Subject information for participation in medical scientific research

Preoperative treatment with FOLFIRINOX or chemoradiotherapy and adjuvant chemotherapy for (borderline) resectable pancreatic cancer.

Official title: De (kosten)effectiviteit van neoadjuvante FOLFIRINOX versus neoadjuvante chemoradiotherapie met gemcitabine en adjuvante gemcitabine voor patiënten met (borderline) resectabel pancreaskanker (PREOPANC-2 trial).

Introduction

Dear Sir/Madam,

You are asked to take part in a medical-scientific study. Participation is voluntary. Participation requires your written consent.

You have received this letter because you have pancreatic cancer, without evidence of metastatic disease and with a tumour for which a resection seems possible. Before you decide whether you want to participate in this study, you will be given an explanation about what the study involves. Please read this information carefully and ask the investigator for an explanation if you have any questions. You can also ask the independent expert, who is mentioned at the end of this document in **Appendix A**, for additional information. You may also discuss it with your partner, friends or family. Additional information about participating in a study can be found in the enclosed general brochure on medical research, **Appendix E**.

1. General information

This study has been designed by the Erasmus M.C. University Medical Center and the Dutch Pancreatic Cancer Group (a national multidisciplinary collaboration; more information on www.dpcg.nl) and is being carried out by doctors and investigators in all hospitals that perform surgery for pancreatic cancer. For this study, 368 study subjects from different hospitals are required.

The Medical Research Ethics Committee of the Erasmus MC has approved this study. General information about the assessment of research can be found in the general brochure on medical research.

2. Purpose of the study

The purpose of this study is to investigate whether neoadjuvant treatment with a combination chemotherapy (FOLFIRINOX) prior to an operation improves survival and the quality of life compared to neoadjuvant treatment with gemcitabine chemotherapy combined with

radiotherapy (chemoradiotherapy) prior to the operation followed by gemcitabine chemotherapy after the operation.

3. Background of the study

Upfront surgery followed by adjuvant chemotherapy is the current standard of care for patients with resectable pancreatic cancer. However, a recently completed study (PREOPANC-1 study) conducted in the Netherlands showed that treatment with a combination of chemotherapy and radiotherapy (chemoradiotherapy) before surgery resulted in less frequent and later recurrence of disease compared to patients who underwent surgery without any preoperative treatment. Furthermore, it was possible to completely remove the local tumor in a higher percentage of patients who received preoperative treatment compared to patients who did not receive preoperative treatment. Other studies have also demonstrated that receiving preoperative treatment improves the outcomes compared to upfront surgery. To date, it is not yet proven which chemotherapy regimen provides best outcomes, and whether the addition of radiotherapy following chemotherapy is beneficial. We know that patients with metastases from pancreatic cancer (who therefore cannot undergo surgery) live 6 months longer on average when they are treated with a combination chemotherapy (FOLFIRINOX) containing 4 agents: folinic acid, fluorouracil, irinotecan and oxaliplatin. Moreover, the quality of life also increases in many patients after treatment with FOLFIRINOX. Although these results are derived from research in patients with metastatic disease, it is expected that this also accounts for patients without evidence of metastases. This is because preoperative treatment with FOLFIRINOX aims to prevent metastases, which may lead to a longer survival and better quality of life. When administered preoperatively, the chance of receiving all chemotherapy cycles is higher compared to patients in which chemotherapy is given after the surgery, because some patients do not recover in time for chemotherapy after surgery. In other patients, the cancer is so aggressive that preoperative treatment does not prevent the tumour from progressing. In these patients, it is possible that the local tumour increases in size or that previously undetectable micrometastases grow and become visible on imaging. These patients will not undergo surgery because this is a high risk intervention and it will not improve survival outcomes. This applies both to patients receiving preoperative chemoradiotherapy and FOLFIRINOX.

