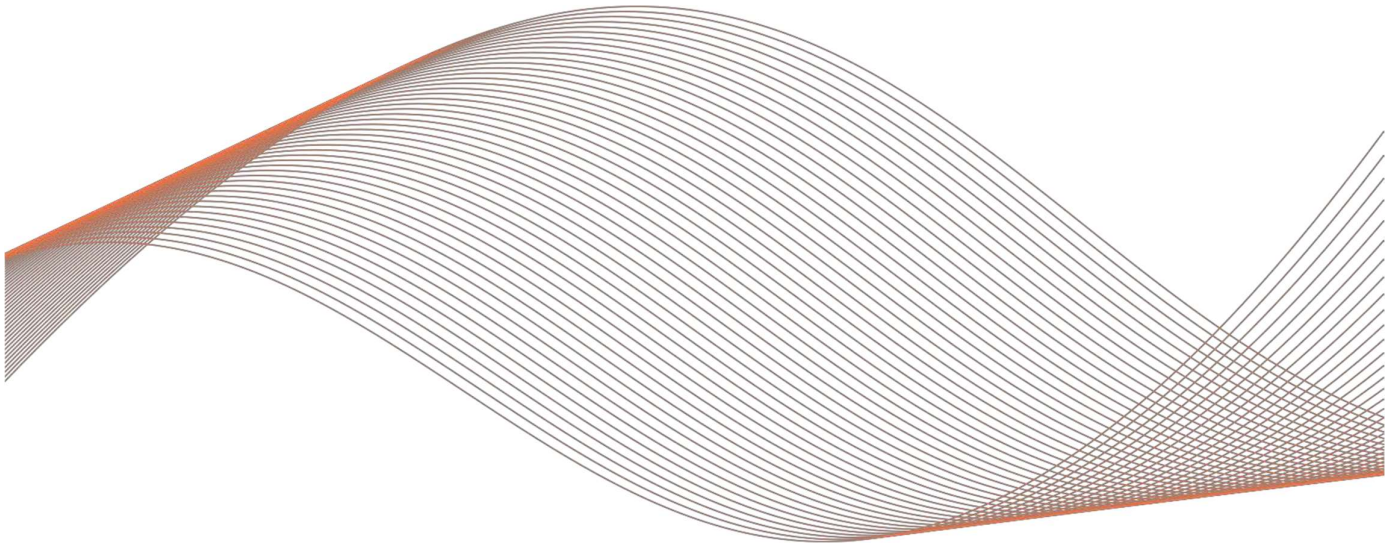
Optune Pax® for Locally Advanced Pancreatic Cancer

Physician Instructions for Use



This manual is intended for physicians prescribing the use of Optune Pax® for Locally Advanced Pancreatic Cancer

Caution: Federal law restricts this device to sale by or on the order of a physician

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1 INDICATION FOR USE

Optune Pax is intended for the treatment of adult patients with locally advanced pancreatic cancer, concomitant with gemcitabine and nab-paclitaxel.

2 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS & NOTICES

Contraindications

Do not use Optune Pax if you have an electrical implant. Use of Optune Pax together with electrical implants has not been tested and may lead to malfunctioning of the implanted device.

Do not use Optune Pax if you are known to be sensitive to gels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Pax may commonly cause increased redness and itching and rarely may even lead to severe allergies such as a fall in blood pressure and breathing difficulty.

Warnings

Warning – Use Optune Pax only after receiving training from Novocure or other qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Your training will include a detailed review of the patient user manual and practice in the use of the device. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune Pax without receiving this training can result in breaks in treatment and may rarely cause increased skin irritation, open sores on your abdomen or back, or allergic reactions or even an electric shock.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), contact your doctor who will prescribe you high potency topical steroids (hydrocortisone cream) to use when replacing the transducer arrays. Using this cream will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin breakdown, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals.

Warning - All device servicing must be performed by qualified and trained personnel. No modification of this equipment is allowed. If you attempt to open and service the device yourself, you may cause damage to the device. You could also get an electric shock by touching the inner parts of the device.

Warning - The transducer arrays are for single use and should not be taken off your body and then put back on again. If you put a used transducer array back on again, it may not stick well to your skin and the device could turn off. The transducer arrays should not be re-used. Re-use of transducer arrays can lead to poor contact with the skin and may cause the device to alarm and stop working. Re-use of transducer arrays can lead to worsening of the skin inflammation and rarely even to local infection. If you suffer from an infection on your skin (pus, swelling and warmth) consult with your doctor immediately

Precautions

Caution - Do not use Optune Pax with any parts that did not come with the device, that were not sent to you by the device manufacturer, or that were not given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment.

Caution - Do not use Optune Pax if any parts look damaged (such as torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case, opening in power supply). Use of damaged components can damage the device and cause a break in treatment.

Caution - Do not get the device, transducer arrays or other parts wet. Getting the device wet may damage it, preventing you from receiving treatment. Getting the transducer arrays very wet is likely to cause them to come loose from your skin. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that Optune Pax power switch is in the OFF position. Disconnecting transducer arrays with the power switch in the ON position may cause a device alarm to go off and could damage the device.

