FOLFIRINOX followed by local therapy (Resection, RT and/or IRE) in patients with locally advanced pancreatic cancer (LAPC)

LAPC-03: A Nordic phase II study
Version 1.5 (14.11.16)

Participating centres:
Odense
Stockholm
Other

Data Center and Serious adverse event reporting:
Research Department of Clinical Oncology, Sdr. Boulevard 29, Entrance 112, 5th
Odense University Hospital, DK-5000 Odense C
Fax: +45 66 13 54 77

Sponsors signature: ____________________________

Investigators signature: ____________________________
# STUDY SUMMARY - LAPC-03

<table>
<thead>
<tr>
<th>Protocol title:</th>
<th>FOLFIRINOX followed by local therapy (resection, RT and/or IRE) in patients with locally advanced pancreatic cancer (LAPC). A Nordic phase II study.</th>
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</thead>
<tbody>
<tr>
<td>Sponsor</td>
<td>Professor Per Pfeiffer, dpt. of Oncology, Odense University Hospital</td>
</tr>
<tr>
<td>Protocol version:</td>
<td>Version 1.4</td>
</tr>
<tr>
<td>Principal investigators:</td>
<td>Jon Bjerregaard, Lars Lundell, Michael Bau Mortensen, Per Pfeiffer</td>
</tr>
<tr>
<td>Protocol Phase:</td>
<td>Phase II</td>
</tr>
<tr>
<td>Indication:</td>
<td>LAPC (Locally advanced pancreatic cancer)</td>
</tr>
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</table>
| Objectives:    | **Primary objective:** 1. 2 year survival for all patients starting chemotherapy  

**Secondary objectives:**  
2. Quality of Life (QoL)  
3. Resection rate (R0 and R1)  
4. PFS  
5. OS  
6. Response rate (RECIST v1.1)  
7. Adverse events grade 2-5 (NCI-CTCAE 4.0)  
8. Surgical complications, including IRE (Clavien) |
| Study design:  | Phase II (Simon two-stage)  
FOLFIRINOX is administered for every second week with CT evaluation of resectability every 2 months. RT or IRE may be added to increase chance of resection.  
The primary objective is 2 year survival but for calculation of number of patients R0/1 resection-rate will be used.  
The sample size is based on Simon’s two stages optimum max design. This design ensures early study termination if there is insufficient effect.  
A resection rate less than 10% after 4 months of preoperative chemotherapy is not clinically acceptable. Assuming a significance level at 0.05 ($\alpha = 0.05$) and a power at 90% ($\beta = 0.10$) it can be calculated, that 21 patients should be included in the first part of the study. The enrolment will continue until 21 patients have completed 4 months of chemotherapy and have been re-evaluated for resection by CT scan (and EUS+LUS, if available). If 2 or less out of the first 21 consecutive patients are being resected we will reject our hypotheses and close the study after the first stage of accrual. If 3 or more patients are resected, an additional 45 patients will be accrued in the second
stage. If at least 11 out of 66 patients are resected, a true resection rate of 25% cannot be excluded, and we will conclude that the treatment is effective enough to continue with future studies. To ensure 66 evaluable patients we will include a total of 75 patients.

**Planned sample size:** 75 patients will be recruited in order to obtain 66 evaluable patients (First stage 21; second stage 45 evaluable patients).

**Number of centers:** Expected 5-10

**Selection criteria:**
- Histologically or cytologically proven adenocarcinoma/carcinoma of the pancreas
- LAPC as judged by the local MDT and the Karolinska criteria
- >18 years of age
- WHO performance status 0-1
- Adequate hematological, renal, and hepatic function
- No prior chemotherapy
- Written informed consent

**Study medication(s):** FOLFIRINOX until local therapy or for at least 6 months

**Main parameters of safety:** Adverse events, graded according to the NCI CTCAE preoperatively, and according to Clavien classification postoperatively.

**Study procedures:** Patients are screened and staged. If judged as LAPC by the local MDT and if LAPC is confirmed according to the Karolinska criteria, patients can be included and registered. When a patient has consented to participate in this study, FOLFIRINOX will start within 10 work days. Patients will attend study specific visits with radiological evaluation every 8th week.

If patients are considered candidates for surgery, a detailed re-evaluation of resectability is performed according to local preferences (e.g. EUS and/or LAP/LUS and/or CT and/or MR and/or PET/CT). If RT or IRE is not planned, the patients should have surgical exploration after a maximum of 8 cycles of FOLFIRINOX.

After local therapy (resection, RT and/or IRE), 30 days complication rate will be gathered. Thirty days and 90 days (in hospital) mortality are registered.

Patients who at any time during the study (after at least 4 cycles of chemotherapy) are assessed as never resectable may be referred for intraoperative or percutaneous Irreversible Electroporation (IRE).

4 weeks (±1 week) after resection patients will be evaluated for 2-3 months of adjuvant therapy depending on patient’s performance, histopathological report and prior therapy.

After completion of chemotherapy patients will be followed according to standard practice in each hospital. Data on local relapse, systemic spread and survival will be collected from medical records.
### Informed consent

Written informed consent must be obtained prior to the patient undergoing any study-specific procedures.

### Screening

Baseline screening includes:
- Informed consent
- Eligibility assessment
- Medical history
- WHO performance status
- Tumor assessment
- Physical examination
- Pregnancy test
- Blood tests

### Assessments during chemotherapy

<table>
<thead>
<tr>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO performance status</td>
</tr>
<tr>
<td>Adverse events according to CTC</td>
</tr>
<tr>
<td>Routine blood test for administration of chemotherapy</td>
</tr>
<tr>
<td>Radiological evaluation every 8 weeks during chemotherapy</td>
</tr>
</tbody>
</table>

### Assessments during Post-Treatment Follow-up:

- At 30 days postoperative visit: WHO performance, concomitant treatment, physical exam, vital signs, hematology, blood chemistry, urinalysis, complication rate according to Clavien.
- Chemotherapy use (number of courses and dose-intensity)
- End of study: survival, disease progression

### Analysis plan

When 21 patients have received at least 4 months of chemotherapy, the decision whether to end or continue the study will be taken.

