Official Title of the study	**PANOVA-3: Effect of Tumor Treating Fields (TTFields, 150 kHz) as Front-Line Treatment of Locally-advanced Pancreatic Adenocarcinoma Concomitant With Gemcitabine and Nab-paclitaxel**
NCT number	**NCT03377491**
Document Date	**August 2, 2022**

PANOVA-3: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields, 150kHz) concomitant with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma

Study	**EF-27 (PANOVA-3)**
Sponsor	**Novocure GmbH** **Park 6** **CH-6039 Root D4** **Switzerland**
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Revision history

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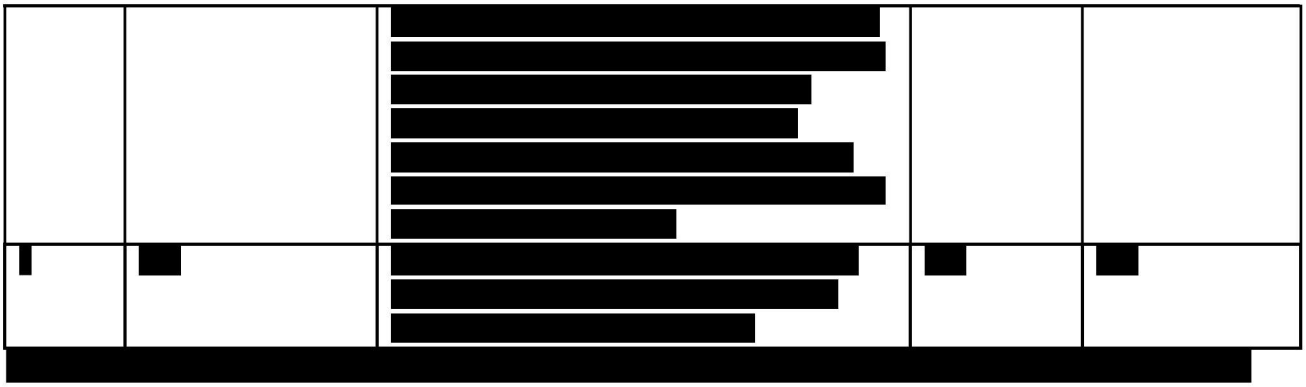

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LIST OF ABBREVIATIONS

5-FU	5-Fluorouracil
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ASADE	Anticipated Serious Adverse Device Effect
AsPC-1	Human Pancreatic Adenocarcinoma
AST	Aspartate Aminotransferase
B16F10	Mouse Malignant Melanoma Cell Line
BxPC-3	Human Pancreatic Adenocarcinoma
C57Bl/6	Mouse Strain
CA	Celiac Axis
CA 19-9	Carbohydrate Antigen 19-9
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular Accident
DD	Device Deficiency
DMC	Data Monitoring Committee
DSS	Device Support Specialist
EBRT	External Beam Radiation Therapy
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EN ISO 14155	Clinical investigation of medical devices for human subjects
EN ISO 13485	Medical devices - Quality management systems - Requirements for regulatory purposes
EORTC QLQ C30	Quality of Life Questionnaire
ERP	Enterprise Recourse Planning
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
gamma-GT	gamma-Glutamyltransferase
GBM	Gliblastoma
GCP	Good Clinical Practice
ICH- E6	International Conference on Harmonisation - Guideline for Good Clinical Practice
IDE	Investigational Device Exemption
INR	International Normalized Ratio
IRB	Institutional Review Board
kHz	Kilohertz
KPS	Karnofsky Performance Score
LDH	Lactatdehydrogenase
LN	Lung
MCV	Mean Corpuscular Volume
MDT	Multi-Disciplinary Team
MGMT	O6-Methylguanin-DNS-Methyltransferase
MOSE	Murine Ovarian Surface Epithelial

MOSE-L_{FFL}	Murine Ovarian Surface Epithelial Cells Expressing Firefly Luciferase
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-Small-Cell Lung Carcinoma
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
PC-1.0	Hamster Pancreatic Cancer Cell Line
PFS	Progression Free Survival
PI	Principal Investigator
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
PV	Portal Vein
QC	Quality Control
QoL	Quality of Life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of the World
RT	Radiation Therapy
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBRT	Stereotactic body Radiation Therapy
SMA	Superior Mesenteric Artery
SMV	Superior Mesenteric Vein
SOP	Standard Operating Procedure
TMZ	Temozolomide
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effects
VAS	Visual Analogue Scale
VX-2	Rabbit Pleural Carcinoma Cell Line
WBC	White Blood Cell

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following: US Code of Federal Regulations (CFR) applicable to clinical studies (CFR Title 21), EN ISO 14155 Clinical investigation of medical devices for human subjects and applicable regional regulation in the various countries the study is conducted in.

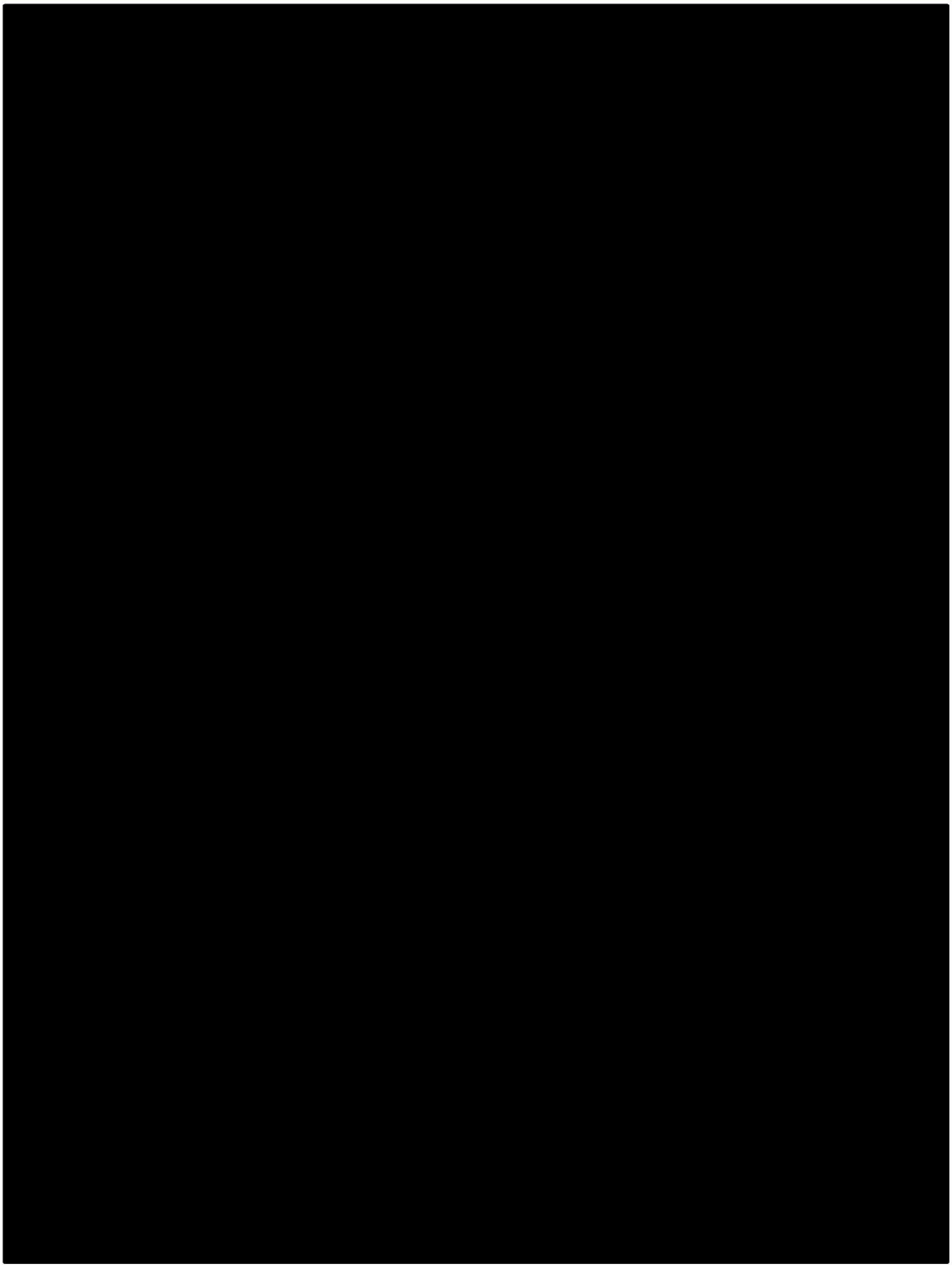
The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Ethics Committee (EC) / Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants.