4. What participation involves

Your participation will last a maximum of 44 weeks, followed by a standard follow-up during 5 years. Half of the participants will receive preoperative chemotherapy treatment with FOLFIRINOX during 16 weeks, followed by surgery. No additional chemotherapy will be given after surgery. The other half of the participants will receive preoperative chemotherapy treatment with gemcitabine during 10 weeks, whereof 3 weeks will be combined with radiotherapy. The preoperative treatment will be followed by surgery and 16 weeks of additional gemcitabine chemotherapy treatment if the tumour has been resected. Patients who do not recover sufficiently within 3 months after surgery will not undergo additional chemotherapy treatment.

Treatment will be allocated by randomisation. Your treating physician and the investigators have no influence on the treatment allocation. If you prefer not to participate in this study, you will receive the standard treatment in your hospital. Your treating physician can give you more information on this standard treatment.

Screening

We will first evaluate whether you may participate. The investigator will evaluate the results from the CT-scans, endoscopic ultrasound and pathology specimen, and will assess whether you are eligible for the study. A blood test will be performed. Before chemotherapy can be safely given, it is important that the bile drains well and you do not have jaundice anymore. In case of jaundice, a small stent will be placed during an endoscopic intervention in order to improve biliary drainage. You will be asked to fill in a questionnaire about your quality of life, and the investigators will perform a physical examination, measure your length, weight, and health status. Furthermore, the investigators will ask about your medical history, medication use, ethnic origin, and alcohol and smoking habits. These factors are important for future studies on pancreatic cancer and may in the future be of predictive value for the diagnosis and treatment of pancreatic cancer.

Treatment

Preoperative treatment with FOLFIRINOX (arm 1)

If you decide to participate with the study and u are randomised for arm 1, you will receive FOLFIRINOX chemotherapy prior to surgery. The preoperative treatment consists of 8 cycles of FOLFIRINOX, which takes 16 weeks in total. The cycles are given every two weeks. One of the agents is administered continuously by intravenous (IV) therapy during 48 hours, and the other agents are administered by IV therapy on the first day of the cycle. Following the fourth (after 8 weeks) and eighth (after 16 weeks) cycle , a CT-scan of the chest and abdomen will be made to evaluate the treatment response. In case the tumour has decreased in size or remained stable during treatment without the emergence of metastatic disease, you may continue to undergo a surgical resection. The surgery will take place within 6 weeks after completion of the last chemotherapy cycle. The total study duration for patients that receive FOLFIRINOX will therefore be 26 weeks. In case of side effects, your doctor may decide to adjust the dosages or postpone the treatment. In that case, the total study duration can be somewhat longer than 26 weeks.

Every two weeks, prior to the start of a new cycle, you will be examined by your treating clinician. Blood tests will be performed on a regular basis during the period in which you will receive chemo(radio)therapy and also following the surgery. In the first two years from the start of your participation, a CT-scan will be performed to evaluate whether a recurrence has occurred. After this period, a CT-scan will be performed once every year until 5 years of follow-up or until progression or recurrence of the tumour has occurred.

Visits and tests

Appendix C gives a schematic overview of the two treatment arms, including an overview of the measurements that will take place at each of the visits.

Preoperative FOLFIRINOX treatment (arm 1)

This study requires that you will visit the hospital 13 times over a period of approximately 26 weeks. A visit for one of the cycles in this arm will take 48 hours. It may be necessary to stay at the hospital for the night. This will be decided with your treating clinician. A follow-up visit will take approximately 30 minutes.

The following will take place:

- We will do a physical examination – at 11 visits.
- A CT- or MRI-scan will be performed – at 3 visits during the treatment phase and at a maximum of 7 visits during the follow-up period.
- We will draw blood – at 12 visits, two tubes each time for routine blood tests.
- We will draw additional blood – at 5 visits during the treatment phase and at a maximum of 5 visits in the follow-up period, five tubes each time for research focused on circulating biomarkers. Circulating biomarkers are biological markers in the blood that may predict the treatment effectiveness.
- A saliva sample will be taken – at 2 visits.
- We will ask you to complete a questionnaire about your quality of life – at 6 moments during the treatment phase and an additional 4 moments during the follow-up period. For this research, you will be contacted by phone.