### First patient included and duration of study:

It is expected that the first patients will be enrolled Q1 2017. Duration of study is expected to be 24 months
Indhold

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1 BACKGROUND

Due to diffuse symptoms pancreatic cancer (PC) is diagnosed in 80% or more when it is already too late for a primary resection [1-4]. For those patients with a resectable PC the 5 year survival is about 20% compared to <5% in all pancreatic cancers and the median survival after a radical resection is about 24 months compared to 6 months if no therapy is offered. Patients with incomplete tumor clearance after resection (R2) is probably not much better off compared to patients with locally advanced pancreatic cancer (LAPC). Margin resection status seems to be of great importance regarding the prognosis. It is therefore of great value to diagnose those patients where there is a reasonable chance to resect the tumour with a negative margin even though there is vascular involvement.

Adjuvant therapy

Recent randomized trials, that have investigated the effect of adjuvant chemotherapy following pancreatic resection, show that the chance of being alive after 5 years has almost doubled [5-9]. Two large randomized trials (ESPAC-1 and CONKO-1) have shown that adjuvant chemotherapy significantly prolongs the median survival and increases the 5-year survival compared to no therapy [5, 7]. However, there was no difference between 5FU and gemcitabine [6], but patients in the Gemcitabine arm had a better toxicity profile. These and other studies confirm that adjuvant gemcitabine increases the estimated 5-year survival by about 10 percentage points after micro-radical surgery (R0 resection) for PC.

The Japanese JASPAC-01 study were presented at ASCO GI 2013 and published in 2016 [8]. Patients were randomized to adjuvant gemcitabine (n = 193) or S1 (n = 192). S1 is given orally and is converted in the body to 5FU. 5 year survival was almost doubled from 24.4% to 44.1% (HR 0.57, p <0.0001) and therefore S-1 now approved in Japan. Probably the S-1 will not be approved based on Japanese data, but it is doubtful whether any side will get data in non-Asian patients.

There are several recently completed or ongoing studies examining effects of gemcitabine [10] compared to combination chemotherapy (GemCap, FOLFIRINOX or GemAbraxane) [11-13], while others investigating neoadjuvant treatment (2 months of chemotherapy before resection). Data from 730 patients in ESPAC-4 study was presented at ASCO 2016 [9] and the combination of gemcitabine and capecitabine increased 5 year survival from 16.3% to 28.8% (HR 0.82, p = 0.03). Although data is not published DPCG recommend adjuvant Gem-Cap as the new standard treatment for patients who are candidates for combination therapy.
Evaluation of resectability

The traditional two main parameters used for evaluating tumour vessel encasement are; the grade of the circumferential involvement and the length that the tumour is in contact with vessels. The importance of both grade and length of such encasements probably differs from arteries to veins in the pancreatic region. For instance a <50% circumferential involvement in a short vein segment is easy to deal with for the trained surgeon, whereas a corresponding involvement of arteries makes it less likely to achieve a R0 resection. It is possible that also peri-arterial stranding has to be taken into account. Moreover, venous narrowing or complete obstruction might jeopardize surgical resection.

About 30-40% of the patients have LAPC at the time of diagnosis, with extensive tumour growth over the adjacent organs particularly due to vascular involvement of the tumour – venous and/or arterial, but without evidence of distant metastases. These tumours are usually considered irresectable due to the fact that complete surgical excision with negative pathologic margins is not possible using standard surgical procedures, with a survival no different than that in metastatic disease. In some of these patients, however, radical (R0) resection may be achieved after pre-operative oncological therapy with the aim to downstage or down-size the primary tumour [3]. The results following resection of LAPC with venous and arterial resection and reconstruction are conflicting, and the data are hampered by the lack of prospective studies with strict definitions regarding both the diagnosis and definition of LAPC. Thus, the recent interest in a neoadjuvant approach to LAPC is faced with two important issues that need careful consideration before embarking on major prospective studies: 1) How is LAPC defined? and 2) How is LAPC diagnosed?

1.1 Defining and diagnosing LAPC

The best staging tool at present time is the latest multi-slice multiphase contrast enhanced computed tomography (CT) with software for 3-D reconstruction. Through a joint effort between dedicated radiologists and pancreatic surgeons at Karolinska University Hospital the following system has been launched and evaluated, to preoperatively categorize all pancreatic tumors according to the CT findings [14]:
The Karolinska classification system for pancreatic cancer

<table>
<thead>
<tr>
<th>Vein</th>
<th>Artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1 None</td>
<td>None</td>
</tr>
<tr>
<td>A2 SMV/PV &lt;50%</td>
<td>None</td>
</tr>
<tr>
<td>B1 SMV/PV &gt;50% and ≤2cm</td>
<td>None</td>
</tr>
<tr>
<td>B2 None or SMV/PV &lt;50%</td>
<td>and HA &lt; 50% and &lt; 2cm, right HA originating from SMA passing through the tumor mass</td>
</tr>
<tr>
<td>C SMV/PV &gt;50% and &gt;2cm</td>
<td>and/or CA or/and SMA &lt;50% and &lt;2cm</td>
</tr>
<tr>
<td>D1 An advanced arterial encasement of the superior mesenteric artery or celiac trunk length, but where anatomical circumstances offer a chance for proper arterial reconstruction after neoadjuvant treatment and resection of the native tumor margins.</td>
<td>and/or Prox. HA or CA or SMA ≥ 50% ≥ 2cm without encasement of mesenteric branching</td>
</tr>
<tr>
<td>D2 Involvement of veins or arteries in the mesenteric root (“kvasten”) as well as the aortic wall as well a situation with encasement the hepatic arteries beyond the proper hepatic artery (except when the right hepatic artery stems from the SMA) is definitely regarded as a sign of irresectablity. Total occlusion or encasement of mesenteric branching</td>
<td>and/or HA or CA or SMA ≥ 50% ≥ 2cm and encasement of mesenteric branching</td>
</tr>
</tbody>
</table>