PROTOCOL SUMMARY

Title:	PANOVA-3: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields, 150kHz) concomitant with gemcitabine and nab-paclitaxel for front-line treatment of locally-advanced pancreatic adenocarcinoma
Objectives:	To test the efficacy and safety of gemcitabine and nab-paclitaxel, with or without TTFields, using the NovoTTF-200T System as a front-line therapy for locally-advanced pancreatic adenocarcinoma patients
Endpoints	Primary Endpoint: Overall survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to overall survival of patients treated with chemotherapy alone Secondary Endpoints: • Progression-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone, using the RECIST V1.1 Criteria • *Local* progression-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone, using the RECIST V1.1 Criteria • Objective response rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone, using the RECIST V1.1 Criteria • 1-year survival rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone • Quality of life of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone, using the EORTC QLQ C30 questionnaire with the PAN26 addendum • Pain-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients

	treated with chemotherapy alone, using the visual analogue scale (VAS) • Puncture-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone • Resectability rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone • Toxicity profile in patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel, compared to that of patients treated with chemotherapy alone
Population:	Unresectable, locally-advanced adenocarcinoma of the pancreas, ECOG 0-2
Phase:	Pivotal
Number of Sites enrolling participants:	160
Number of enrolled patients:	556
Description of Study Device:	The NovoTTF-200T is a portable, battery operated system intended for continuous home use, which delivers TTFields at a frequency of 150kHz to the patient by means of insulated transducer arrays. The NovoTTF-200T produces electric forces intended to disrupt cancer cell division.
Study Duration:	48 months (30 months of patient accrual)
[redacted]	[redacted]

SCHEMATIC OF STUDY DESIGN



1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1. BACKGROUND INFORMATION

Adenocarcinoma of the pancreas

Ductal adenocarcinoma of the pancreas comprises more than 95% of malignant neoplasms of the pancreas, compared to 5% of pancreatic neuroendocrine tumors. It is the eighth leading cause of cancer mortality in men and ninth in women worldwide[1], and the fourth leading cause of cancer mortality in the United States (US). In the US, around 53,000 patients are diagnosed annually and almost all are expected to die from the disease[2]. Incidence rises after the age of 45[3,4]. Family history of pancreatic cancer is found in 5-10% of the patients, and is related to either known syndromes or familiar pancreatic cancer without a known genetic aberration[5]. Other risk factors include non-O blood group[6], chronic pancreatitis[7], diabetes [8], cigarette smoking[7] and obesity[9]. Unfortunately, at the time of symptom appearance, only 15% of the patients are candidates for curative surgical resection, and the others have locally advanced (30-40%) or metastatic (~40%) cancer due to disease spread[2].

As surgical resection is the only potentially curative modality of treatment, an initial assessment is done based upon preoperative triple-phase staging contrast-enhanced CT scan. Distant metastases in the liver, peritoneum, omentum, or any extraabdominal site categorize pancreatic cancer as unresectable.

Locally-advanced, unresectable and borderline resectable adenocarcinoma of the pancreas

Local unresectability is often due to vascular invasion, particularly of the superior mesenteric artery (SMA). Many consider the cancer to be locally advanced and unresectable if it is associated with encasement (more than one-half of the vessel circumference) of the SMA or celiac artery (CA) or if there is occlusion of the superior mesenteric vein (SMV) or SMV-portal vein (PV) confluence without suitable vessels above and below the tumor to allow for reconstruction. “Borderline” resectable pancreatic cancer[10] may refer to cases where there is focal (less than one-half of the circumference) tumor abutment of the visceral (superior mesenteric, celiac) arteries or short-segment occlusion of SMV or SMV/PV confluence or hepatic artery. Many centers have demonstrated the feasibility of SMV reconstruction in the event of encasement (more than one-half of the vessel circumference) or occlusion/thrombus of the SMV or the SMV-PV confluence[11], and this is now considered by many to represent borderline resectable disease.

The National Comprehensive Cancer Network (NCCN) defined criteria for determining unresectability/borderline[12], based on a 2014 consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association[13]. These have also been adopted by the European Society for Medical Oncology (ESMO)[14]. It has been demonstrated in a number of clinical trials that the prognosis of locally-advanced disease is significantly better than that of a metastatic disease[15], improving the outcome of most clinical trials normally conducted in a mixed population of advanced pancreatic cancer patients. In addition, due to the lack of standard definition for staging, progression and agents used as standard of care, there is a significant variation in the reported median progression free survival (PFS), which is in the range of 6-10 months, and the reported median overall survival (OS), which is in the range of 9-16 months[16–31].

Review of treatments for locally-advanced adenocarcinoma of the pancreas

Most unresectable pancreatic cancer cases are managed with initial chemotherapy with or without chemoradiotherapy. In some cases, a sufficient response will allow the consideration of subsequent resection.

Due to the variability in study criteria and the lack of additional prospective, randomized trials, there is no consensus regarding the treatment of locally-advanced disease. Either FOLFIRINOX (leucovorin, 5-FU, irinotecan, oxaliplatin) or gemcitabine (alone or combined with nab-paclitaxel), with or without radiotherapy are commonly prescribed for patients, following the significantly higher overall response rate reported in metastatic disease for these agents, and despite the lack of evidence from prospective trials proving benefit in locally-advanced disease.

FOLFIRINOX

FOLFIRINOX is normally reserved for patients with a good performance status, a total bilirubin level that is below 1.5 times the upper limit of normal, a favorable comorbidity profile, and support systems to permit aggressive medical therapy. Results from the PRODIGE trial evaluating FOLFIRINOX versus gemcitabine in patients with metastatic pancreatic cancer and good performance status demonstrated an improvement in median PFS (6.4 months vs. 3.3 months; P<0.001) and median OS (11.1 months vs. 6.8 months; P<0.001) in favor of FOLFIRINOX-treated patients[32]. It is arguable whether patients treated in this trial reflect the pancreatic cancer population, due to strict selection of good prognosis patients[33]. A systemic review of 11 studies that included a total of 315 patients with locally advanced disease treated with FOLFIRINOX demonstrated a median OS of 24.2 months[34], although it led to significantly higher toxicity compared to gemcitabine[32]. Nevertheless, there are few data on rates of resectability, perioperative morbidity, and mortality in patients who undergo surgery after receiving FOLFIRINOX for locally advanced unresectable disease, no data on long-term outcomes, and no randomized trials proving benefit over less intensive chemotherapy regimens in this setting[34–37]. Extrapolation led the NCCN pancreatic cancer committee to recommend this regimen in locally advanced unresectable disease[12].

Gemcitabine plus nab-paclitaxel

Gemcitabine in combination with nab-paclitaxel is commonly the selected initial regimen for locally-advanced pancreatic cancer. In a phase III study, nab-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival and response rate in patients with metastatic disease[38]. The OS was 8.5 months in the nab-paclitaxel plus gemcitabine group as compared with 6.7 months in the gemcitabine group (hazard ratio for death, 0.72; 95% confidence interval [CI], 0.62 to 0.83; P<0.001). Rates of peripheral neuropathy and myelosuppression were increased in the nab-paclitaxel-gemcitabine group. Updated results of the same trial demonstrated that 3% of the patients from the nab-paclitaxel plus gemcitabine arm were still alive at 42 months, while no patients were alive from the control arm at this timepoint. Higher KPS score (≥70) and absence of liver metastases were predictors of long term survival[39,40]. Extrapolation of this data led the NCCN panel for pancreatic adenocarcinoma to recommend this combination in locally advanced, good performance status patients as well[12]. There are currently no data from prospective, randomized trials comparing FOLFORINOX with gemcitabine-nab-paclitaxel in unresectable, locally-advanced pancreatic cancer patients.