Preoperative chemoradiotherapy treatment (arm 2)

This study requires that you will visit the hospital 36 times over a period of approximately 44 weeks. A visit for the chemotherapy in this arm will take half a day, a visit for the radiotherapy will take approximately 1.5 hours, and a follow-up visit will take approximately 30 minutes.

The following will take place:

- We will do a physical examination – at 10 visits.
- A CT- or MRI-scan will be performed – at 2 visits during the treatment phase and at a maximum of 7 visits during the follow-up period.
- We will draw blood – at 23 visits, two tubes each time for routine blood tests.
- We will draw additional blood – at 4 visits during the treatment phase and at a maximum of 5 visits in the follow-up period, five tubes each time for research focused on circulating biomarkers. Circulating biomarkers are biological markers in the blood that may predict the treatment effectiveness.
- We will ask you to complete a questionnaire about your quality of life – at 6 moments during the treatment phase and an additional 4 moments during the follow-up period. For this research, you will be contacted by phone.

Other than standard care

If you are randomised to the preoperative chemoradiotherapy treatment (arm 2), you will need to visit the hospital every day for 3 weeks for the radiotherapy treatment. In case of standard care, no radiotherapy treatment will be given. Following the operation, you will only receive 4 instead of 8 cycles of chemotherapy, and the type of chemotherapy is different. If you are randomised to the preoperative FOLFIRINOX treatment (arm 1), the number and type of chemotherapy cycles are exactly the same as standard care, but you will receive all chemotherapy cycles before instead of after the operation.

Compared to the standard care, additional blood will be drawn for research focused on circulating biomarkers and you will be asked to complete questionnaires in both treatment arms. The blood will be used for other research within the department of surgery of the Erasmus MC, focusing on immune monitoring in patients with pancreatic cancer (NL59131.078.16), and focusing on circulating biomarkers during chemotherapy treatment in patients with pancreatic cancer (NL65025.078.18). By combining these blood sampling moments, you only need to draw blood once per sampling moment instead of three times for these three studies. If you are randomised to the preoperative FOLFIRINOX treatment (arm 1), a saliva sample will be taken twice.

5. What is expected of you

In order to carry out the study properly and for your own safety, it is important that you follow the study instructions.

The study instructions require that you:

- keep appointments for visits.

It is important that you contact the investigator:

- before you start using other medicines. Even if they are homeopathic or natural remedies, vitamins and/or over-the-counter medicines.
- if you are admitted to hospital or are going for treatment there.
- if you suddenly develop any health problems.
- if you no longer want to participate in the study.
- if your contact details change.

Your or your partner's pregnancy

Women who are pregnant or breast-feeding cannot participate in this study. Women must not become pregnant during the study. Men should keep in mind that their partner must not become pregnant during the study. Inform your partner about this. It is because this study may have consequences for an unborn child. The consequences are not known. It is important for you to tell your partner about it. The investigator will talk to you about the most suitable contraceptives. If you still become pregnant during the study, you should immediately tell the investigator. If your partner becomes pregnant during the course of the study, please ask her for permission to inform the investigator. The pregnancy can then be monitored more

closely. Separate consent will be asked for monitoring of the pregnancy (and for collecting of information from other health providers on the clinical course and the outcome of pregnancy).

6. Possible side effects

Preoperative FOLFIRINOX (arm 1)

FOLFIRINOX may cause side effects. These side effects are common (occur in 1 out of 10 people or more):

- Nausea, vomiting, diarrhoea, abdominal pain, hair loss, tingling and numbness in your fingertips and toes (peripheral neuropathy)
- The number of white and red blood cells and thrombocytes may decrease, leading to fatigue, increased risk of infection, bruising and bleeding. Following each cycle, you will receive an injection to stimulate the production of white blood cells. This injection may cause flu-like symptoms such as sore muscles or shivering.