Caution - If you have an underlying serious skin condition on the abdomen, discuss with your doctor whether this may prevent or temporarily interfere with Optune Pax treatment.

Caution - Do not use Optune Pax if you are pregnant, you think you might be pregnant or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Pax was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant, or if it will be effective.

Caution – There is a hazard of falling due to entanglement in the connection cable. You may consider clipping the cable to your belt.

Caution – The device dropping on the user may result in injury.

Notices

Notice - Optune Pax and transducer arrays will activate metal detectors.

Notice - If you plan to be away from home for more than 1 hour, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply, you may have a break in your treatment.

Notice - Make sure you have at least 12 extra transducer arrays at all times. This will last until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays on time, you may have a break in your treatment.

Notice - Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1 hour from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment.

Notice - You should carry the Troubleshooting Guide from the Patient Information and Operation Manual at all times. This guide is necessary to ensure Optune Pax works properly. If you do not work the device correctly, you may have a break in your treatment.

Notice - Do not block the device vents located on the front and back of the device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this

happens, unblock the vents, wait 5 minutes and restart the device. In case the vents are blocked with pet hair/dust, return the device to the manufacturer for service.

Notice - Do not block the battery charger vents located on the sides of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging. In case the vents are blocked with pet hair/dust, return the battery charger to the manufacturer for service.

Notice - Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice - Keep the device out of the reach of children and pets.

Notice – The device has a cord that may cause tripping when connected to an electric socket.

Notice – Do not cover the device or power supply. This can lead to overheating of the device and cause superficial thermal injury.

3 DEVICE DESCRIPTION

Optune Pax is a portable, battery-powered or mains-powered device that produces alternating electrical fields, called tumor treating fields ("TTFields") within the body. TTFields are applied to the patient by non-invasive, electrically-insulated surface transducer arrays that are placed on the patient's abdomen and connected to the Electric Field Generator. TTFields physically disrupt the rapid cell division exhibited by cancer cells.

Optune Pax is comprised of two main components: (1) an Electric Field Generator (the Optune Pax device) and (2) Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included: power supply, battery, battery charger, connection cable and carrying bag.

Optune Pax delivers TTFields at 150 kHz to the entire abdominal cavity. The device's treatment parameters are preset by Novocure. No adjustments can be made to the device by the physician or patient. Patients are initially trained on the use of the device by a Novocure device support specialist (DSS). The patient should learn to switch out and recharge depleted device batteries, connect to an external power supply and replace the transducer arrays every 3-4 days according to the array layout recommended by you, their physician.

The physician should follow the *Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies*) to select the optimized layout for their patient. However, at their discretion, the physician may select an alternative configuration tailored to the patient's needs or may include more than one recommended layout in the prescription (For example, substituting large arrays with smaller ones for patients who prefer them).

Optune Pax is designed to accompany the patient throughout their daily activities for continuous treatment, with short breaks for personal needs, such as to shower or replace the arrays. Patients can carry the device and battery in the specially designed bag to receive continuous treatment without changing their daily routine.

Optune Pax should be used for at least 12 hours per day, on average.

4 PRINCIPLES OF OPERATION

Optune Pax produces TTFields within the human body through transducer arrays placed on the abdomen. TTFields physically disrupt the rapid cell division exhibited by cancer cells.[1] TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 150 kHz for pancreatic cancer).

In contrast, TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult cells proliferate very slowly, if at all, they are hypothesized to be little affected by TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the lungs), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the abdomen, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. In addition, various in vitro experiments have demonstrated abnormal mitotic process outcomes following TTFields application, which can lead to different forms of cellular death. Specifically, the abnormal chromosome segregation induced by TTFields can lead to mitotic cell death, or to the formation of abnormal daughter cells experiencing endoplasmic reticulum (ER) stress and autophagy, leading them to downstream immunogenic cell death. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature (Kirson et al. 2004; Giladi et al 2015).

5 PRECLINICAL DATA

TTFields have been shown in vitro to inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to inhibit different cancer cell types, due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase.[2]

Specifically, TTFields have been shown to inhibit pancreatic cancer cells in vitro at a frequency of 150 kHz and an intensity of 1 V/cm. Based on realistic finite element mesh simulations, Novocure has concluded that therapeutic TTFields intensities can be generated in the abdomen of large animals and humans.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for TTFields has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

6 CLINICAL DATA

Pilot Clinical Study in Locally Advanced Pancreatic Cancer

The PANOVA study was a multicenter, non-randomized, open-label pilot study designed to assess the safety and preliminary effectiveness of TTFields therapy when used together with gemcitabine or gemcitabine + nab-paclitaxel (GnP) in advanced pancreatic adenocarcinoma (a mix of locally-advanced and metastatic patients). The primary endpoint was safety. Secondary endpoints were progression free survival (PFS), overall survival (OS) and usage rates of TTFields therapy. Forty (40) patients with advanced pancreatic cancer were enrolled. All patients had unresectable tumors, an ECOG performance score of 0-1, and no prior therapy. Study subjects received continuous daily TTFields at 150 kHz (18 hours per day recommended) to the abdomen together with standard doses of either gemcitabine or GnP per their approved package inserts. TTFields treatment continued until radiological disease progression, death or unacceptable device-related adverse events. Chemotherapy continued until disease progression, death or unacceptable toxicity.