Gemcitabine alone and in combination with other agents

Phase III studies of combinations of gemcitabine with biologic agents such as bevacizumab or cetuximab led to disappointing results[41–44]. The combination of gemcitabine with erlotinib was initially reported to increase overall survival in patients suffering from locally advanced or metastatic disease, but the benefit was small (median OS of 6.24 months and 1-year survival of 23% in erlotinib-gemcitabine-treated patients, compared with 5.91 months and 17% in the control arm, HR=0.82; P=0.038)[41–43,45]. Recently, the phase III LAP07 study[18] assessed chemoradiotherapy with either gemcitabine or gemcitabine plus erlotinib versus chemotherapy alone in locally-advanced, unresectable patients, following 4 months of gemcitabine-based induction chemotherapy. The median OS was 13.6 months for patients who received gemcitabine and 11.9 months for patients who were treated with gemcitabine and erlotinib. There was no statistically significant difference between the outcome of the two treatments and no difference between patients who received chemotherapy versus chemoradiotherapy following induction chemotherapy. An interim analysis determined that the study should be stopped for futility.

Gemcitabine alone remains another standard approach for locally advanced disease when chemotherapy alone is indicated. The optimal number of courses of neoadjuvant combination chemotherapy has not been established in this setting.

Chemoradiotherapy

For patients who do not progress following initial chemotherapy and for whom a resection is being considered, combined treatment with external beam radiotherapy (EBRT) plus concomitant low-dose infusional 5-FU is a possible approach in an attempt to increase the complete resection rate. It is unknown if radiotherapy (RT) contributes to a higher resection rate. Stereotactic body RT (SBRT) is another alternative to chemoradiotherapy, although there are no trials establishing the comparable efficacy of SBRT and standard fractionation EBRT in this setting. Despite the above, the rate of resectability remains very low following maximal therapy: The LAP07 trial[18] mentioned above directly compared chemoradiotherapy with continued chemotherapy in patients treated initially with chemotherapy. Only 4% of study participants responded to treatment sufficiently to enable pancreatectomy. Patients who received chemoradiotherapy following a 4-month chemotherapy induction treatment with either gemcitabine or gemcitabine and erlotinib did not have an OS advantage over patients who received chemotherapy alone. In addition, trials evaluating different chemotherapy combinations in mixed populations of patients with locally advanced and metastatic pancreatic cancer suggest that the impact of gemcitabine-based chemotherapy on survival among patients with locally advanced disease may be of approximately the same magnitude as that achieved by chemoradiotherapy[22,46–48]. Finally, two separate meta-analyses of trials comparing initial chemoradiotherapy (with or without subsequent chemotherapy) versus chemotherapy alone concluded that there was no survival benefit (and greater toxicity) for chemoradiotherapy compared with chemotherapy alone[49,50]. Moreover, it was reported that following initial chemoradiotherapy, many locally advanced pancreatic cancers metastasize rapidly, which has diminished the use of chemoradiotherapy as initial treatment[51]. Nevertheless, chemoradiotherapy is still commonly used by many institutions, in particular after chemotherapy, and is part of multiple consensus guidelines[12,14].

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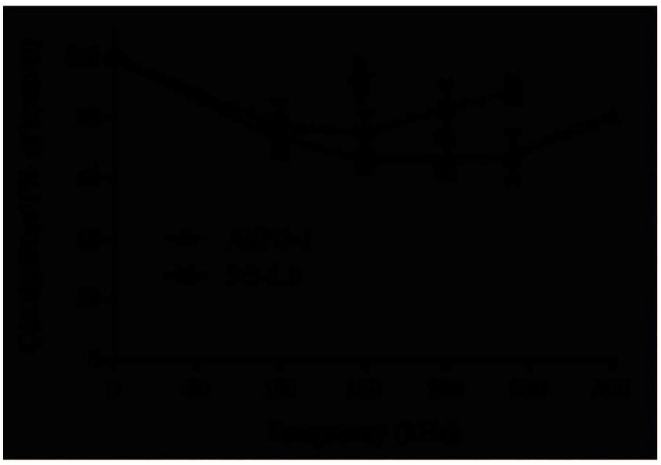

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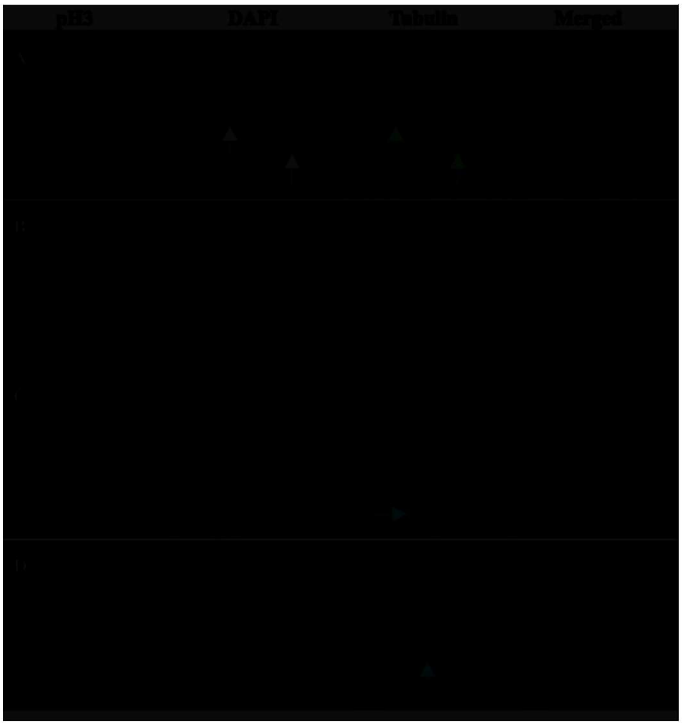

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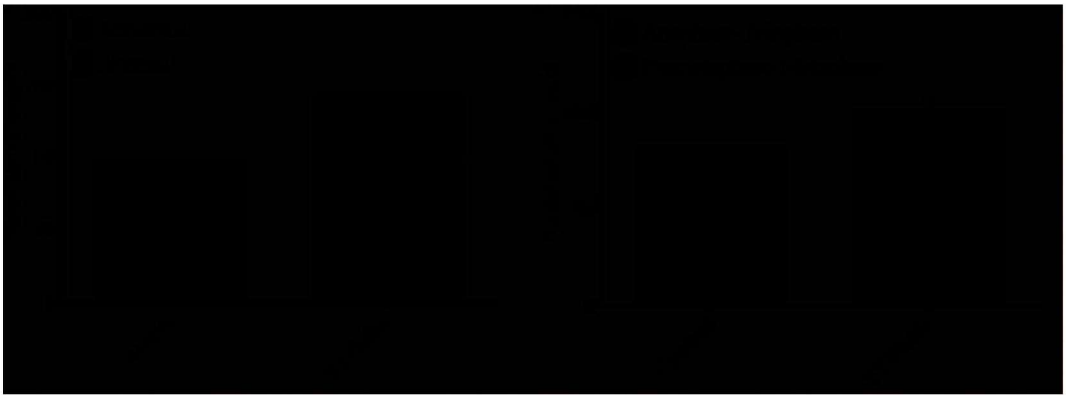

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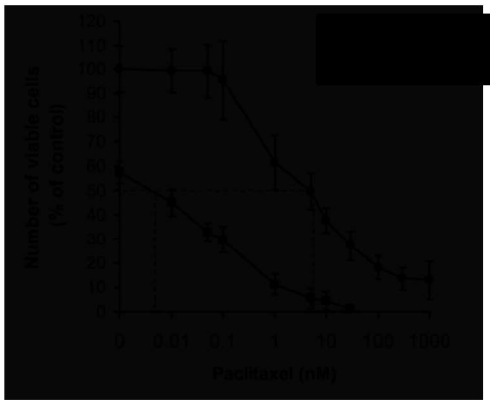