Preoperative chemoradiotherapy (arm 2)

Gemcitabine may cause side effects. These side effects are common (occur in 1 out of 10 people or more):

- Nausea, vomiting, abdominal pain, constipation, diarrhoea, weight loss. Hand- and foot syndrome including redness, sensitivity, shedding skin. Fatigue, weakness, sleeping problems. Headache, dizziness. Allergic skin reaction, itching, hair loss, oedema.
- Flu-like symptoms, including fever, shivering, and sore muscles, mostly present during the first two days following chemotherapy.
- The number of white and red blood cells and thrombocytes may decrease, leading to fatigue, increased risk of infection, bruising and bleeding.

Radiation therapy may also cause side effects. The most common side effect is fatigue, but gastro-intestinal problems such as nausea, loss of appetite, diarrhea and weight loss may also occur. In the long term (after several months), a gastric ulcer can occur as late complication. To prevent this, you will receive medication to prevent ulcers for 6 months. You will also receive medication in case of nausea and/or diarrhoea.

Tests

Drawing blood may be painful or cause some bruising.

Exposure to radiation

For the CT scans, X-rays are used. The total amount of radiation you will be exposed to in this study is 8.4 mSv per CT-scan. To compare: the background radiation in the Netherlands is ~2.5 mSv per year. If you participate in scientific research involving exposure to radiation more often, you should discuss with the investigator whether participation at this moment would be safe. The radiation used during the study may lead to damage to your health. However, this risk is small. We nevertheless advise you not to participate in another scientific

study involving exposure to radiation in the near future. Examinations or procedures involving radiation for medical reasons are not a problem.

7. Possible advantages and disadvantages

It is important that you properly weigh up the possible benefits and disadvantages before you decide to join. Listed below are the possible benefits and disadvantages of participating in the study in general, and for randomisation with FOLFIRINOX (arm 1) specifically.

Advantages of participating in the study compared to upfront surgery may be:

- It is expected that most patients live longer;
- It is expected that your quality of life will be better;
- In case of rapidly progressive disease with local progression or the detection of previously invisible micrometastases during the preoperative treatment, you will not undergo an operation. This is because this major surgery would not provide any survival benefit. The tumour has shown to be very aggressive, and we can therefor prevent you from undergoing futile but major surgery.

Disadvantages of participation in the study compared to upfront surgery may be:

- Possible side effects of both preoperative treatments;
- Possible discomfort of the additional hospital visits.

Advantages of participating in the study when randomised to preoperative FOLFIRINOX:

- Less hospital visits compared to preoperative chemoradiotherapy;
- The total treatment duration is shorter compared to preoperative chemoradiotherapy.

Disadvantages of participating in the study when randomised to preoperative FOLFIRINOX:

- Possible side effects may be more common compared to preoperative chemoradiotherapy;
- Possible discomfort of additional or longer hospital stays compared to preoperative chemoradiotherapy.

All these aspects have been described above under points 4, 5 and 6.

8. If you do not want to participate or you want to stop participating in the study

It is up to you to decide whether or not to participate in the study. Participation is voluntary. If you do not want to participate, you will be treated as usual for your disease. The investigator can tell you more about the various treatment options that exist and the benefits and risks associated with them.

If you do participate in the study, you can always change your mind and decide to stop, at any time during the study. You will then be treated as usual for your disease. You do not have to say why you are stopping, but you do need to tell the investigator immediately. The data collected until that time will still be used for the study.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to continue your participation.

9. End of the study

Your participation in the study stops when

- you have completed all the visits as described under point 4;
- you choose to stop;
- you become pregnant;
- the investigator considers it best for you to stop;
- the Erasmus MC, the government or Medical Research Ethics Committee, decides to stop the study.

The study is concluded once all the participants have completed the study.

After processing the data, the investigator will inform you about the most important results of the study. The investigator will also tell you about the outcome of the questionnaires.

10. Usage and storage of your data and bodily material

Your personal data and bodily material will be collected, used and stored for this study. This concerns data such as your name, address, date of birth and data about your health. Blood and saliva (if randomised to arm 1) samples are required for this study, and pancreatic tissue in case the tumour has been surgically removed. The collection, use and storage of your data and your bodily material is required to answer the questions asked in this study and to publish the results. We ask your permission for the use of your data and bodily material.