The results of the pilot PANOVA study demonstrated the safety and effectiveness of TTFields therapy in an advanced pancreatic cancer population.

- Safety: In the TTFields + gemcitabine cohort, fourteen patients (70%) had serious adverse events (AEs) during the study period. Ten patients (50%) had treatment-related skin toxicity, of which only 2 were grade 3, and both resolved with appropriate treatment. No TTFields-related serious AEs were reported. In the TTFields+GnP cohort, ten patients (50%) had serious AEs during the study period. Eleven patients (55%) had treatment-related skin toxicity, of which 5 had grade 3 toxicity. No TTFields-related serious AEs were reported.

- Preliminary Efficacy: In the TTFields+gemcitabine cohort, the median PFS was 8.3 months (95% CI 4.3, 10.3). In locally-advanced patients specifically, the median PFS was 10.3 months. The median OS was 14.9 months (95% CI 6.2, NA) in the TTFields+gemcitabine cohort; 1-year survival rate was 55% (95% CI 29, 75). In locally-advanced patients specifically, the 1-year survival rate was 86%. In the TTFields+GnP cohort, the median PFS was 12.7 months (95% CI 5.4, NA). In locally-advanced patients specifically, the median PFS was not reached (PFS6 was 87.5%). Median OS was not reached for the TTFields+GnP cohort; the 1-year survival rate was 72% (95% CI 44, 88). In locally-advanced patients specifically, the 1-year survival rate was 87.5%.

- Device Usage: In the TTFields+GnP group, the median TTFields usage rate was 12.2 hours per day. The median TTFields usage rate in the gemcitabine alone cohort was 14 hours per day. In patients experiencing a grade 3 skin toxicity, there was a median decrease in daily usage of the device of 12.5% (3 hours).

Pivotal Clinical Study in Locally Advanced Pancreatic Cancer – The PANOVA-3 Study

Study Design: The PANOVA-3 study was a pivotal, randomized, open-label, two-arm, multi-center study evaluating the effectiveness and safety of Optune Pax concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer. GnP is approved for the treatment of pancreatic cancer, and is one of only a few accepted treatments for patients with locally-advanced pancreatic cancer. Gemcitabine and nab-paclitaxel were administered according to their approved package inserts in both study arms. Subjects in the study were randomized in a 1:1 ratio to receive TTFields together with GnP (TTFields+GnP Arm) or GnP (GnP Alone Arm). A total of 138 sites enrolled 571 subjects globally (285 in the TTFields+GnP Arm; 286 in the GnP Alone Arm).

Eligibility Criteria: The inclusion and exclusion criteria were as follows:

Inclusion Criteria

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 (per Al-Hawary MM, et al., Radiology 201413; NCCN Clinical Practice Guidelines in Oncology))*
    a. *Head/uncinate process:*
        i. *Solid tumor contact with SMA>180°*
        ii. *Solid tumor contact with the CA>180°*
        iii. *Solid tumor contact with the first jejunal SMA branch*
        iv. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
        v. *Contact with most proximal draining jejunal branch into SMV*
    b. *Body and tail:*
        i. *Solid tumor contact of >180° with the SMA or CA*
        ii. *Solid tumor contact with the CA and aortic involvement*
        iii. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
    c. *No distant metastasis, including non-regional lymph node metastasis*
    d. *No borderline resectable (per Al-Hawary MM, et al., Radiology 201413)*
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 independently or with the help of a caregiver*
8. *Signed informed consent form for the study protocol*

Exclusion Criteria

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 nonmelanomatous 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 109/L and platelet count <100 x 109/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. Subjects 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 subject to receive protocol therapy*
f. *History of any psychiatric condition that might impair subject'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 subjects 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 subjects 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*

Study Procedures:

TTFields+GnP Arm: Participants received Optune Pax together with gemcitabine and nab-paclitaxel (GnP). TTFields therapy was initiated within 7 days of randomization, and ± 3 days of administering GnP. Participants received uninterrupted multiple single month courses of continuous TTFields therapy. Treatment was to be stopped in cases of intolerable toxicity or disease progression in the abdomen ("local disease progression"). The recommended transducer array layout was determined by the investigator for each participant using the *Clinical Practice Guidelines-Layout Optimization in Pancreatic Malignancies*, which was developed to maximize TTFields intensity in the area of maximal disease burden in the abdomen (based on the patient's baseline CT scan). After being trained on how to use the device and place the arrays, participants continued TTFields therapy at home. Participants were instructed to replace the arrays two to three times per week. At array replacement, the skin was re-shaved if needed, and treated using topical steroids or antibiotic creams, if recommended. The concomitant chemotherapy, GnP, was administered as described below.