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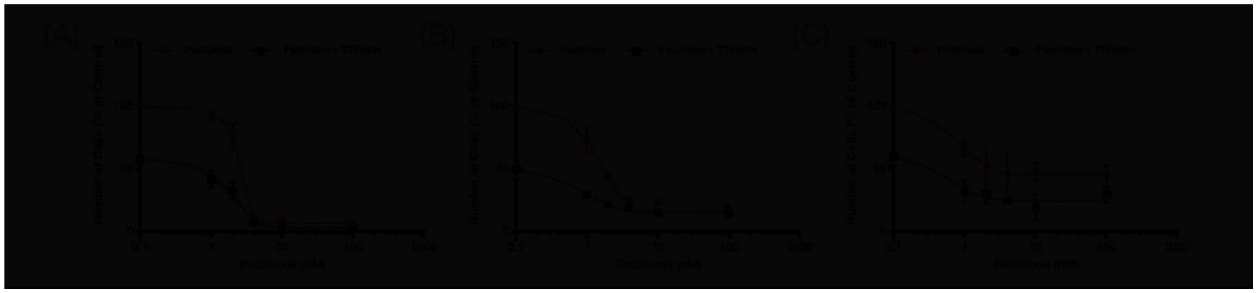
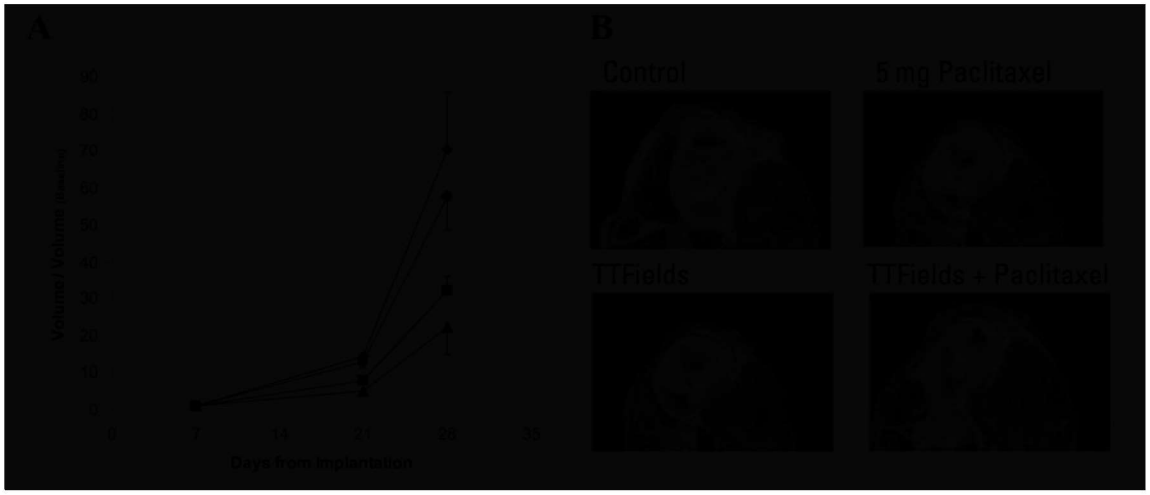
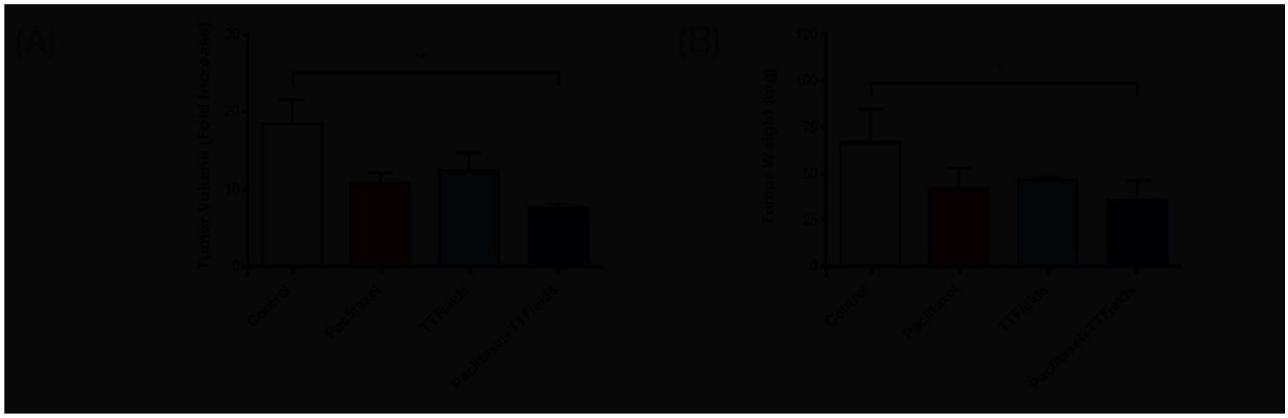



A
B
Control
5 mg Paclitaxel
TTFields
TTFields + Paclitaxel
Volume (mm³)
Days from implantation



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1.2. RATIONALE

Pancreatic cancer is a leading cause of cancer-related mortality. The diagnosis is almost always done when the disease is no longer resectable. Despite extensive clinical research, new systemic therapies offer little improvement in overall survival, and radiation therapy has also failed to demonstrate such benefit.

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1.3. POTENTIAL RISKS AND BENEFITS

[redacted]

1.3.1. Known Potential Adverse Events

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1.3.2. Known Potential Benefits

[redacted]

[redacted]

2. OBJECTIVES AND PURPOSE

The purpose of the study is to test if the addition of TTFields, delivered using the NovoTTF-200T System, to gemcitabine and nab-paclitaxel as first line treatment in unresectable, locally-advanced pancreatic cancer patients, significantly improved the clinical outcome of patients, compared to the chemotherapy treatment alone.

2.1.1. Primary Objective

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the overall survival of patients, compared to chemotherapy treatment alone.

2.1.2. Secondary Objectives

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the progression-free survival of patients, compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the *local* progression-free survival of patients, compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients leads to a higher rate of objective response rate, compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients leads to a higher 1-year survival rate, compared to chemotherapy treatment alone.

To assess if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients affects the quality of life of patients, compared to chemotherapy treatment alone.

To evaluate if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the pain-free survival of patients, compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients prolongs the puncture-free survival of patients, compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients increases the probability of the cancer becoming resectable (with a curative intention), compared to chemotherapy treatment alone.

To determine if TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients is a safe treatment compared to chemotherapy treatment alone.

3. STUDY DESIGN AND ENDPOINTS

3.1. DESCRIPTION OF THE STUDY DESIGN

Pivotal, randomized (1:1), open-label, two-arm, multi-center study of the NovoTTF-200T system.

[redacted]

3.2. STUDY ENDPOINTS

3.2.1. Primary Endpoint

Overall survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to overall

survival of patients treated with chemotherapy alone, measured as the period between the time of randomization and the time of death.

3.2.2. Secondary Endpoints

Progression-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the progression-free survival of patients treated with chemotherapy alone, measured from the time of randomization and based on CT scans collected on the study, using the revised RECIST V1.1 Criteria[70].

*Local p*rogression-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the *local* progression-free survival of patients treated with chemotherapy alone, measured from the time of randomization and based on CT scans collected on the study, using the revised RECIST V1.1 Criteria.

Objective response rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the objective response rate of patients treated with chemotherapy alone, measured as the proportion of patients with partial- or complete response between the time of randomization and the time of death according to the revised RECIST Criteria V1.1.

One-year survival rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the 1-year survival rate of patients treated with chemotherapy alone.