Confidentiality of your data and bodily material

To protect your privacy, your data and your bodily material will be given a code. Your name and other information that can directly identify you, will be omitted. Data can only be traced back to you with the encryption key. The encryption key remains safely stored in the local research institute. The data and bodily material that is sent to the sponsor and other investigators involved will only contain the code, not your name or other data with which you can be identified. The data cannot be traced back to you in reports and publications about the study.

Access to your data for verification

Some people can access all your data at the research location. Including the data without a code. This is necessary to check whether the study is being conducted in a good and reliable

manner. Persons who have access to your data for review are the investigational team, the committee that monitors the safety of the study, a monitor which has been hired by the investigator of the study, national and international supervisory authorities, for example, the Healthcare and Youth Inspectorate. They will keep your data confidential. We ask you to consent to this access.

Retention period of your data and bodily material

Your data must be kept for 15 years at the research location and 15 years at the sponsor. Your bodily material will be destroyed immediately after use. Your bodily material will not be destroyed immediately after use. It will be kept in order to be able to perform new assessments in connection with this study, in the course of this study.

Storage and use of data and bodily material for other research

Your data and bodily material will be used for other scientific research in the field of pancreatic cancer as described under point 4. Your data and bodily material may also be of importance for other scientific research after the finalization of this study. To this end, your data and bodily material will be stored for 15 years. You can indicate on the consent form whether or not you agree with this. If you do not agree with this, you can still participate in the current study.

Information about unexpected findings

During this study, something may be found by chance that is not important to the study, but may be important to you. If this is important for your health, you will be informed by the treating specialist. You can then discuss with your doctor or specialist what needs to be done. You also consent to this.

Withdrawing consent

You can withdraw your consent to the use of your personal data at any time. This applies to this study and also to storage and use for future research. The study data collected until the moment you withdraw your consent will still be used in the study. Your bodily material will be destroyed after your consent has been withdrawn. If measurements have already been made with that bodily material, then this data will still be used.

More information about your rights when processing data

For general information about your rights when processing your personal data, you can consult the website of the Dutch Data Protection Authority.

If you have questions about your rights, please contact the person responsible for the processing of your personal data. For this study, that is the department of surgery of the Erasmus MC. See **Appendix A** for contact details.

If you have questions or complaints about the processing of your personal data, we advise you to first contact the research location. You can also contact the Data Protection Officer of the institution (contact details in **Appendix A)** or the Dutch Data Protection Authority.

Registration of the study

Information about this study is included in a list of medical-scientific studies namely www.trialregister.nl. It does not contain any information that can be traced to you. After the study, the website may display a summary of the results of this study. You can find this study under PREOPANC-2.

11. Study subject insurance

Insurance has been taken out for everyone participating in this study. This insurance covers damage caused by the study. The insurance does not cover all damages. **Appendix B** contains more information about the insurance and the exclusions. It also tells you who to report damage to.

12. Will my GP and/or treating specialist and/or pharmacist be informed if I participate?

We will always send your GP, treating specialist, and pharmacist a letter or email to let them know that you are participating in the study. This is for your own safety. If you do not agree to this, you cannot participate in this study. You cannot participate in the study if you do not have a GP.

13. Compensation for participation

The study medication, additional tests and treatment for the study are free of charge for you. You will not be paid for your participation in this study. You will be reimbursed for your travel costs.

14. Any questions?

If you have any questions, please contact the investigators. If you would like any independent advice about participation in this study, you may contact an independent expert. He or she knows about the study but is not involved in it.

If you have any complaints about the study, you can discuss this with the investigator or your treating specialist. If you prefer not to do this, you may contact the complaints committee at your institution. All the relevant details can be found in **Appendix A**: Contact details.

15. Signing the consent form

When you have had sufficient time for reflection, you will be asked to decide on participation in this study. If you give permission, we will ask you to confirm this in writing on the appended consent form. By your written permission you indicate that you have understood the

information and consent to participation in the study. Both yourself and the investigator will receive a signed copy of the consent form.