GnP Alone Arm: Participants received gemcitabine and nab-paclitaxel according to their approved package inserts. Gemcitabine was administered as follows: 1000 mg/m^2 over 30-minute infusion administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment. Nab-paclitaxel was administered as follows: 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment.

Follow-Up: During the treatment period, participants were seen ever four weeks until local disease progression, with the following assessments performed: concomitant medication recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry including CA-19-9, AE and device deficiency collection and recording, documentation of ascitic fluid drainage (if applicable), pain assessment using VAS and device usage time assessment (only for subjects in the TTFields+GnP Arm). In addition, every eight weeks, the following assessments were performed until local disease progression: CT/MRI scan of the chest and

abdomen, assessment of local and distant disease status per RECIST v1.1. Furthermore, EORTC QLQ C30 questionnaires with the PAN26 addendum were completed by the participating subjects. In addition, bone scan and/or CT/MRI of the brain were performed if clinically indicated. One month following treatment discontinuation, the following assessments were performed: concomitant medications recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry panel including CA-19-9, AE and device deficiency collection and recording and documentation of ascitic fluid drainage were performed during this visit. In addition, following local disease progression, telephone follow-up was conducted every four weeks for survival status until study completion or death.

Analyses: Primary and secondary effectiveness endpoints were analyzed in the ITT (Intent-to-Treat) and modified Per Protocol (mPP)[1] populations. The ITT population includes all 571 randomized participants (285 in the TTFields+GnP arm and 286 in the GnP Alone arm). The mPP population includes only those participants who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms), and for the TTFields+GnP Arm, also received at least 4 weeks (28 days) of TTFields therapy (198 in the TTFields+GnP arm and 207 in the GnP Alone arm). Safety endpoints were analyzed in the Safety population, which included all 547 randomized participants who received any amount of TTFields or GnP treatment (274 participants in the TTFields+GnP arm, and 273 participants in the GnP Alone arm).

Protocol Deviations: Protocol deviations were categorized per the definitions set forth in the ICH E3 Guideline. Of the deviations categorized as "Major and Important", eleven were identified as deviations with the potential to impact study outcomes and/or subject safety, and involved either enrollment of patients who did not meet the eligibility criteria or incorrect dose or administration timing of a study treatment. Following a careful evaluation, it was determined that these deviations did not impact study outcomes and/or subject safety. Overall, protocol deviations were generally balanced between the two arms. The majority of protocol deviations involved failure to report SAEs within 24 hours or missed/out of window assessments that in many cases were included at future visits, allowing for an appropriate clinical and safety evaluation during the study period.

Participant Demographics and Baseline Characteristics: Demographics and baseline characteristics were well balanced between treatment groups. Overall, participants' median age was 67 years (range: 31-90 years), with 3.9% ECOG performance score of 2, 57.6% with score of 1 and 38.5% with score of 0. The median time from diagnosis to study enrollment was 3.6 weeks (range: 0.1- 53.7).

[1] *Referred to as the Modified Intent-to-Treat (mITT) population in the PANOVA-3 protocol and SAP.*

Demographics and Baseline Characteristics – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Age (Years) Median (range)	67 (31, 90)	67.5 (40, 88)	67 (31, 90)
Gender, n (%)			
Male	147 (51.6)	125 (43.7)	272 (47.6)
Female	138 (48.4)	161 (56.3)	299 (52.4)
Race, n (%)			
American Indian or Alaska Native	9 (3.2)	4 (1.4)	13 (2.3)
Asian	44 (15.4)	44(15.4)	88 (15.4)
Black or African American	16 (5.6)	14 (4.9)	30 (5.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	202 (70.9)	204 (71.3)	406 (71.1)
Other	3 (11)	5 (1.7)	8 (1.4)
Not Reported	11 (3.9)	15 (5.2)	26 (4.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (11.2)	22 (7.7)	54 (9.5)
Not Hispanic or Latino	238 (83.5)	247 (86.4)	485 (84.9)
Not Reported/Unknown	15 (5.3)	17 (5.9)	32 (5.6)
Region, n (%)			
North America	123 (43.2)	125 (43.7)	248 (43.4)
Eastern Europe	43 (15.1)	42 (14.7)	85 (14.9)
Western Europe and Israel	62 (21.8)	61 (21.3)	123 (21.5)
Rest of the World	57 (20.0)	58 (20.3)	115 (20.1)
ECOG Performance Status, n (%)			
0	109 (38.2)	111 (38.8)	220 (38.5)
1	166 (58.2)	163 (57.0)	329 (57.6)
2	10 (3.5)	12 (4.2)	22 (3.9)
BMI Group, n (%)			
< 25 kg/m^2	166 (58.2)	174 (60.8)	340 (59.5)
≥ 25 kg/m^2	117 (41.1)	108 (37.8)	225 (39.4)
CA-19.9, n (%)			
Low (≤37 U/mL)	48 (16.8)	44 (15.4)	92 (16.1)
Moderate (38-1,000 U/mL)	140 (49.1)	152 (53.1)	292 (51.1)
High (>1,000 U/mL)	88 (30.9)	79 (27.6)	167 (29.2)
Untested	9 (3.2)	11 (3.8)	20 (3.5)
Target Lesion Site, n (%)			
Head of Pancreas	164 (57.5)	160 (55.9)	324 (56.7)
Body of Pancreas	82 (28.8)	81 (28.3)	163 (28.5)
Tail of Pancreas	9 (3.2)	19 (6.6)	28 (4.9)
	55 (19.3)	49 (17.1)	104 (18.2)
Other			
Multiple regions in pancreas	26 (9.1)	22 (7.7)	48 (8.4)
Extra-pancreatic	29 (10.2)	27 (9.4)	56 (9.8)