Quality of life of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to quality of life of patients treated with chemotherapy alone, assessed using the EORTC QLQ C30 questionnaire with the PAN26 addendum.

Pain-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to pain-free survival of patients treated with chemotherapy alone, measured as the duration between the time of randomization until a greater than or equal to two-point decline from a baseline measurement in a patient self-reported visual analogue scale (VAS) is recorded or death, whichever occurrs first.

Puncture-free survival of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to puncture-free survival of patients treated with chemotherapy alone, measured as the duration between randomization until the first need for paracentesis or death, whichever occurrs first.

Resectability rate of patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to

resectability rate of patients treated with chemotherapy alone, measured as the precentage of patients whose tumors were deemed resectable by a multi-disciplinary team (MDT) consisting of at least a surgeon, a medical oncologist and a radiologist, prior to local disease progression as defined in the protocol.

Toxicity profile in patients treated with TTFields concomitant with gemcitabine and nab-paclitaxel in the first line treatment of unresectable, locally advanced pancreatic cancer patients, compared to the toxicity profile of patients treated with chemotherapy alone, measured by the rate of treatment-emergent toxicities in both arms.

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1. PARTICIPANT INCLUSION CRITERIA

Individuals must meet all of the following inclusion criteria in order to be eligible to participate in the study:

1. 18 years of age and older
2. Life expectancy of ≥ 3 months
3. Histological/cytological diagnosis of *de novo* adenocarcinoma of the pancreas
4. Unresectable, locally advanced stage disease according to the following criteria[12,13]:
    - Head/uncinate process:
        a. Solid tumor contact with SMA>180°
        b. Solid tumor contact with the CA>180°
        c. Solid tumor contact with the first jejunal SMA branch
        d. Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)
        e. Contact with most proximal draining jejunal branch into SMV
    - Body and tail
        a. Solid tumor contact of >180° with the SMA or CA
        b. Solid tumor contact with the CA and aortic involvement
        c. Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)
    - No distant metastasis, including non-regional lymph node metastasis
    - No borderline resectable (per Al-Hawary MM, et al., *Radiology* 2014[13])
5. ECOG score 0-2
6. Amenable and assigned by the investigator to receive therapy with gemcitabine and nab-paclitaxel
7. Able to operate the NovoTTF-200T System independently or with the help of a caregiver
8. Signed informed consent form for the study protocol

4.2. PARTICIPANT EXCLUSION CRITERIA

All individuals meeting any of the following exclusion criteria will be excluded from study participation:

1. Prior palliative treatment (e.g. surgery, radiation) to the tumor

2. Cancer requiring anti-tumor treatment within the 5 years before inclusion, excluding treated stage I prostate cancer, in situ cervical or uterus cancer, in situ breast cancer and non-melanomatous skin cancer.
3. Serious co-morbidities:
   a. Clinically significant (as determined by the investigator) hematological, hepatic and renal dysfunction, defined as: Neutrophil count < 1.5 x 10^9/L and platelet count < 100 x 10^9/L; bilirubin > 1.5 x Upper Limit of Normal (ULN); AST and/or ALT > 2.5 x ULN; and serum creatinine > 1.5 x ULN.
   b. History of significant cardiovascular disease unless the disease is well controlled. Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea).
   c. History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the study.
   d. History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable.
   e. Active infection or serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.
   f. History of any psychiatric condition that might impair patient's ability to understand or comply with the requirements of the study or to provide consent.
4. Concurrent anti-tumor therapy beyond gemcitabine and nab-paclitaxel
5. Implantable electronic medical devices in the torso, such as pacemakers
6. Known severe hypersensitivities to medical adhesives or hydrogel, or to one of the chemotherapies used in this study.
7. Pregnancy or breast-feeding (female patients with reproductive potential and their partners must accept to use effective contraception throughout the entire study period and for 3 months after the end of treatment). All patients who are capable of becoming pregnant must take a pregnancy test which is negative within 72 hours before beginning study drug administration. The definition of effective contraception is left up to the decision of the investigator.
8. Unable to follow the protocol for medical, psychological, familial, geographic or other reasons.
9. Admitted to an institution by administrative or court order.

4.3. PARTICIPANT WITHDRAWAL OR TERMINATION

4.3.1. Reasons for Withdrawal or Termination

[redacted]

[redacted]

4.3.2. Handling of Participant Withdrawals or Termination

[redacted]

4.4. PREMATURE TERMINATION OR SUSPENSION OF STUDY

[redacted]

5. STUDY TREATMENTS

5.1. STUDY DEVICE

5.1.1. The NovoTTF-200T System (Investigational Device)

[redacted]

The NovoTTF-200T System is an investigational medical device for a front-line treatment of adult patients with locally advanced pancreatic cacner, concomitant with gemcitabine and nab-paclitaxel. It is intended to be used exclusively by patients in a clinical study.

The device is a portable, battery operated system which delivers TTFields at 150 kHz to the patient by means of insulated

[redacted]

[redacted]

The NovoTTF-200T System is manufactured by [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]			[redacted]	
	[redacted]			[redacted]	
	[redacted]			[redacted]	

[redacted]

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.2. Appearance, Labeling and Storage Conditions

See EF-27 User Manual.

5.1.3. Applying TTFields Using the NovoTTF-200T System

[redacted] Treatment planning: [redacted]

[redacted] Patient training: [redacted]

[redacted] Treatment initiation: It is the responsibility of the investigator to oversee the treatment start supported by the Novocure Device Support Specialist (DSS). [redacted]

[redacted]

[redacted] Transducer Array replacement: [redacted]

[redacted] Usage assessment: [redacted]

[redacted]

5.1.4. Duration of Therapy

TTFields application will be continuous [redacted]

[redacted]

5.1.5. Skin Care Guidelines

[redacted]

[redacted]

5.1.6. Device Specific Considerations

[redacted]

5.1.7. Study Device Accountability Procedures

[redacted]

5.2. STUDY CHEMOTHERAPEUTIC AGENTS

[redacted]

In the event of chemotherapy toxicities, dose modifications or interruptions may be employed as per the prescribing information in the gemcitabine and nab-paclitaxel package inserts or according to local practice. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