Thank you for your attention.

16. Appendices to this information

A. Contact details
B. Insurance information
C. Overview/description of study procedures
D. Informed Consent Form(s)
E. Medical Scientific Research Brochure. General Information for Study Subjects (version 01-02-2019)

Appendix A: contact details for Erasmus MC

Principle investigator

In case you have any questions or complaints during the study, you can contact the study team during working hours.

- Dr. B. Groot Koerkamp, surgeon, email b.grootkoerkamp@eramusmc.nl
- Drs. Kiki Janssen, study coördinator, email q.janssen@erasmusmc.nl, phone number 010-7034519 / 06-50032973.
- Monica Seijbel, secretary, email m.seijbel@erasmusmc.nl phone number 010-7033854.

Independent expert

In case of doubts about participation, you can consult an independent expert, who is not involved in this study, but who is an expert in the field of this research. Also if you have any questions during the study which you would rather not discuss with the investigators, you can consult the independent expert.

- Dr. S.M. Lagarde, surgeon Erasmus MC, phone number 010-7040080.

Complaints

If you are not satisfied about the study, you can contact the complaints committee at the Erasmus MC. De complaints committee can be contacted by calling 010-7033198.

Data Protection Officer of Erasmus MC:

For more information about your rights, contact:
Secretary Legal Affairs
Phone number 010-7034986

Appendix B: Insurance Information

Insurance has been taken out by the Erasmus MC for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of your participation in the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text. This is set out in the Medical Research (Human Subjects) Compulsory Insurance Decree. This decree is available (in Dutch) on the 'Wettenbank' of the Dutch government (https://wetten.overheid.nl).

In the event of damage please contact the insurance company directly.

The insurance company for the study is:	
Name	CNA Insurance Company Europe S.A.
Address:	Polarisavenue 140, 2134 JX Hoofddorp
Telephone number:	023-3036004 or 06-38059413
E-mail:	ClaimsNetherlands@cnahardy.com or esther.vanherk@cnaeurope.com
Contact person:	Mrs. Esther van Herk

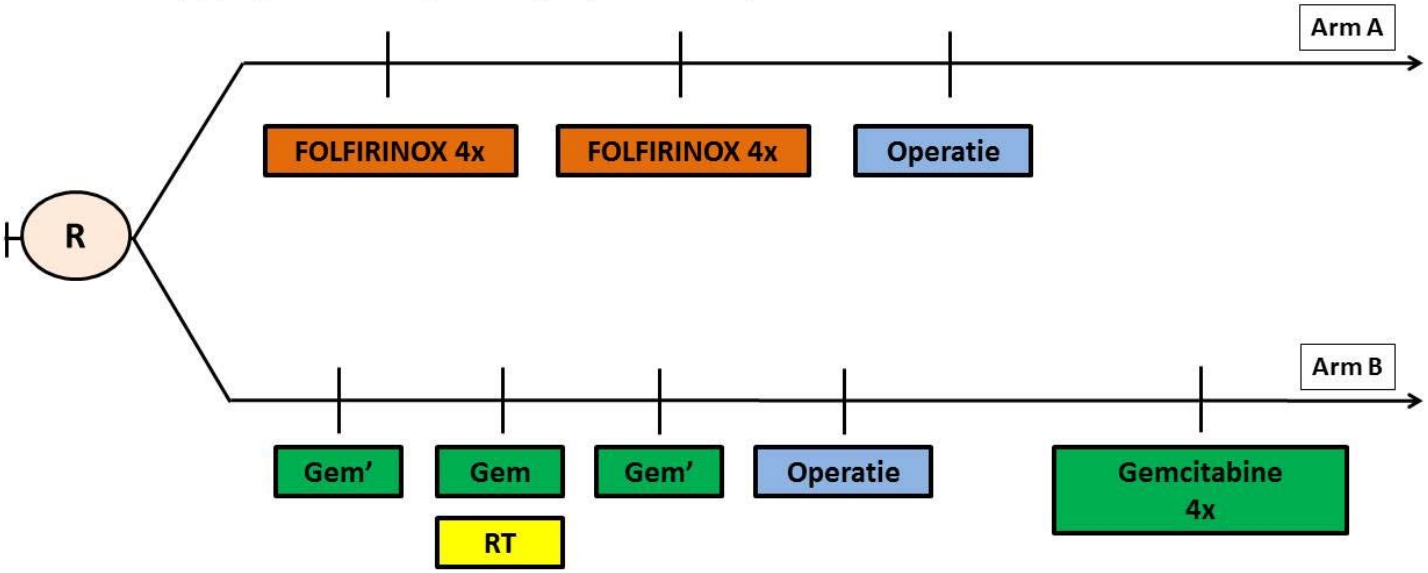
The insurance offers a cover of € 650,000 per study subject and € 5,000,000 for the entire study (and € 7,500,000 annually for all studies from the same sponsor).