SMV, superior mesenteric vein; PV, portal vein; HA, hepatic artery; CA, celiac artery; SMA, superior mesenteric artery

In the present study LAPC is defined as tumours presenting on preoperative imaging as Type B-D.
It should be noted, that preoperative EUS and laparoscopy with laparoscopic ultrasonography (LUS) may add significant information on local resectability (e.g. biopsy proven metastatic lymph nodes outside the planned resection area) based on CT, and that the above criteria may also be used and assessed by a combination of CT, EUS and LUS. Therefore, advanced CT 3-D reconstruction should be supplemented with these techniques when available, and laparoscopy with LUS should be performed to rule out peritoneal or liver metastases [15].

1.2 Diagnosis of malignancy
Cytological or histological verification of malignancy must be secured prior to the start of neoadjuvant therapy. EUS guided fine-needle aspiration biopsy or EUS guided trucut biopsy (i.e. SharkCore™ needle system) are the safest and easiest ways to obtain the correct diagnosis [16, 17].

1.3 Therapy of locally advanced disease (LAPC)
Patients with LAPC have a local tumor that is so widespread that the curative resection is not possible. This group represents 20-30% of all patients with pancreatic cancer. In the past, these patients were often treated as patients with metastatic disease. However, research has shown that some of these patients after treatment can achieve tumor shrinkage, which allow subsequent resection [18-25]. It is therefore important that all patients are evaluated at MDT before starting therapy, but also while treatment is ongoing. Presently, it is not established whether the optimal therapy is chemotherapy or chemo-radiation (CRT) but the sequence of combination chemotherapy followed by CRT is the most promising and most widely used.

1.4 Re-evaluation after neo-adjuvant therapy
The re-evaluation after attempted downstaging of LAPC is insufficient with the present imaging technology [26, 27]. One of the major problems is the differentiation between infiltration caused by inflammation and cancer. This probably means that all patients with response or even stable disease over a longer period should undergo laparotomy with resection if possible. The only way to get more information on the relationship between re-evaluation imaging after attempted downstaging and final histology (or laparotomy) is to compare these findings in patients participating in studies with a strict LAPC diagnosis, treatment and pathology evaluation protocol.
2 STUDY RATIONALE

Aim of the study

To evaluate the effect of pre-operative treatment in patients with LAPC

2.1 Primary endpoint

2 year survival for all patients starting chemotherapy

2.2 Secondary endpoints

Quality of Life (EORTC QLQ-PAN26)

PFS, OS, Response rate (RECIST v1.1)

Histological tumor regression (TRG)

Adverse events grade 2-5 (NCI-CTCAE 4.0)

Surgical complications, including IRE (Clavien)

Number of patients with progression during chemotherapy

Number of patients with R0 resection

Evaluation of biomarkers

3 STUDY DESIGN

This is an open multicentre phase II trial.

4 STUDY POPULATION

Inclusion and exclusion criteria

- LAPC (Karolinska Type B, C or D).
- Cytologically or histologically verified adenocarcinoma/carcinoma
- The patient is operable (i.e. no co-morbidity which can preclude anaesthesia or surgery).
- No sign of M1 disease.
- WHO performance status 0-1.
- Age ≥ 18 years.
- Adequate hematological, renal, and hepatic function: WBC > 3.0 \(\times\) 10\(^9\)/l, platelets > 100 \(\times\) 10\(^9\)/l, creatinine <1.5 \(\times\) UNL (Upper normal limit), bilirubin <3.0 \(\times\) UNL, PP % 0.5 – 1.3, APTT < 1.5 \(\times\) UNL
• Patients with obstruction of bile duct or gut must be drained before start of therapy.
• Oral and written informed consent must be obtained prior to registration with planned date of first treatment within 14 days from registration.
• No prior radiotherapy to abdominal cavity.
• No pregnancy or breast-feeding. Fertile patients must use adequate contraceptives.
• No sign of other severe uncontrolled concomitant illness (e.g. clinically significant cardiac disease or myocardial infarction within 12 months).
• No prior chemotherapy for PC.
• No prior chemotherapy or other oncologic therapy within 12 months.
• No contraindications towards FOLFIRINOX.

5 NUMBER OF PATIENTS & STATISTICS
To ensure 66 evaluable patients we will include a total of 75 patients.

5.1 Definition of populations to be analysed
Intention-to-treat-population: consist of all eligible patients who received at least one course of chemotherapy.
Eligible population: Consist of the patients who do not have major deviations from inclusion and exclusion criteria.

5.2 Statistical methods
Non-parametric statistical methods will be used.
PFS and OS will be analysed in the intention-to-treat population and will be estimated using Kaplan-Meier’s.