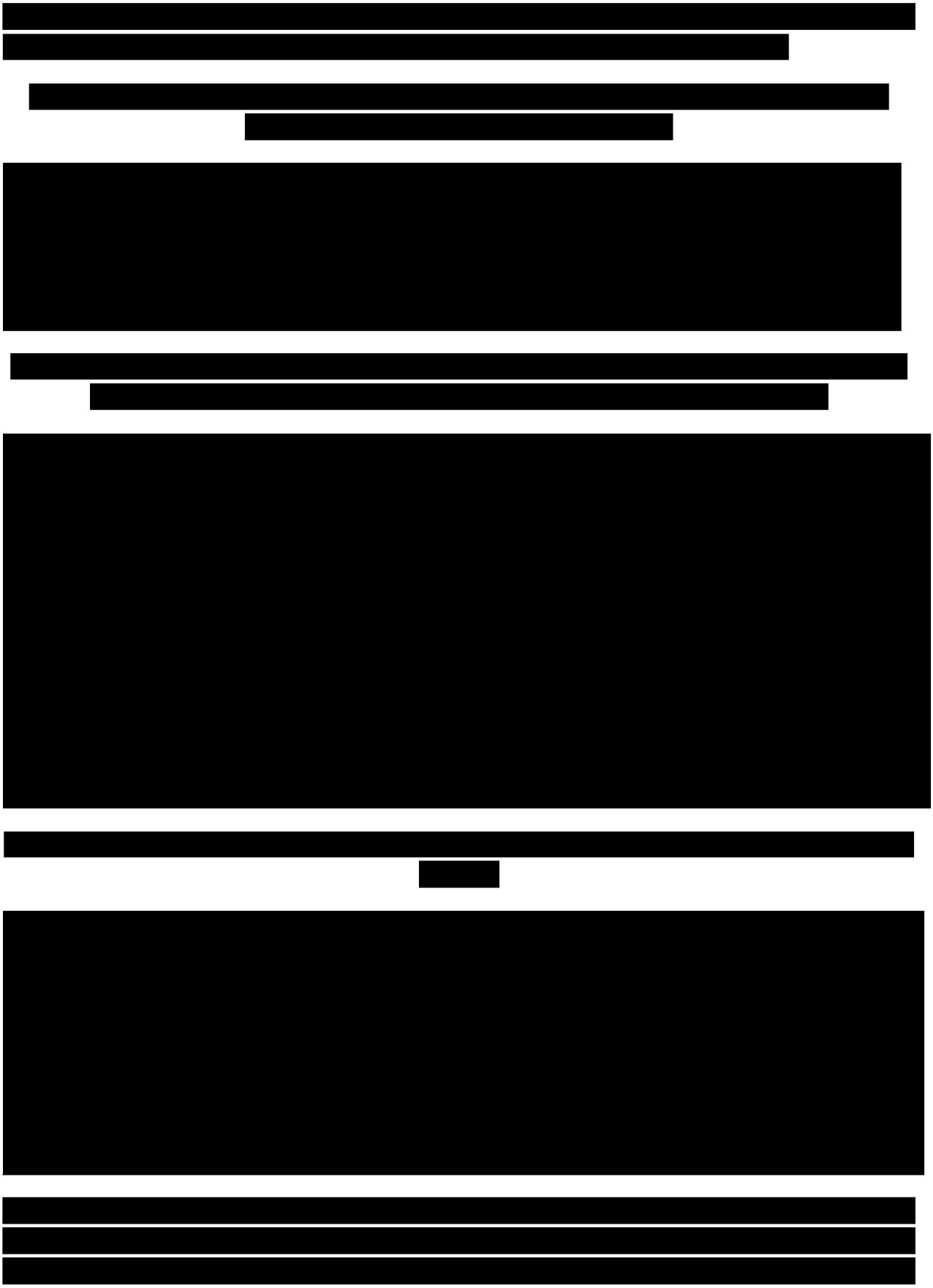
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[redacted]

5.3. SUPPORTIVE THERAPY

Patients on both arms of the study should also receive the best supportive care available at each site . All medications used throughout the study will be documented. [redacted]

5.4. SALVAGE THERAPY

Following progression per revised RECIST Criteria version 1.1, patients may be offered standard pancreatic cancer-directed therapy and salvage therapy based on local practice at each site [redacted] Salvage therapy should be recorded in the CRFs. [redacted]

6. STUDY PROCEDURES AND SCHEDULE

6.1. STUDY PROCEDURES/EVALUATIONS

6.1.1. Study Specific Procedures

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] EORTC QLQ C30 questionnaire with the PAN26 addendum. [redacted]

[redacted]

[redacted]

6.1.2 Standard of Care Study Procedures

All study treatments except for the NovoTTF-200T System, including chemotherapy used during the study, will be administered as part of the standard-of-care treatment for locally-advanced pancreatic cancer. Most follow-up procedures performed in the study are standard-of-care, and there may be variation between centers in the standard follow up for the patient population.

6.2. LABORATORY EVALUATIONS

6.2.1 Clinical Laboratory Evaluations

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.2.2 Other Assays or Procedures

[redacted]

[redacted]

[redacted]

6.3. STUDY SCHEDULE

6.3.1. SCREENING/BASELINE

The following will be performed within [redacted] prior to randomization:

[redacted]

The following will be performed within [redacted] prior to randomization:

[redacted]
EORTC QLQ C30 questionnaire + PAN26 addendum questionnaire
[redacted]

6.3.2. Enrollment/Randomization

[redacted]

[redacted]

6.3.3. Follow-Up

All follow up procedures refer to both arms of the study, unless otherwise specified.

[redacted]

EORTC QLQ C30 questionnaire with the PAN26 addendum

[redacted]

6.3.4. Post-Treatment Termination Visit

[redacted]