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your health that would also have occurred if you had not participated in the study;
- damage resulting from not or not entirely following directions or instructions;
- damage to descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

Appendix C – Overview of tests

FOLFIRINOX: 1x per 2 weeks, 48h
Gemcitabine (Gem): 3 weeks on day 1, followed by 1 week rest (total 4 weeks)
Gemcitabine' (Gem'): 2 weeks on day 1, followed by 1 week rest (total 3 weeks)
Radiotherapy (RT): Every working day for 3 weeks, +- 1h



Preoperative FOLFIRINOX treatment (arm 1)

Study visit number	Eligibility & Randomisation	1 Baseline	2	3	4	5	6	7	8	9	10	11	12 EOT	13 1st postoperative hospital visit	14 1st follow-up 6months
Week		0-4	4	6	8	10	11	12	14	16	18	21	23-26	24-42	26
Patient information and informed consent	X														
CT-scan of chest and abdomen	X	X[1]					X					X	X[2]		X[2]
Endoscopic ultrasound	X														
Stent placement in case of obstructive jaundice		X													
Placement of mediport (i.e. port-a-cath)		X													
FOLFIRINOX treatment			X	X	X	X		X[3]	X[3]	X[3]	X[3]				
Surgery													X[3]		
Medical history	X														
Physical examination	X	X	X	X	X	X		X	X	X	X		X		X
Blood test for routine examinations	X		X	X	X	X		X	X	X	X		X		
Blood test for tumour markers			X[4]				X[4]					X[4]			X[4]
Blood test for circulating biomarkers			X[5]	X[5]			X[5]						X[5]	X[5]	

X[1]	Only if most recent scan occured > 6 weeks before start of treatment
X[2]	Only if most recent scan occured > 4 weeks before surgery or follow-up moment
X[3]	Only for patients without local progression or metastastic disease during preoperative treatment
X[4]	Blood tests for tumour markers will be performed before cycle 1, at evaluation after 4 and 8 cycles of FOLFIRINOX, and at CT-evaluation moments during follow-up
X[5]	Blood tests for circulating biomarkers will be performed before cycle 1 and 2, at evaluation after 4 cycles, preoperative, within 45 days postoperative, and once every year from date of randomisation.

Preoperative chemoradiotherapy treatment (arm 2)

Study visit number	Eligibility & Randomisation	1 Baseline	2	3-17	18	19	20	21 1st postoperative hospital visit	22 1st follow-up 6months	23	24	25	26 EOT
Week		0-4	4	7	11	15	17-20	18-26	26	32	36	40	44
Patient information and informed consent	X												
CT-scan of chest and abdomen	X	X[1]				X	X[2]		X[2]				
Endoscopic ultrasound	X												
Stent placement in case of obstructive jaundice		X											
Preoperative gemcitabine treatment			X	X	X								
Preoperative chemoradiotherapy				X									
Surgery							X[3]						
Postoperative gemcitabine treatment										X[3]	X[3]	X[3]	X[3]
Medical history	X												
Physical examination	X	X	X	X	X		X		X	X	X	X	X
Blood test for routine examinations	X		X	X	X		X			X	X	X	X
Blood test for tumour markers			X[4]			X[4]			X[4]				
Blood test for circulating biomarkers			X[5]	X[5]			X[5]	X[5]					