6 STUDY PROCEDURES
Summary of study procedures in Table 1.

6.1 Pre-treatment work-up
The investigator will perform clinical and laboratory assessments to confirm that the subject meets all entry criteria. This must include documentation in the subject’s medical record of the following:

Before inclusion
Inclusion criteria
CT scan (and EUS/LUS where available) within 4 weeks before registration
Informed consent
Within 2 week before inclusion
Medical history (with registration of symptoms) and physical examination.
Body surface area
Performance status
Blood tests:
Haematology: hemoglobin (Hb), absolute neutrophil count (ANC), platelet count (Pl).
Liver chemistry: bilirubin, ALAT, LDH, alkaline phosphatase
Renal chemistry: creatinine, albumin.
Other blood tests: CRP, CA 19.9, AFP, CEA, PP %, APTT.
Serum tumour markers (appendix 1).

If the subject’s characteristics comply with all the clinical and laboratory criteria necessary for registration, the local investigator or sub-investigator should send registration form to the Clinical Research Unit, OUH, which then return confirmation of study entry including the patient’s registration number.

6.2 Evaluation during neoadjuvant therapy
After first course of chemotherapy
• Nadir hematology
Before each course of chemotherapy (before day 1 in each cycle)
• Platelet count, absolute neutrophil count and other blood tests according to clinical practice in treating department
• Serum creatinine
After each course of chemotherapy
• Toxicity
After 4 cycles of FOLFIRINOX
• CT scan (may be supplemented by other investigations according to local preferences)
• New referral to local MDT and decision on treatment strategy (surgery, continue FOLFIRINOX, SBRT/RCT, IRE).
6.3 Evaluation before surgery

- 2-4 weeks after last course of chemotherapy the patient will be re-evaluated and the local MDT will determine if surgery is considered possible based on response imaging (CT, EUS and LUS where available)

6.4 Evaluation after surgery

- Status of resection (R0, R1 or R2) and pathological report will be evaluated at the local MDT and further adjuvant therapy will be discussed (further adjuvant monotherapy for 3 months is recommended in most cases).
- Patients will be followed with CT scan every 6 months for 2 years.

Table 1: Study procedures

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Before each chemo</th>
<th>Every 2 months</th>
<th>Weekly during CRT</th>
<th>After surgery</th>
<th>Follow up every 6 months for 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
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</tr>
<tr>
<td>Physical examination, BSA</td>
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<td>X</td>
<td>X</td>
<td></td>
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<td>Haematology</td>
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<td>X</td>
<td></td>
<td></td>
<td>X³</td>
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</tr>
<tr>
<td>Creatinine</td>
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<td></td>
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<td></td>
<td>X¹</td>
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</tr>
<tr>
<td>Other blood tests</td>
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<td>CT scan.</td>
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<td>X¹</td>
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<td>PS, symptoms and toxicity</td>
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<tr>
<td>Blood samples for biomarkers</td>
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<td></td>
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<td>X until PD</td>
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<tr>
<td>Measured GFR</td>
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<td></td>
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<tr>
<td>Pathology report</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

1: Within 2 weeks before inclusion
2: Within 4 weeks before inclusion
3: Nadir haematology after first cycle
4: MDT: With as decision to recommend surgery, SBRT/RCT, IRE, continue FOLFIRINOX, or stop further therapy.
5: MDT: Discuss pathology report and adjuvant therapy (often for 3 months)
6: CT scan every 6 months
7: Blood test at the discretion of the threatening physician

Haematology: Hemoglobin (Hb), absolute neutrophil count (ANC), platelet count (Pl).
Other blood tests: Creatinine, albumin, bilirubin, ALAT, LDH, alkaline phosphatase, ALAT, LDH, CRP, CA 19.9.

7 THERAPY

7.1 Chemotherapy

Standard FOLFIRINOX will be administered every 2 weeks with CT evaluation every 4 cycle with the following start doses:

- Oxaliplatin - 85 mg/m$^2$ iv day 1 as 30-120 min infusion
- Irinotecan - 180 mg/m$^2$ iv day 1 as 30-120 min infusion
- Folinic acid - 400 mg/m$^2$ iv day 1 as 120 min infusion
- 5-Fluorouracil - 400 mg/m$^2$ iv bolus day 1
- 5-Fluorouracil - 2400 mg/m$^2$ iv as continuous infusion over 46 hours

In the original FOLFIRINOX oxaliplatin is administered as a 120 min infusion, followed by leucovorin as a 120 min infusion and irinotecan is administered as a 90 min infusion with leucovorin (last 90 min of leucorin infusion). The infusion time of oxaliplatin and irinotecan may be reduced (until 30 min infusion) according to local guidelines.

The following is an example of a FOLFIRINOX schedule:

<table>
<thead>
<tr>
<th>Oxaliplatin 85 mg/m$^2$</th>
<th>Leucovorin 400 mg/m$^2$</th>
<th>5-FU 400 mg/m$^2$</th>
<th>5-FU 2,400 mg/m$^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 min</td>
<td>120 min</td>
<td>10 min</td>
<td>46 timer</td>
</tr>
</tbody>
</table>

**Irinotecan 180 mg/m$^2$ 90 min**

7.2 Radiotherapy

The protocol allows the site-investigator to choose between Stereotactic Body Radio Therapy (SBRT) and concomitant chemo-radiotherapy (CRT), based on patient and tumor characteristics. A delay between combination systemic chemotherapy and radiotherapy of at least 2 weeks is mandatory.

**Stereotactic Body Radiotherapy**

Target Dose: Patients should be treated with 6 daily (week-days) fractions of 7.5 Gy to a total dose of 45 Gy within a total of 14 days. Fractions can be divided between weeks, with a min-
imum of 3 fractions given the first week. SBRT should only be performed if the internal movement can be reduced to zero, using fiducials etc.

**Concomitant chemo-radiotherapy**
Target dose: Patients will receive 28 daily fractions of 1.8 Gy up to a total dose of 50.4 Gy. The treatment is given in combination with chemotherapy (capecitabine) on all days with radiotherapy. Capecitabine will be given at a dose of 1500 mg/m² BID.