Pancreatic Cancer History – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Time Since Initial Pathological Diagnosis (weeks) Median (range)	3.7 (0.1, 53.7)	3.6 (0.1, 21.4)	3.6 (0.1, 53.7)

Histologic Subtype at Baseline – ITT Population

Histology at Baseline	TTFields + GnP (N=285)	GnP Alone (N=286)
	n (%)	
Pancreatic Adenocarcinoma, Not Otherwise Specified	251 (88)	258 (90)
Adenosquamous carcinoma	2 (1)	1 (0.3)
Ductal adenocarcinoma	27 (9)	24 (8)
Histology not further specified	5 (2)	3 (1)

Treatment exposure to GnP was similar between the two arms, both in terms of number of cycles received and duration of exposure. Median duration of TTFields exposure was similar, at 27.6 weeks, with average daily usage 59.3%, and median daily usage 62.1%. The most common reason for discontinuation of concomitant treatments in both arms was disease progression or clinical deterioration. The most common reason for TTFields discontinuation was local disease progression.

Exposure to GnP by Study Arm (Safety Population)

	TTFields + GnP (N=274)	GnP Alone (N=273)
Gemcitabine Number of Cycles Received Median (range)	6.0 (1.0, 57.0)	6.0 (1.0, 30.0)
Duration of Exposure (weeks) Median (range)	24.1 (0.1, 232.4)	22.1 (0.1, 134.1)
Nab-paclitaxel Number of Cycles Received Median (range)	6.0 (1.0, 57.0)	5.0 (1.0, 30.0)
Duration of Exposure (weeks) Median (range)	23.0 (0.1, 232.4)	21.4 (0.1, 134.1)

TTFields Therapy Usage Duration (Safety Population)

	TTFields + GnP (N=274)
Duration of Exposure (weeks)	
Median (range)	27.6 (0.1, 234.4)
Average Usage	
Mean (SD)	59.3 (21.2)
Median (range)	62.1 (0, 99)
Average Usage, (%)	
≤75%	200 (73.0)
>75%	74 (27.0)

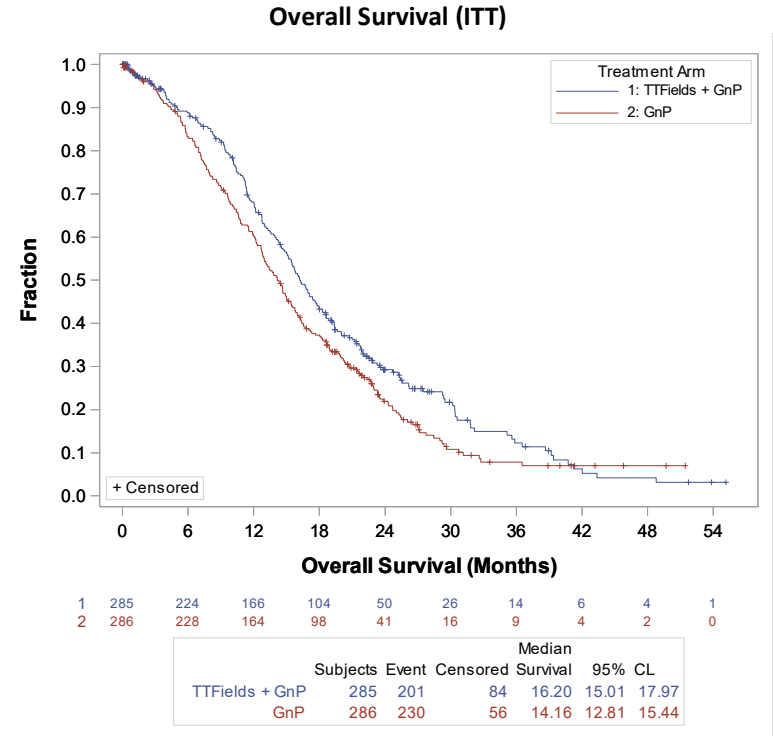
Effectiveness Results:

Analysis Populations

- Intent to Treat (ITT): All randomized patients, regardless of whether the treatment was received. The ITT population consists of 285 patients in the TTFields+GnP arm and 286 patients in the GnP Alone arm.
- Modified Per Protocol (mPP): All patients who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms) and at least 4 weeks (28 days) of TTFields therapy (in the TTFields+GnP arm). The mPP population consists of 198 patients in the TTFields+GnP arm and 207 patients in the GnP Alone arm.