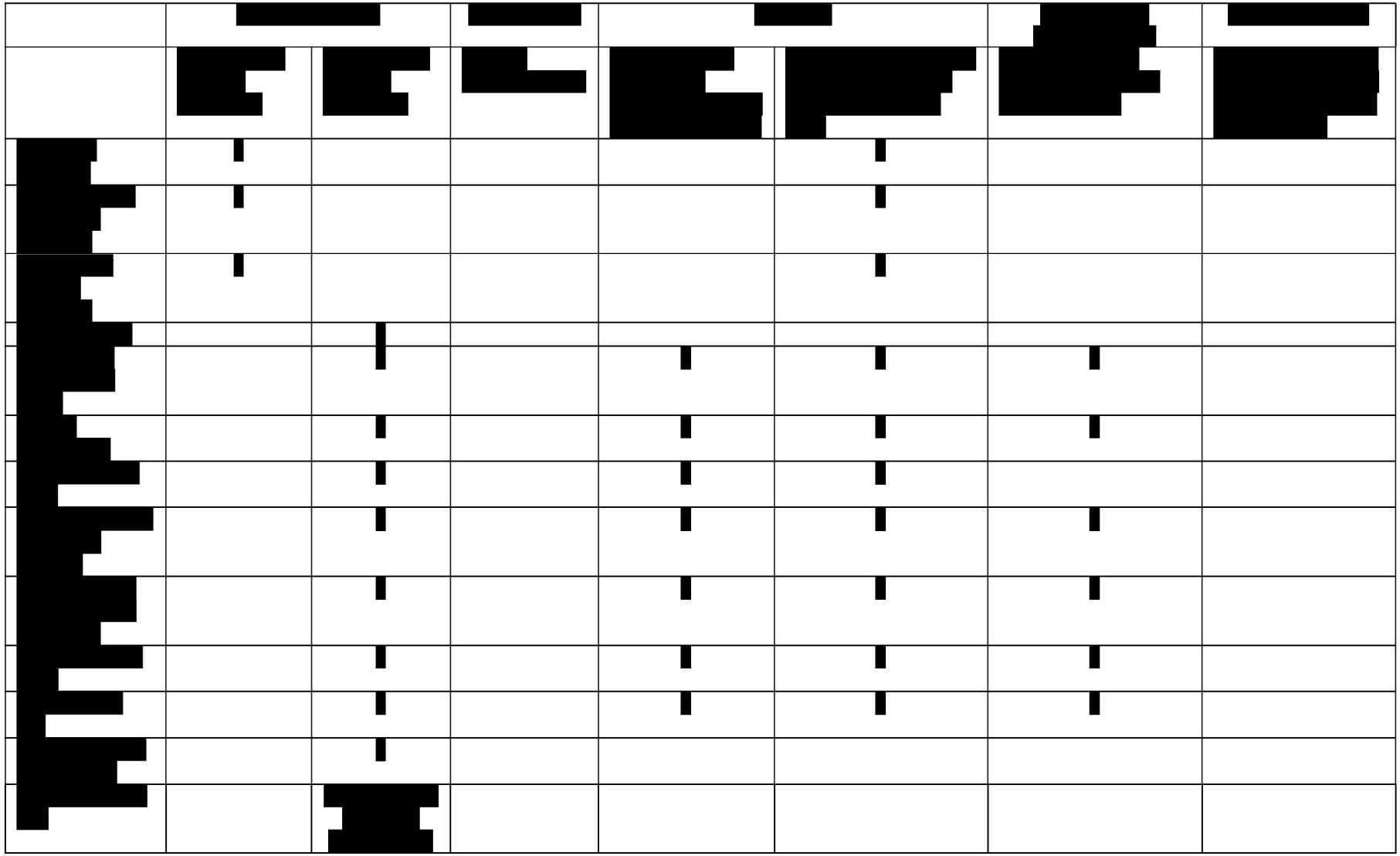
6.3.5. Survival Follow Up

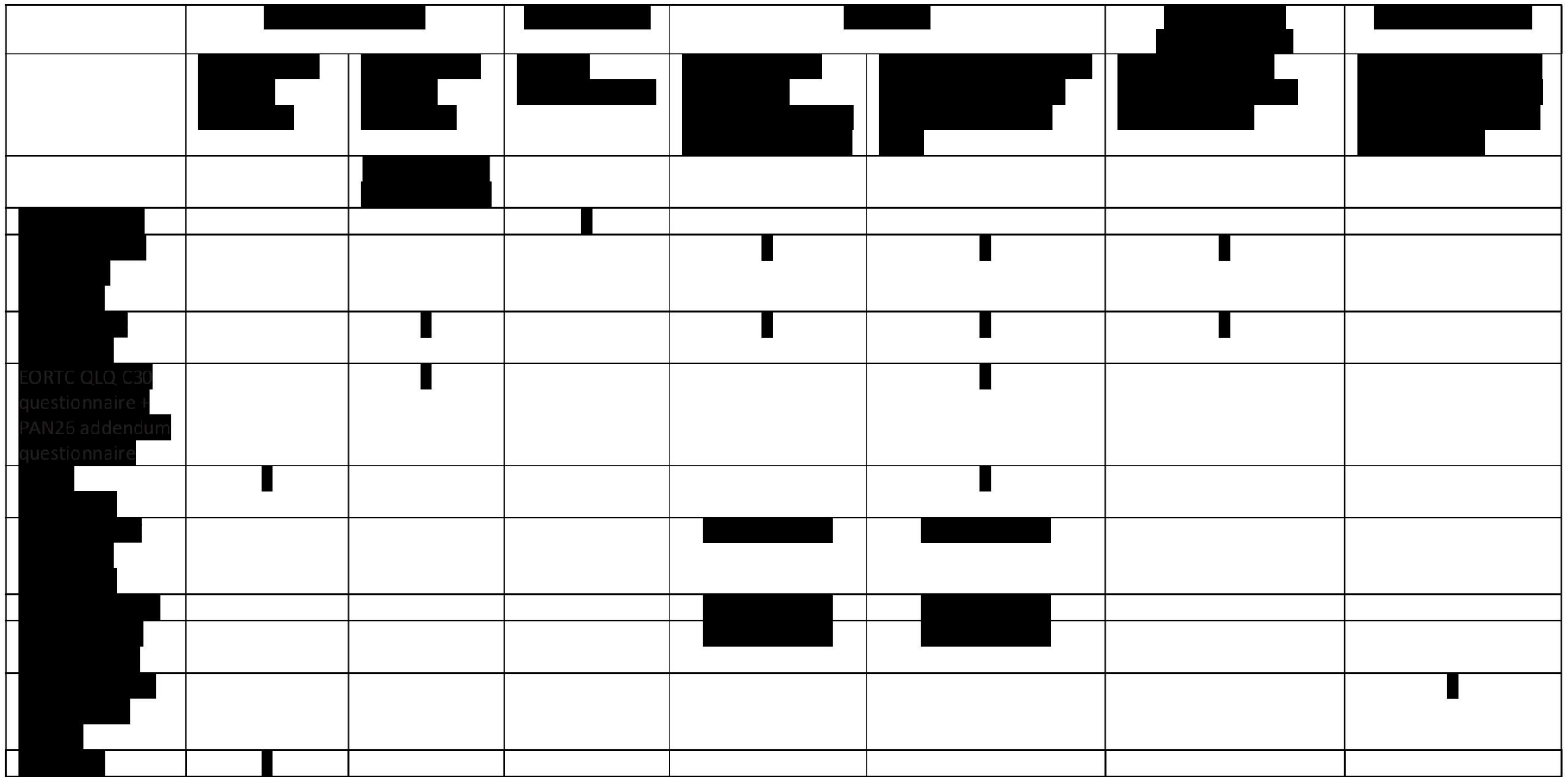
Following *local* disease progression or visit discontinuation due to any other reason, patients will be followed every [redacted] for survival [redacted]. Patient death date will be captured in the CRFs.

[redacted]

6.3.6. Schedule of Events

Table 6: Schedule of Events




EORTC QLQ C30 questionnaire + PAN26 addendum questionnaire

As described in section 5.1.3 NovoTTF-200T will be initiated [redacted]

[redacted]

Radiological review includes assessment of local and distant progression per the revised RECIST criteria version 1.1.

[redacted]

[redacted]

6.4. PARTICIPANT ACCESS TO STUDY DEVICE AT STUDY CLOSURE

[redacted]

7. ASSESSMENT OF SAFETY

7.1. SPECIFICATION OF SAFETY PARAMETERS

7.1.1. Definition of Adverse Events (AEs)

As defined by EN ISO 14155 (2011), an adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This includes events related to the investigational medical device or the comparator, events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

7.1.2. Definition of Serious Adverse Events (SAEs)

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- led to a death,
- led to a serious deterioration in health of the subject that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient hospitalization or prolongation of existing hospitalization, or
  - in medical or surgical intervention to prevent life threatening illness
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

[redacted]

[redacted]

7.1.3. Definition of Adverse Device Effect (ADE)

Adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event resulting from use error or from intentional misuse of the investigational medical device.

7.1.4. Definition of Device Deficiency (DD)

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

7.1.5. Definition of Serious Adverse Device Effect (SADE)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

7.1.6. Definition of Unanticipated Serious Adverse Device Effects (USADEs)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

7.1.7. Definition of Unanticipated Adverse Device Effect (UADE)

Serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.2. ADVERSE EVENT COLLECTION AND REPORTING

The adverse event collection and reporting will be handled as required and in accordance [redacted]

Safety evaluation and reporting will be managed through the following actions:

[redacted]

DeviceSafety@novocure.com

7.3. Classification of an Adverse Event

7.3.1. Severity (Grading) of Event

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for assessing severity of adverse events. [redacted]

[redacted]

7.3.2. Modified Grading for TTFields-Related Skin Adverse Events

[redacted]

7.3.3. Relationship to Study Treatments (Causality Assessment)

The relationship of the adverse event to study treatments must be specified using the following definitions:

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7.4. TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

7.4.1. Eliciting Adverse Event Information

[redacted]

7.4.2. Adverse Event Reporting Period

The adverse event reporting period will begin immediately following randomization. Adverse events will be collected until last study follow up visit or for [redacted] following treatment termination, the later of the two. All adverse events that occur in study patients during the adverse event reporting period specified in the protocol must be reported on the CRFs, [redacted]

[redacted]

[redacted]

[redacted]

7.5. REPORTING PROCEDURES

7.5.1. Reportable Events

- Any SAE
- Any Device Deficiency that might have led to a SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate
- New findings/updates in relation to already reported events.
- UADE

7.5.2. Reporting Timelines

The Investigator is to report reportable events immediately but not later than 1 business day after awareness of the event.

Novocure must report to the [redacted]

[redacted]

7.5.3. Reporting of Pregnancy

Pregnancy will be reported to Novocure immediately but not later than 1 business day after awareness of the pregnancy. [redacted]

7.6. STUDY HALTING RULES

Novocure may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons. A Principal Investigator, EC/IRB, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible. If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, Novocure shall suspend the clinical investigation while the risk is assessed. Novocure shall terminate the clinical investigation if an unacceptable risk is confirmed.

Novocure shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation [redacted]

If, for any reason, Novocure suspends or prematurely terminates the investigation at an individual investigation site, Novocure shall inform the responsible regulatory authority as appropriate and ensure that the IRB/EC is notified, either by the Principal Investigator or by Novocure. If the suspension or premature termination was in the interest of safety, Novocure shall inform all other Principal Investigators.

If suspension or premature termination occurs,

[redacted]

7.7. SAFETY OVERSIGHT

Safety oversight will be under the direction of a DMC composed of individuals with the appropriate expertise, [redacted]. The DMC will meet [redacted] to assess safety and

efficacy data on each arm of the study. [redacted] Specifically, DMC review will be performed [redacted]

The DMC will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DMC. At this time, each data element that the DMC needs to assess will be clearly defined. The DMC will provide its input to the Novocure, the Study Sponsor.