**Radiotherapy planning**
Radiotherapy will be delivered on a linear accelerator in the supine position. IMRT or V-MAT technique is allowed. All beams are treated on a daily basis. The dose distribution and calculation should be performed on CT scans specified according to the ICRU 50 guidelines. Placement of fiducial markers and the use of individual 4D-CT scans to modify planning target volumes are allowed per local standards.

**Target Volume**
Tumor bed with a margin plus regional lymph nodes is used (Figure 1). The vessels that are involved leading to non-resectability should be included in the GTV at the level of the tumor.

**Target delineation**

**Gross Tumor Volume (GTV)**
The tumor volume is delineated using local procedures. Planning MRI or PET/CT are allowed per local routine.

**Clinical Target Volume (CTV)**
This volume will vary according to choice of SBRT or chemo-radiotherapy.

**Chemo-radiotherapy CTV**
This volume contains an area with potential microscopic spread. The volume is generated by adding 1.5 cm to the GTV. The volume should include/be expanded to lymph nodes with increased risk of regional spread (Figure 1): Para-aortic retroperitoneal lymph nodes between the celiac trunk and the superior mesenteric artery with a margin of 1 cm in all direc-
tions. However, the volume should be retracted from the lateral duodenal wall, the gastric wall, inferior v. cava and bone.

**Figure 1.** Lymph node stations with increased risk of regional spread.

---

**SBRT**

No CTV is used. The vessels that are the reasons for non-resectability are included in the GTV.

**PTV margins**

This margin is chosen per institution, and can be modified by placing fiducials, utilizing cone-beam CT scans etc.

**Organs at risk**

The organs at risk are listed below. They should all be drawn on the simulation scan so that a 3D dosimetric study can be performed with the Dose Volume Histogram (DVH), to confirm that maximum-tolerated doses are not exceeded. The maximum-tolerated doses are the following:

<table>
<thead>
<tr>
<th>Organ</th>
<th>SBRT</th>
<th>Chemo-radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>(Vtot-V21Gy) &gt; 700 cm³</td>
<td>D30% &lt; 30 Gy</td>
</tr>
</tbody>
</table>
| Kidney                    | V15Gy < 35%                 | 2 kidneys:
|                           |                             | Vone kidney < 20 Gy         |
|                           |                             | 1 kidney:
|                           |                             | 2/3 outside radiation field|
| Spinal Cord               | D1 cm³ < 18Gy               | Dmax = 45 Gy                |
| Small Bowles (-PTV)       | D3 cm³ < 36Gy               | V195 cm³ < 45 Gy            |
| Duodenum (-PTV)           | D1 cm³ < 36Gy               | As low as possible          |
| Duodenum (incl. PTV)      | D1 cm³ < 45Gy               | D½ cm³ < 50.4 Gy            |

A bilateral renal isotopic scintigraphy is recommended to evaluate function in each kidney separately.

**Radiotherapy toxicity**
In general, patients have more or less marked asthenia during radiotherapy. Radiation of one part of the stomach and of the celiac region can result in the following symptoms: nausea, loss of appetite, weight loss, and stress ulcers. A preventive anti-emetic treatment 1 hour before each radiation session is recommended. Radiation of one part of the large intestine can cause an increase in the frequency of bowel movements. To diagnose and manage side effects, patients will be monitored once a week throughout radiation therapy. During this weekly consultation, a clinical examination will be performed including the patient’s weight, performance status and consumption of analgesics as well as any new symptoms or side effects. Moreover, the patients will undergo a blood count, creatinine level and liver tests (ALT, alkaline phosphatases (AP), bilirubin) to evaluate hematological and liver tolerance to treatment. All clinical or biological side effects will be graded according to the Common Terminology Criteria for Adverse Events v4.1 (CTCAE). If necessary, anti-emetic or anti-diarrhoea treatment can be prescribed to treat symptoms. The systematic prescription of anti-gastric secretion medicine (PPI) is highly recommended during radiation as well as at least six months afterwards to reduce gastric acid secretion and prevent the risk of upper gastrointestinal ulcer.

7.3 Summary of treatment strategy in LAPC-03

All patients with LAPC are staged (MDT-1) and registered as LAPC Type B through D. After 4 (and 8 and 12) cycles of FOLFIRINOX patients are re-evaluated (MDT-2 and MDT-3) and subsequent treatment strategy is decided at the local MDT (Resection, SBRT, CRT, IRE or continue FOLFIRINOX)(Figure 2). If no SBRT, CRT or IRE is planned then the patient should be surgically explored after a maximum of 8 cycles of FOLFIRINOX.

4-8 weeks after SBRT or CRT or IRE resectability are re-evaluated by the local MDT.

Figure 2. Treatment strategy
NOTE: If no SBRT, CRT or IRE is planned then the patient should be surgically explored after a maximum of 8 cycles of FOLFIRINOX.

