOLF(IRIN)OX-based CHEmotherapy - A multicenter, randomized Phase II Trial
Purpose	The objective is to evaluate the safety and efficacy of two modes of neo-adjuvant chemotherapy (FOLF(IRIN)OX) relative to the current reference treatment (surgery and then adjuvant chemotherapy). The main study outcomes are overall survival at 12 months and the percentage of patients undergoing the full therapeutic sequence.
Rational	<p>At time of diagnosis, less than 10% of pancreatic adenocarcinomas (PDAC) are considered to be immediately operable (i.e. resectable) (Siegel, 2012). In view of the poor overall survival, only tumours without vascular invasion (NCCN 2014) should be considered for resection, i.e. those for which resection with disease-free margins (R0) is theoretically possible in absence of presurgery treatment (Chun, 2010). In fact, standardised pathological analyses show that the proportion of R1 resections (i.e. resection with involved margins) is above 61% (Delpero, 2012). These high R1 rates and undetectable locoregional metastatic spreading prior to surgery explain (at least in part) the observed 1-year relapse and mortality rates of 50% and 25%³.</p> <p>Immediate surgery followed by adjuvant chemotherapy is the reference treatment in Europe. No previous prospective study has compared this approach to a neoadjuvant approach for resectable PDAC. In retrospective studies, oncological results in term of survival were quite similar when multimodality therapy (adjuvant or neoadjuvant chemotherapy and surgery) was completed, between 20 and 30 months^{1,4}. The main limitation of the adjuvant approach was the low rate of completion of the full therapeutic sequence. Indeed, only 47 to 60% patients received any adjuvant therapy after resection compared to more than 75% for neoadjuvant therapy^{1,4,5}</p> <p>Moreover, treatment with a combination of 5-FU and a platinum salt (together with irinotecan as an option: FOLFIRINOX) is efficacious in terms of clinical response and tumour control. In metastatic situations, FOLFIRINOX is associated with a significant improvement (relative to gemcitabine alone) in overall survival (11.1 vs. 6.8 months) and response rate (31% vs. 9.4%)². These results have been confirmed by several studies evaluating FOLFIRINOX for the treatment of non-metastatic, non-resectable lesions, with tumour control in 83% of cases (with a partial response in 30%) (Hosein, 2012; Beone, 2013), 100% feasibility and a median of 8 treatment cycles.</p> <p>These data mean that the two combination treatments (5-FU, leucovorin and oxaliplatin in the presence or absence of irinotecan) are potential candidates for neoadjuvant use with a view to optimising oncological outcomes in resectable PDAC.</p>
Study design	Multicentre, randomised Phase II trial, Bryant and Day two-stage design
Primary endpoint	This study has co-primary endpoints assessing OS rate at 12 months with the feasibility of delivering a full therapeutic sequence. This type of criterion is intended to evaluate both efficacy and feasibility of neoadjuvant strategy. OS is defined as time from randomisation to death from any cause. Feasibility is defined as the proportion of patients having undergone the full

	<p>therapeutic sequence (regardless of the study arm). Clear definition is required in each study arm and so "full therapeutic sequence" is defined as:</p> <ul style="list-style-type: none"> • "two or more cycles of neo-adjuvant chemotherapy followed by surgical resection" in the neo-adjuvant arms. • "surgical resection completed by four or more cycles of adjuvant chemotherapy" in the control arm. <p>Hence, this parameter represents an objective evaluation in the control arm (no pre-operative chemotherapy) and the two neoadjuvant chemotherapy arms (FOLFIRINOX & FOLFOX).</p> <p>The criteria used to justify a lack of feasibility are as follows:</p> <ul style="list-style-type: none"> - Failure to perform resection because of locoregional or metastatic tumour progression (imaging, surgical investigation, etc.) - The performance of fewer than 2 cycles of chemotherapy in the neo-adjuvant arm and fewer than 4 cycles in the adjuvant arms, due to: <ul style="list-style-type: none"> o treatment-related complications (allergic reactions, persistent grade 3 or 4 haematological toxicity despite treatment delays and/or dose reduction) o a change in overall health status (performance status (PS)≥2) o prolonged post-surgical complications
<p>Secondary endpoints</p>	<p>The study's secondary criteria are as follows:</p> <ul style="list-style-type: none"> - Chemotherapy-related toxicity, graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4 dated 15/09/2009) - Overall postsurgical morbidity, graded according to the Dindo/Clavien classification - Specific morbidity due to pancreatic fistula, graded according to the International Study Group of Pancreatic Fistula (ISGPF) criteria. - Overall survival after 3 years of follow-up - Disease-free survival after 3 years of follow-up (DATECAN consensus definition for the pancreas) - R0 resection rate - N status, lymph node ratio - Histological tumour response to neo-adjuvant treatment (stage pT stage, according to the College of American Pathologists (CAP) grading system and the Evans grading system) - Quality of life (QLQ-C30, QLQ-PAN26) - Constitution of biological collections (tissue and serum banks) - The correlation between "circulating tumour DNA" on the one hand and tumour response and disease-free survival on the other
<p>Main inclusion criteria</p>	<ul style="list-style-type: none"> - Histology-proven, adenocarcinoma of the pancreas. - Resectable adenocarcinoma (according to the NCCN classification 2014): absence of distant organ or distal lymph node metastases, absence of evidence of superior mesenteric vein (SMV) and portal vein distortion, tumour thrombus, or venous encasement, the existence of clear fat planes around the celiac axis, hepatic artery and superior mesenteric artery (SMA). Resecability is evaluated on arterial-phase and portal-phase IV contrast-enhanced multislice CT-scan of the pancreas (slice thickness: 2.5 mm), as evaluated in a multidisciplinary staff meeting including at least one radiologist and one expert surgeon.