Primary Endpoint – Overall Survival (OS)

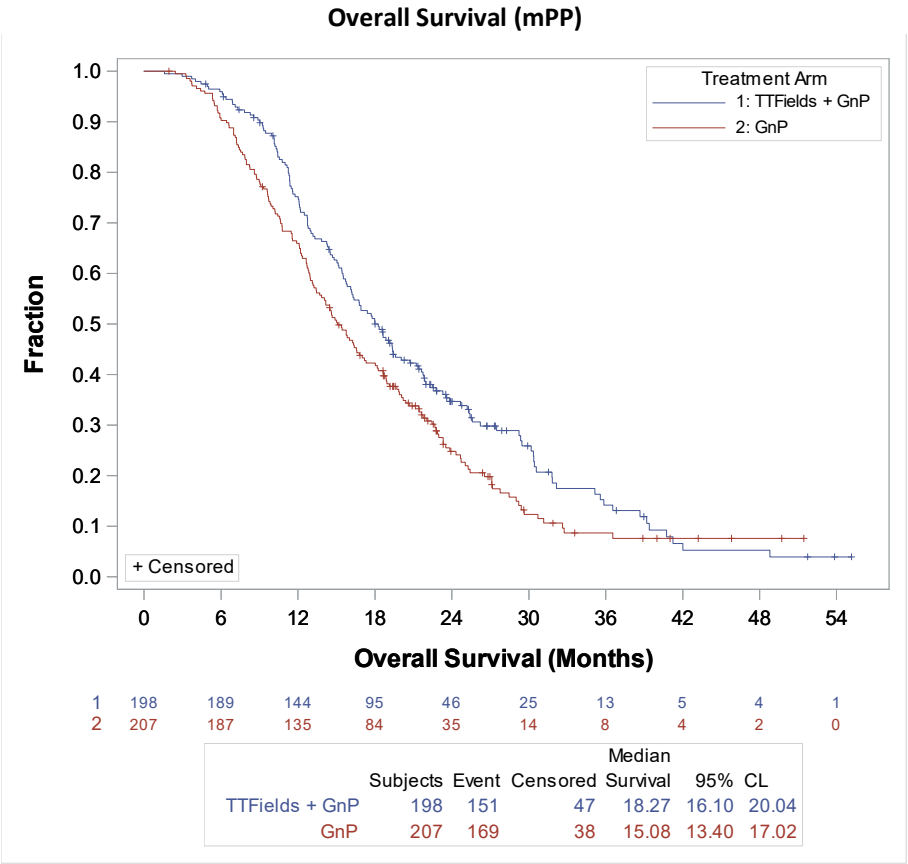
***Overall Survival (ITT)*:** Overall survival was measured from the date of randomization to the date of death (in months). At the time of analysis, patients lost to follow-up or still on protocol follow-up were censored at the last date when they were known to be alive. The OS at the final analysis in the ITT population met the threshold for statistical significance which was pre-defined as p=0.04794. A statistically significant difference in the OS distribution between study arms was observed (log-rank P=0.039). The median OS in the TTFields+GnP arm was 16.2 months (95% CI 15.0-18.0) compared to 14.2 months (95% CI 12.8-15.4) in the GnP Alone arm. A 2-month improvement in median OS was observed in favor of the TTFields+GnP arm. The hazard ratio (HR) for OS was 0.82 (95% CI 0.68 – 0.99). A descriptive analysis of the Kaplan-Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	88.8 (84.3, 92.1)	83.3 (78.3, 87.2)	6.6
9 Months	82.4 (77.1, 86.6)	71.6 (65.9, 76.5)	15.1
12 Months	68.1 (62.0, 73.5)	60.2 (54.2, 65.7)	13.1
24 Months	29.2 (23.4, 35.2)	21.9 (16.9, 27.3)	33.3
36 Months	12.3 (7.6, 18.2)	7.8 (4.4, 12.5)	NE
42 Months	6.3 (2.8, 11.7)	7.0 (3.7, 11.6)	NE
48 Months	4.2 (1.5, 9.2)	7.0 (3.7, 11.6)	NE
54 Months	3.1 (0.9, 7.8)		NE
Log Rank P-value	0.039		
Hazard Ratio (95% CI)	0.82 (0.68, 0.99)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Overall Survival (mPP): OS was also analyzed in the mPP population. The median OS in the TTFields+GnP Arm was 18.3 months (95% CI 16.1-20.0) compared to 15.1 months (95% CI 13.4-17.0) in the GnP Alone Arm. A statistically significant difference in the overall survival distribution between treatment arms was observed (log-rank P=0.023). A 3.2 months improvement in median OS was observed in favor of the TTFields+GnP arm. The HR for OS was 0.77 (95% CI 0.62-0.97). A descriptive analysis of the Kaplan–Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.