8. CLINICAL MONITORING

Study monitoring will be performed by [redacted] and according to a detailed monitoring plan. Study monitoring functions will be in compliance with recognized Good Clinical Practices, EN ISO 14155, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. § 812.46. The principal function of the clinical monitor is to observe and assess the quality of the clinical study. The monitor's duties include: [redacted]

On-site monitoring visits will take place at each center, during the course of the study [redacted], at the frequency defined in the monitoring plan, and a final visit at the close of the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure [redacted]

[redacted]

[redacted]

Beyond reviewing safety data, the DMC will determine at the pre-specified interim analysis if the study should be stopped for efficacy purposes (further details are provided below).

9. STATISTICAL CONSIDERATIONS

9.1. STATISTICAL AND ANALYTICAL PLANS

A statistical analysis plan (SAP) [redacted] detailed statistical analysis details for each of the study endpoints.

9.2. STATISTICAL HYPOTHESES

The null hypothesis is that the overall survival is the same in the two study groups, i.e., hazard ratio=1. The alternative hypothesis is that overall survival is not the same, i.e., hazard ratio≠1.

9.3. ANALYSIS DATASETS

All analyses except for safety will be performed on the Intention-to-Treat (ITT) dataset (i.e. all randomized patients).

OS, PFS, local PFS and ORR will also be performed on a modified ITT dataset (i.e. patients who received at least one complete cycle of study treatments)

The safety analysis dataset will include all patients who received any amount of TTFields in the experimental arm, and any amount of chemotherapy in the control arm.

9.4. DESCRIPTION OF STATISTICAL METHODS

9.4.1. General Approach

[redacted]

9.4.2. Analysis of the Primary Efficacy Endpoint

[redacted]The statistical hypothesis will be tested by comparing Kaplan-Meier overall survival curves of the two groups using a log-rank test.

In order to allow for two efficacy analyses of the primary endpoint in the study the alpha level used at each time point was calculated according to [redacted] method using the [redacted] function (approximately [redacted] at the interim analysis and [redacted] at the final analysis).

[redacted]

9.4.3. Analysis of the Secondary Endpoint(s)

A hierarchical approach will be used to first test the primary endpoint of OS and then the secondary endpoint of progression free survival to avoid problems with statistical multiplicity [redacted]

[redacted]

Progression free survival

This secondary endpoint would be achieved if the PFS will be significantly greater in the TTFields plus the chemotherapy arm than in the chemotherapy alone arm by comparing Kaplan-Meier PFS curves of the two groups using a [redacted]. [redacted]

[redacted]

Local progression-free survival

[redacted]

This secondary endpoint would be achieved if the local PFS will be significantly greater in the TTFields plus the chemotherapy arm than in the chemotherapy alone arm by comparing Kaplan-Meier local PFS curves of the two groups using [redacted]

[redacted]

1-Year overall survival rates

The analyses will be performed based on the Kaplan-Meier estimated proportions of patients who are alive at 12 months in both arms of the study. These secondary endpoints will be tested [redacted], assuming the TTFields plus the chemotherapy arm would have higher 1-year survival rate than the chemotherapy alone arm.

Objective Radiological Response Rate

The objective response rate of the tumor will be assessed using CT scans and according to the revised RECIST Criteria V1.1 as the proportion of patients with partial- or complete response between the time of randomization and the time of death. Unevaluable and missing follow up data will be removed from the analysis. The best response rate will be compared between the two arms of the study using [redacted] assuming the TTFields plus the chemotherapy arm would have a higher response rate than the chemotherapy alone arm.

Quality of life

Quality of life (QoL) will be assessed using the EORTC QLQ C-30 questionnaire with EORTC QLQ-PAN26 (Pancreatic Cancer symptom) supplement. [redacted]

[redacted]

Pain-free survival

This secondary endpoint would be achieved if TTFields concomitant with chemotherapy prolongs the pain-free survival of patients, compared to chemotherapy treatment alone. We will compare Kaplan-Meier curves of the two groups using a log-rank with a 5% type I error.

Pain-free survival will be measured as the duration between the time of randomization until a greater than or equal to two-point decline from a baseline measurement in a patient self-reported visual analogue scale (VAS) is recorded or death, whichever occurs first.

Puncture-free survival

This secondary endpoint would be achieved if TTFields concomitant with chemotherapy prolongs puncture-free survival of patients, compared to chemotherapy treatment alone. We will compare Kaplan-Meier curves of the two groups using [redacted] Puncture-free survival will be measured as the duration between randomization until the first need for paracentesis or death, whichever occurs first.

Resectability rate

This secondary endpoint will be measured as the percentage of patients whose tumors were deemed resectable by a multi-disciplinary team (MDT) consisting of at least a surgeon, a medical oncologist and a radiologist, prior to disease progression. Resectability rate will be compared between groups [redacted] assuming the TTFields plus the chemotherapy arm would have a higher resectability rate than the chemotherapies alone arm.

Toxicity

This secondary endpoint will be measured as the severity and frequency of reported adverse events in patients treated with TTFields concomitant with chemotherapy compared to patients treated with chemotherapy alone.

9.4.4. Safety Analyses

[redacted]

9.4.5. Additional Sub-Group Analyses

[redacted]

9.4.6. Multiple Comparison/Multiplicity

No adjustment will made for multiple hypothesis testing.

9.5. SAMPLE SIZE

[redacted]

[redacted]

[redacted]

The assumptions used in the sample size calculations will be evaluated at the interim analysis [redacted]

[redacted]

[redacted]

10. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this study, in compliance with ISO 14155, ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. [redacted]

[redacted]

[redacted]

11. QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

12. ETHICS/PROTECTION OF HUMAN SUBJECTS

12.1. ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6, EN ISO 14155 and/or local regulations, whichever provides most protection to human subjects.

12.2. ETHICS COMMITTEE / INSTITUTIONAL REVIEW BOARD

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the [redacted]

12.3. INFORMED CONSENT PROCESS

12.3.1. Consent Forms Provided to Participants

[redacted]

[redacted]

12.3.2. Consent Procedures and Documentation

Prior to carrying out any protocol-specific procedures, investigators or designated staff will [redacted] All patients must provide written informed consent prior to registration and treatment.

[redacted]

Informed consent will comply with EN ISO 14155, 21 C.F.R 50 and other regional and national laws as applicable.

12.4. PARTICIPANT AND DATA CONFIDENTIALITY

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices, as applicable. If the subject has not already done so, personnel of the relevant participating Center must try to obtain acknowledgment before the patient participates in this study. The Center's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/EC and Privacy Board.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor and its agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor or representatives of the EC/IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local EC/IRB and Institutional regulations. [redacted]

Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites, CROs and sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in a certified storage place.

13. DATA HANDLING AND RECORD KEEPING

13.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical study staff at the site [redacted] The [redacted] is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or

corrections, cross out the original entry with a single line, initial and date the change and add reason for correction. Do not erase, overwrite, or use correction fluid or tape on the original.

[redacted]

[redacted]

13.2. STUDY RECORDS RETENTION

Sites will retain organized subject, laboratory, and study device inventory records relating to the study for the period of time required by applicable federal law or regulation. [redacted]

13.3. PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or any study procedure. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. [redacted]

[redacted]

13.4. PUBLICATION AND DATA SHARING POLICY

The results of the clinical investigation will be made publicly available in case of positive or negative results following the completion of the study.

14. STUDY ADMINISTRATION

14.1. STUDY LEADERSHIP

[redacted]

15. CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

16. INVESTIGATOR SIGNATURE PAGE

[redacted]

[redacted]

[redacted]

_____	_____	_____
PI Name	Signature	Date

[redacted]

17. LITERATURE REFERENCES

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APPENDIX 1 CLINICAL PRACTICE GUIDELINES: OPTIMIZING THE TRANSDUCER ARRAY LAYOUT IN TTFIELDS-TREATED PATIENTS (PANCREATIC MALIGNANCIES)

APPENDIX 2 LIST OF INVESTIGATORS