8 DOSE ADJUSTMENTS

Hematological toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>Current cycle, day 1</th>
<th>Any time during cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia 2-3</td>
<td>ANC ≥ 0.5 x 10⁹/l</td>
<td>Delay treatment until toxicity has resolved to grade 0-1. No dose modification</td>
</tr>
<tr>
<td>Neutropenia 4 or Febrile neutropenia</td>
<td>ANC &lt; 0.5 x 10⁹/l</td>
<td>Delay treatment until toxicity has resolved to grade 0-1 (ANC ≥ 1.5 x 10⁹/l) Delay treatment until toxicity has resolved to grade 0-1. Administer prophylactic G-CSF in subsequent cycles. Reduce to 80% if G4 despite G-CSF</td>
</tr>
<tr>
<td>Thrombopenia 2-3</td>
<td>T ≥ 25 x 10⁹/l</td>
<td>Delay treatment until toxicity has resolved (T ≥ 100 x 10⁹/l) No dose modification</td>
</tr>
</tbody>
</table>
Thrombopenia 4  T < 25 x 10⁹/l  Delay treatment until toxicity has resolved (T ≥ 100 x 10⁹/l)  Delay treatment until toxicity has resolved to grade 0-1  Reduce to 80%

Non-hematological toxicities

<table>
<thead>
<tr>
<th>Grade</th>
<th>At day 1 of cycle</th>
<th>At any time during previous cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity grade 2 (excluding nausea, emesis, alopecia)</td>
<td>Delay treatment until toxicity has resolved.</td>
<td>No dose modification.</td>
</tr>
<tr>
<td>Toxicity grade 3-4 (excluding nausea III)</td>
<td>Delay treatment until toxicity has resolved, and then continue treatment at 80% of prior dose</td>
<td>Delay treatment until toxicity has resolved, and then continue treatment at 80% of previous dose</td>
</tr>
</tbody>
</table>

Dose modifications for abnormal liver enzyme results (bilirubin, alkaline phosphatase, ASAT, ALAT) are left to the discretion of the individual investigator.

9 ADVERSE EVENTS

Definitions

9.1 Adverse events (or adverse experience)(AE)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance - reporting of (S)AEs - commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the End of Study Visit has been performed. Therefore events occurring in the period between the signed informed consent and beginning of the study drug administration are to be designated as AEs. This procedure complies with requirements by some authorities.
9.2 **Serious adverse event or reaction/experience (SAE):**

A serious AE (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is an important medical event

In addition laboratory value changes may require reporting unless otherwise specified in the protocol.

End organ toxicity as a medically significant event or clinically laboratory change, in which a patient not necessarily may be hospitalised or disabled, but is found clinically significant to demand further monitoring.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignant tumors when they are histologically different from the primary tumor.

9.3 **Events not to be treated as SAEs**

Progression of disease is not to be regarded as a SAE. Due to the seriousness of the disease in this study, certain conditions defined, as SAEs will be excluded from expedited reporting on a SAE report form: Elective hospitalization and surgery for treatment of disease.
The following will not be considered serious for this study:
An event that results in hospitalization or prolongs an existing hospitalization if the only reason for the hospitalization or prolongation is for the following:

- Hospitalization is secondary to expected chemotherapy morbidity e.g.
  - Myelosuppression
  - Fever
  - Nausea and vomiting.
- Hospitalization is secondary to expected cancer morbidity e.g.
  - Weight loss
  - Fatigue
  - Electrolyte disturbances
  - Pain management
  - Anxiety
  - DVT or pulmonary embolism
  - Admission for palliative care
  - Admission of chemotherapy
  - Transfusion of blood product
  - Administration of study procedure
  - Placement of permanent intravenous catheter
  - Hospice placement for terminal care

These events will be recorded on the data collection form. Any patient’s death must be recorded on the data collection form.

### 9.4 Recording of Adverse Events
All AEs must be documented in the appropriate section of the CRF.

The following aspects must be recorded for each event in the CRF:

- A description of the AE in medical terms, not as reported by the subject
- The date of onset (start date)
- The date of recovery (stop date)

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination.
All AE’s occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization or until it has been determined that study treatment or participation is not the cause. SAE’s which are still on-going at the end of the study period must be followed up to determine the final outcome.

Any SAE, which occurs after the study period and is considered to be possibly related to study treatment or study participation should be recorded and reported immediately.

The grade as assessed by the investigator according to the definitions in NCI-CTC, version 4.0: grade 1 – 4:

- Grade 1 = mild
- Grade 2 = moderate
- Grade 3 = severe
- Grade 4 = life-threatening or disabling
- Grade 5 = death related to AE (only for NCI-CTC version 3.0)

The causal relationship to chemotherapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and chemotherapy. The following judgments of the causality to chemotherapy or study procedures are to be used:

Not Related: There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

Not Likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE.

Possible: There is a reasonable causal relationship between the study drug and the AE. Dechallenge information (information referring to withdrawal of drug) is lacking or unclear.

Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge (withdrawal of study drug). Rechallenge is not required.

Certain/Definite: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge and recurs with rechallenge, when clinically feasible.
9.5 Reporting of SAE and SUSAR

In the case of a Serious Adverse Event the investigator must immediately (within 1 working day) SEND (preferably by fax or by e-mail) SAE-CRF to sponsor at OUH.

Any deadly or life-threatening SAE that is both unexpected and suspected to be related to treatment (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC and as per national regulatory requirements in participating countries (i.e. as soon as possible, and in no case later than seven days after knowledge by the investigator of such an event, and relevant follow-up information is subsequently communicated within 15 days total).

Unexpected means that the AE is not described in paragraph 4.8 of each SPC.

The principal investigator at each site is responsible for SUSAR reporting as described above, and also for informing the international coordinating investigator (by delegation of the sponsor), as well as informing the sponsor.

Any SUSAR grade 3 or less will be reported to the regulatory authorities and relevant ethics committee within 15 days of the event having been brought to the attention of the investigator. Additional relevant information regarding the event will be sent to the authorities as soon as possible.

Death on Study

Any death occurring between the study inclusion and 30 days following the last dose will be reported to the Regulatory Authorities and ethics committees according to local rules. Death occurring during the study follow-up period (i.e. later than 30 days after the last dose) need only to be reported as serious adverse event if it is thought that there is a possible relation to study drug(s) (possible, probable). All deaths should be reported on the death report form section on the CRF regardless of cause.