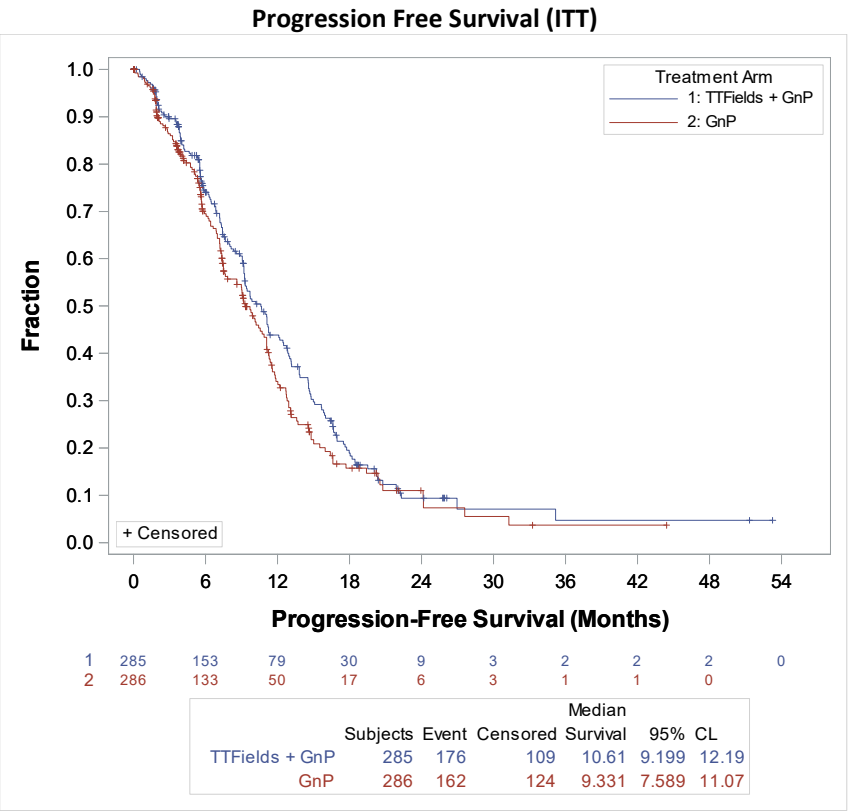


	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	96.0 (92.1, 98.0)	90.8 (85.9, 94.0)	5.7
9 Months	90.3 (85.3, 93.7)	78.2 (71.9, 83.2)	15.6
12 Months	75.2 (68.5, 80.7)	65.9 (59.0, 72.0)	14.0
24 Months	34.7 (27.8, 41.7)	24.8 (18.8, 31.3)	39.7
36 Months	14.2 (8.5, 21.3)	8.7 (4.6, 14.3)	NE
42 Months	6.6 (2.7, 13.0)	7.6 (3.8, 13.2)	NE
48 Months	5.3 (1.9, 11.4)	7.6 (3.8, 13.2)	NE
54 Months	4.0 (1.1, 9.8)		NE
Log Rank 2-sided P-value	0.023		
Hazard Ratio (95% CI)	0.77 (0.62, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Key Secondary Endpoint – Progression Free Survival (PFS)

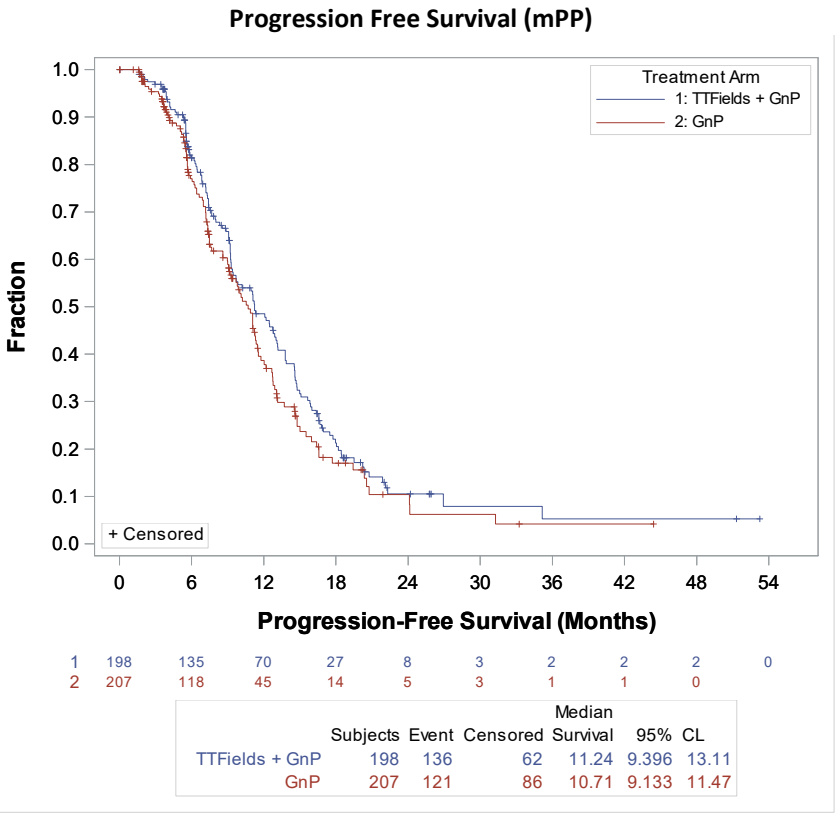
***Progression Free Survival (ITT)*:** Treatment with TTFields+GnP. showed no statistically significant improvement in PFS compared to GnP Alone (logrank test p = 0.137). The hazard ratio was 0.85 (95% CI 0.68 – 1.05). Median PFS was 10.6 months (95% CI: 9.2 – 12.2) with TTFields+GnP compared to 9.3 months (95% CI: 7.6 – 11.1) with GnP Alone.