X[1] Only if most recent scan occured > 6 weeks before start of treatment

X[2] Only if most recent scan occured > 4 weeks before surgery or follow-up moment

X[3] Only for patients without local progression or metastastic disease during preoperative treatment

X[4] Blood tests for tumour markers will be performed before cycle 1, after neoadjuvant treatment, and at CT-evaluation moments during follow-up

X[5] Blood tests for circulating biomarkers will be performed before cycle 1 and 2, preoperative, within 45 days postoperative, and once every year from date of randomisation.

Follow-up visits

Study visit number	FU 1	FU 2	FU 3	FU 4	FU 5	FU 6	FU 7	FU 8	FU 9	FU 10	FU 11	FU 12	FU 13
Months (after randomisation)	6	9	12	15	18	21	24	30	36	42	48	54	60
CT-scan of chest and abdomen	X[1]		X		X		X		X		X		X
Physical examination	X	X[2]	X	X[2]	X	X[2]	X	X	X	X	X	X	X
Blood test for tumour markers	X[3]		X[3]		X[3]		X[3]		X[3]		X[3]		X[3]
Blood test for circulating biomarkers			X[4]				X[4]				X[4]		X[4]

X[1] Only if most recent scan occured > 4 weeks before follow-up moment

X[2] Follow-up visits at 9, 15 en 21 months after randomisation may be perfomed by phone. In that case no physical examination will be performed.

X[3] Blood tests for tumour markers will take place at CT-evaluation moments, untill progression of disease

X[4] Blood test for circulating biomarkers will take place every year from date of randomisation, untill progression of disease, together with CT-scans

Quality of Life Questionnaires

Study visit number	QoL 1 Baseline	QoL 2	QoL 3	QoL 4	QoL 5	QoL 6	QoL 7	QoL 8	QoL 9	QoL 10
Months (after randomisation)	0	3	6	9	12	18	24	36	48	60
Quality of Life questionnaires (QoL)	X	X	X	X	X	X	X	X	X	X

Appendix D: Subject Consent Form

Preoperative treatment with FOLFIRINOX or chemoradiotherapy and adjuvant chemotherapy for (borderline) resectable pancreatic cancer.

- I have read the subject information form. I was also able to ask questions. My questions have been answered to my satisfaction. I had enough time to decide whether to participate.
- I know that participation is voluntary. I know that I may decide at any time not to participate after all or to withdraw from the study. I do not need to give a reason for this.
- I give permission for my GP and treating specialist(s) to be informed that I am participating in this study.
- I give permission for the collection and use of my data, blood samples, and body material to answer the research question in this study.
- I know that some people may have access to all my data to verify the study. These people are listed in this information sheet. I consent to the inspection by them.
- I know that I should not become pregnant / avoid pregnancy of my partner during the study.
- The investigator has discussed with me the most suitable contraception for me and / or my partner if this applies to me.
- I agree that I will be informed of coincidental findings that (may) be of interest for my health.
- I agree that my data and body material will be stored at the research location until 15 years after completion of this study.
- I □ **do**
  □ **do not**
  consent to keeping my personal data longer and to use it for future research in the field of pancreatic cancer.
- I □ **do**
  □ **do not**
  consent to keeping my bodily material after this study and to use this later for other / more research, as indicated in the information sheet.
- I □ **do**
  □ **do not**
  consent to being contacted again after this study for a follow-up study.
- I want to participate in this study.

Name of study subject:

Signature: Date: __ / __ / __

I hereby declare that I have fully informed this study subject about this study.

If information comes to light during the course of the study that could affect the study subject's consent, I will inform him/her of this in a timely fashion.

Name of investigator (or his/her representative):

Signature: Date:__ / __ / __

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* Delete as appropriate.

The study subject will receive the full information sheet, together with a signed copy of the consent form.

Appendix E: Medical Scientific Research Brochure. 'General Information for Study Subjects'