9.6 Follow-up

Patients withdrawn from the study treatment due to any AE will be followed at least until the outcome is determined even if it implies that the follow-up continues after the patient has left the trial, and where appropriate until the end of the planned period of follow-up.
9.7 Safety instructions specific to the trial

Adverse events will be recorded for all Patients (including those withdrawing from the study treatment because of toxicity) for 28 days following the last dose of study drug. Adverse events related to study drug(s) that are observed, either during study treatment, or prior to the twenty-eighth day following the last dose of study drug(s), will be followed until resolution or stabilization.

10 STATISTICS

The primary efficacy variable is percentage of patients alive at 2 years calculated from the day of registration.

Secondary objectives are to determine:
- Quality of Life (EORTC QLQ-PAN26)
- Number of patients with progression during chemotherapy
- OS (deaths of all causes)
- PFS
- Overall RR (investigator evaluated) according to the RECIST criteria version 1.1 in patients with measurable disease.
- Number of patients with R0 resection
- Safety and toxicity of the treatment, including surgical complications
- Histological tumor regression (TRG)
- The relations between treatment effect and potentially predictive and prognostic tumour biomarkers.

Efficacy analysis

OS and DFS will be calculated from the date of registration to the date of documented progressive disease, according to the RECIST criteria, or death.

The sample size is based on Simon’s two stages Mini-max design. This design ensures early study termination if there is insufficient effect.

A resection rate less than 10% after 4 months of preoperative chemotherapy is not clinically acceptable. Assuming a significance level at 0.05 (α = 0.05) and a power at 90% (β = 0.10) it can be calculated, that 21 patients should be included in the first part of the study. The enrolment will continue until 21 patients have completed 4 months of chemotherapy and have been re-evaluated for resection by CT scan (and EUS+LUS, if available). If 2 or less out of the
first 21 consecutive patients are being resected we will reject our hypotheses and close the study after the first stage of accrual. If 3 or more patients are resected, an additional 45 patients will be accrued in the second stage. If at least 11 out of 66 patients are resected, a true resection rate of 25% cannot be excluded, and we will conclude that the treatment is effective enough to continue with future studies.

To ensure 66 evaluable patients we will include a total of 75 patients.

We will use non-parametric methods for calculation of patient characteristics, side effects and disease control. DFS (and PFS) and OS will be calculated and reported as median survival (Kaplan-Meier method).

11 SURGERY

11.1 Selecting patients for surgery

After having established a malignant diagnosis, and following the pre-treatment evaluation and subsequent MDT, patients are allocated to one of the resectability groups B through D. After 4 (and 8 and 12) cycles of FOLFIRINOX patients are re-evaluated (MDT-2 and MDT-3) and subsequent treatment strategy is decided at the local MDT (Resection, SBRT, CRT, IRE or continue FOLFIRINOX)(Figure 2). If no SBRT, CRT or IRE is planned then the patient should be surgically explored after a maximum of 8 cycles of FOLFIRINOX.

4-8 weeks after SBRT or CRT or IRE resectability are re-evaluated by the local MDT. Patients responding to SBRT/CRT/IRE according to detailed re-evaluation should be referred for surgery. Synchronous laparoscopy with LUS may be used to avoid laparotomy in non-detected progression (e.g. carcinosis or liver metastases).

11.2 Surgical procedure

The details of the surgical procedures may vary between institutions, but the overall goal of R0 resection should be pursued regardless of the surgical approach. Intraoperative measurement of vessel infiltration should be documented (photo with ruler), and type of vessel reconstruction noted (None/longitudinal/transverse venorrhaphy/segmental resection/patch graft/interposition graft). Sampling of lymph nodes should be performed systematically (i.e. according to local protocols), and the total operating time and bleeding (ml)/transfusion (units) is recorded. The pancreatic anastomosis (when relevant) is classified according to the International Study Group of Pancreatic Surgery (ISGPS).
11.3 Irreversible Electroporation (IRE)

Patients, who are assessed as definitely non-resectable at the time of the diagnosis, at any time during the downstaging attempts or during laparotomy may be referred for IRE. IRE can be done intraoperatively or by percutaneous route.

11.4 Postoperative care and registration of complications

Postoperative care, including the decision to use additional anticoagulation treatment in case of vessel reconstruction, should follow local preferences. Postoperative morbidity is registered and classified according to Clavien together with 30 days and 90 days (in hospital) mortality. Postoperative haemorrhage, delayed gastric emptying (DGE) and pancreas fistulas (PFs) are classified and noted according to ISGPs.

12 ASSESSMENT OF THE RESECTED SPECIMEN

The surgical pancreas specimens in this study should be examined by a standardized protocol as suggested by Caroline Verbeke in 2006 [28]. In short, this protocol involves multicolour margin staining, axial slicing, extensive tissue sampling showing the relation of the tumour to the different margins (at least 10 blocks (or 1 whole-mount block and 5 additional blocks)), and measurement of the distance from the tumour to all relevant margins in mm. Various histological grading schemes have been used for the assessment of tumour regression after NAT in PC. The most widely used system was published by Evans et al. in 1992 [29]. However, more recently, systems focusing on the ratio between residual tumour cells and stroma have been proposed, amongst others by the College of American Pathologists (CAP) [30]. Chatterjee found that the CAP scheme could be simplified without losing prognostic information [31]. Hence, in this study, the modified CAP scheme, as proposed by Chatterjee, will be used in those patients who undergo pancreatic surgery after pre-operative therapy [32].