- No prior chemotherapy.
- Age 18 years or over.
- Ability to understand and willingness to consent to formal requirements for study participation
- Provision of written informed consent prior to any study-specific screening procedures.

Treatment

Patients will be randomised between immediate surgery, neoadjuvant chemotherapy with FOLFIRINOX or neoadjuvant chemotherapy with FOLFOX. Randomisation will be stratified according to:

- Centre
- Topography of tumour (uncinate/head/neck versus body/tail)
- Bilirubin level (<1.5N versus >1.5N)
- CA19-9 level CA19-9 level (≤200 U/ml vs. >200 U/ml)

Standard arm

Step 1: Surgery

- Pancreatic tumour resection according to current French guidelines (*Slim, J Chir 2009)

Step 2: Adjuvant chemotherapy

- Adjuvant chemotherapy: 6 months; the choice of drug (5FU or gemcitabine) will be left to the medical teams involved

FOLFIRINOX arm

Step 1: Neoadjuvant FOLFIRINOX chemotherapy

- Biliary drainage via a short coated stent will be required, before the first cycle of chemotherapy administration, in case of bilirubin level higher than 1.5N
- 4 cycles of FOLFIRINOX neo-adjuvant chemotherapy

Step 2: Surgery

- Pancreatic tumour resection according to current French guidelines (*Slim, J Chir 2009)

Step 3: Adjuvant chemotherapy

- Adjuvant chemotherapy: 4 months; the choice of drug (5FU or gemcitabine) will be left to the medical teams involved.

FOLFOX arm

Step 1: Neoadjuvant FOLFOX chemotherapy

- Biliary drainage via a short coated stent will be required, before the first cycle of chemotherapy administration, in case of bilirubin level higher than 1.5N
- 4 cycles of FOLFOX neo-adjuvant chemotherapy

Step 2: Surgery

- Pancreatic tumour resection according to current French guidelines (*Slim, J Chir 2009)

Step 3: Adjuvant chemotherapy

- Adjuvant chemotherapy: 4 months; the choice of drug (5FU or gemcitabine) will be left to the medical teams involved.

FOLFIRINOX Arm	FOLFOX Arm
- Oxaliplatin: 85mg/m ² over 2 hours on D1 - Leucovorin: 400mg/m ² over the same 2 hours on D1	
- Irinotecan: 180 mg/m ² over 90 min on D1 - a continuous perfusion of 5FU (2400 mg/m ² over 48 hours, so 1200 mg/m ² on D1 and on D2)	- a 400mg/m ² bolus of 5FU followed by continuous perfusion of 5FU (2400 mg/m ² over 48 hours, so 1200 mg/m ² on D1 and on D2)

	Every two weeks for 2 months (4 cycles)
Statistical analysis	<p>Bryant and Day two-stage design One-sided type 1 error = 5% Power =85%</p> <p>With the following hypotheses, an overall survival rate at 12 months of 70% and feasibility of the full therapeutic sequence in 55% of patients in the neo-adjuvant FOLFOX and FOLFIRINOX groups will be considered as poor outcomes (hypothesis 0)</p> <p>The hoped-for outcome corresponds to an overall survival rate at 12 months of 85% and 75% feasibility in the neo-adjuvant FOLFOX and FOLFIRINOX groups (hypothesis 1)</p> <p>In all, we shall have to randomize 160 subjects (2:2:1) into the FOLFOX, FOLFIRINOX and control arms in order to verify our hypothesis in the study population, with an intermediate analysis once 27 patients with 12 months of follow-up have been included in each of the arms.</p> <p>The results will be submitted to an independent Data and Safety Monitoring Committee.</p>
Planned study period	<p>Anticipated duration of recruitment: 160 patients in 24 months, corresponding to 7 patients/month <u>Number of recruiting centres: 26</u> Maximum duration of treatment: 9 months Minimum duration of follow-up for the last included patient: 36 months <u>Corresponding to a total study duration of 60 (+/-3) months, approximately 5 years</u></p>
Translational research	<p>Two translational research studies will be considered, with independent funding from the PHRC call for funds</p> <ol style="list-style-type: none"> 1. Prognostic value of circulating tumour DNA levels 2. Prognostic value of intra and peri-tumor immune infiltration
References	<ul style="list-style-type: none"> - 1 Gillen et al. PLoS Med. (2010); 7:e1000267 - 2 Conroy et al. N Engl J Med (2011); 364: 1817-25 - 3 Oettle et al. JAMA (2007); 297: 267-277 - 4 Tzeng et al. J Gastrointest Surg (2014); 18:16-25 - 5 Merkow et al. Ann Surg (2013); 00:1-6