In short, the modified CAP system distinguishes 3 grades of tumour regression: Grade 0, no residual carcinoma; Grade 1, patients with minimal residual carcinoma (single cells or small groups of cancer cells, <5% residual carcinoma); and Grade 2, patients with 5% or more residual carcinoma. This system should overcome most of the difficulties in distinguishing the NAT-related regressive fibrosis from the typical desmoplastic fibrosis in PC, the latter of which is not related to NAT. To exclude inter-observer bias, the archival hematoxylin and
eosin slides from all cases should be uniformly reviewed by 1 pathologist (i.e., Sönke Detlefsen, Dept. of Pathology, Odense University Hospital, Denmark).

13 ETHICS

The study will be conducted in compliance with the protocol and in accordance with the ethical principles put forward in the second Declaration of Helsinki and in accordance with GCP rules. The rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society. Study personnel involved in conducting this trial will be qualified by education, training and experience to perform their respective tasks.

In this study we will treat patients with resectable disease with pre-operative chemotherapy. Preoperative chemotherapy has so far only been sparsely studied in patients with BTC. Previous studies have shown a very low risk of progression during 3 months of chemotherapy. Even though the tumor burden is much lower in patients who are candidates for neoadjuvant therapy, there is a still risk of 10 - 20% that the disease will progress during pre-operative chemotherapy and in some patients (around 10%) the disease may become non-resectable. However, it is expected that neoadjuvant therapy will increase the chance of cure and that this benefit will outweigh a possible harm.

The primary objective of this study is to investigate the effect of chemotherapy

Informed consent

Before inclusion in study the patients will be informed about the planned aim of the study and risk of possible adverse events. Every patient shall give informed consent after having been informed about the clinical investigation. This will be documented by the dated signature of the patient. Information will further be supplied from the ministry of Science and the Ethical Committee: “Your rights as a study person in a biomedical investigation.”

Information of the Patient

Participation in the investigation is voluntary. If the patient denies participation this will not have any consequences or lack of opportunities for any other treatment of the patient. If the patient denies participation in the study this will not in any way, result in consequences or the lack of opportunities for any other possible treatment option.
Rights and responsibilities
At any time the patient have the right to withdraw from the investigation without this will have any influence on further treatment.
The patient must be aware that personal information will be examined closely under audit of relevant authorized personal, but that this personal information will be handled strictly confidential and will not be published in a medical periodical. In this case the patient is guaranteed to remain anonymous.
Data that may identify the patient will be found in the hospital records. Material from the patient will only include what is mentioned in the section on biomarkers.

14 TIME SCHEDULE
The trial is expected to start Q1 2017 after approval of the protocol has been granted from the Ethics Committee and the Danish Health and Medicines Authority, respectively. Target recruitment period is estimated to be 12 months and follow-up period/end date is estimated to be one year from last infusion.

15 PUBLICATIONS
The Vancouver declaration should be followed in all publications based on this study and we plan that the study will be published in international peer-reviewed journals. The manuscript will be prepared by the Sponsor-Investigator who will also decide who will be the first author. Co-authors are an oncologist and a surgeon from those centres that have included at least 10% of the patients. The protocol committee writes the first and final version. In publication of tumour biological sub-studies the researchers are the main authors and co-authors are the protocol committee and representatives from each centre participating in the tumour biological collection including at least 10% of the patients.

16 ECONOMY
This study is initiated and conducted by doctors in Denmark and Sweden. There is no economic benefit for neither the participating departments nor the hospital employees.
REFERENCES


APPENDIX 1 LAPC-03: TUMOUR MARKERS

Purpose
Blood sampling for bio-banking will be performed during the trial. These samples will later be analysed for potential prognostic and/or predictive markers for the disease or treatment. Serum, plasma and blood cells will be collected.

Procedure for blood-sampling:
Blood is drawn from a peripheral vein and divided into
a) 10 ml blood for serum
b) 10 ml blood for EDTA-plasma
c) 10 ml blood for Na-citrate
All samples should be processed and stored within 2 hours of collection.

PLASMA and CELLULAR MATERIAL COLLECTION: EDTA
NOTE: Processing of all EDTA plasma tubes can be combined.
1. Manually and gently invert EDTA blood tube 5 times
2. Centrifuge EDTA tubes. Speed 2000 g, 10 mins, Temperature: 4ºC
3. Using a sterile transfer pipette, carefully aspirate plasma from tube and combine in 5 tubes (Sarstedt vials).
4. Store
5. Record processing details on Sample Processing Information Sheet

Cellular material (EDTA):
1. Add steril water to the cell material in a dilution 1:1.
2. Manually and gently invert the tube for one minute.
Using a sterile transfer pipette, carefully aspirate plasma from tube and combine in 5 tubes (Sarstedt DNase free vials).

PLASMA COLLECTION: Na Citrate
Procedure
1. Manually and gently invert Na Citrate blood tubes 5 times
2. Centrifuge Na Citrate tubes. Speed 2000 g, 10 mins, Temperature: 4ºC
3. Aliquot plasma into 5 Sarstedt vials
4. Record processing details on Sample Processing Information sheet
SERUM COLLECTION

Procedure
1. Invert Serum tube and allow to clot at room temperature for a minimum of 30 minutes
2. Centrifuge 2000g, Spin: 10 minutes. Temperature: 4ºC
3. Aliquot serum into 5 Sarstadt vials
4. Store
5. Record processing details on Sample Processing Information Sheet

Record procedure
The vials are labeled with the patient number, date and code for timing. It should be clearly marked what container is in question, EDTA Serum etc. By text and color.

Blood sampling frequency
Patients will be asked to donate blood for biobanking
1) Before initiation of chemotherapy
2) Before surgery
3) At the end of chemotherapy
Should the patient refuse to donate blood to the biobank he/she can still participate in the study.

Initial analysis
Blood samples can only be used after the approval of the protocol committee. Initial analysis include YKL-40 and TIMP-1. Other analysis will not be performed before accept from the local ethical committee is obtained.