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Progression-Free Rate % (95% CI)			
6 Months	74.0 (67.9, 79.2)	69.5 (63.0, 75.1)	6.5
9 Months	60.5 (53.7, 66.7)	54.0 (46.9, 60.5)	12.2
12 Months	43.9 (36.9, 50.6)	34.1 (27.1, 41.2)	28.8
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Log Rank 2-sided P-value	0.137		
Hazard Ratio (95% CI)	0.85 (0.68, 1.05)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

***Progression-Free Survival (mPP)*:** In the mPP population, the median progression-free survival (PFS) per RECIST v1.1 was 11.2 months (95% CI: 9.4–13.1) in participants treated with TTFields + GnP, compared to 10.7 months (95% CI: 9.1–11.5) with GnP Alone (HR: 0.84; 95% CI: 0.66–1.08; log-rank P = 0.183).

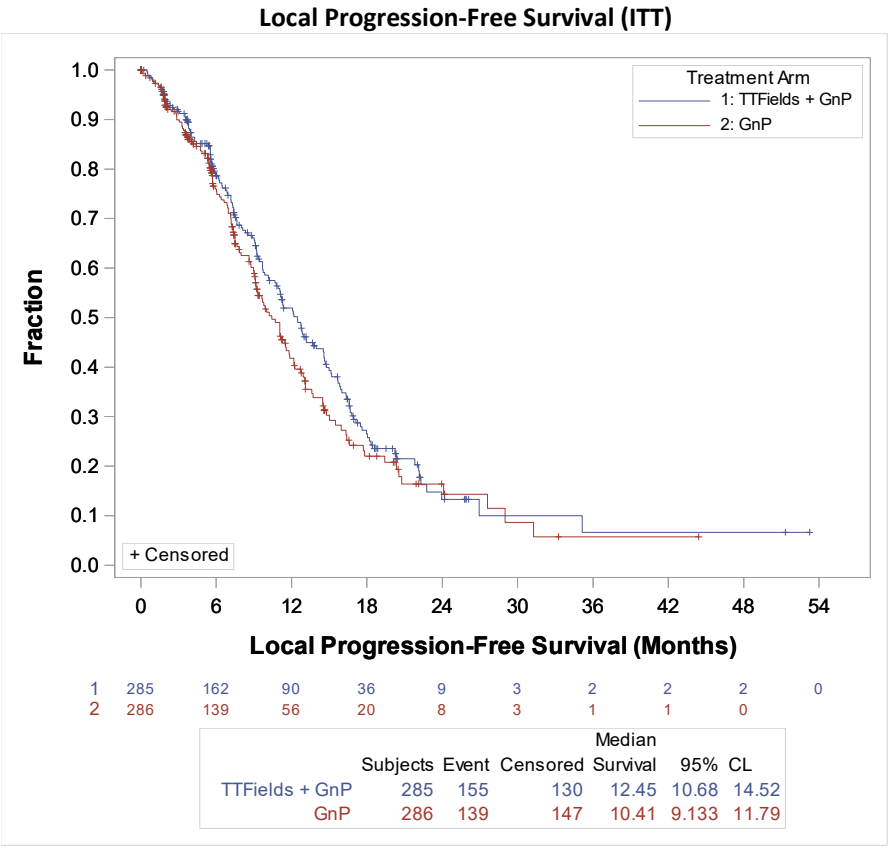


	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
PFS Survival Rate % (95% CI)			
6 Months	81.4 (74.9, 86.3)	77.0 (70.0, 82.6)	5.7
9 Months	65.9 (58.2, 72.5)	59.6 (51.5, 66.8)	10.5
12 Months	48.5 (40.5, 56.0)	38.7 (30.5, 46.8)	25.4
24 Months	10.5 (5.6, 17.1)	10.4 (4.9, 18.2)	NE
36 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
42 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
48 Months	5.2 (1.3, 13.3)	0	NE
Log Rank 2-sided P-value	0.183		
Hazard Ratio (95% CI)	0.84 (0.66, 1.08)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Additional Secondary Effectiveness Endpoints

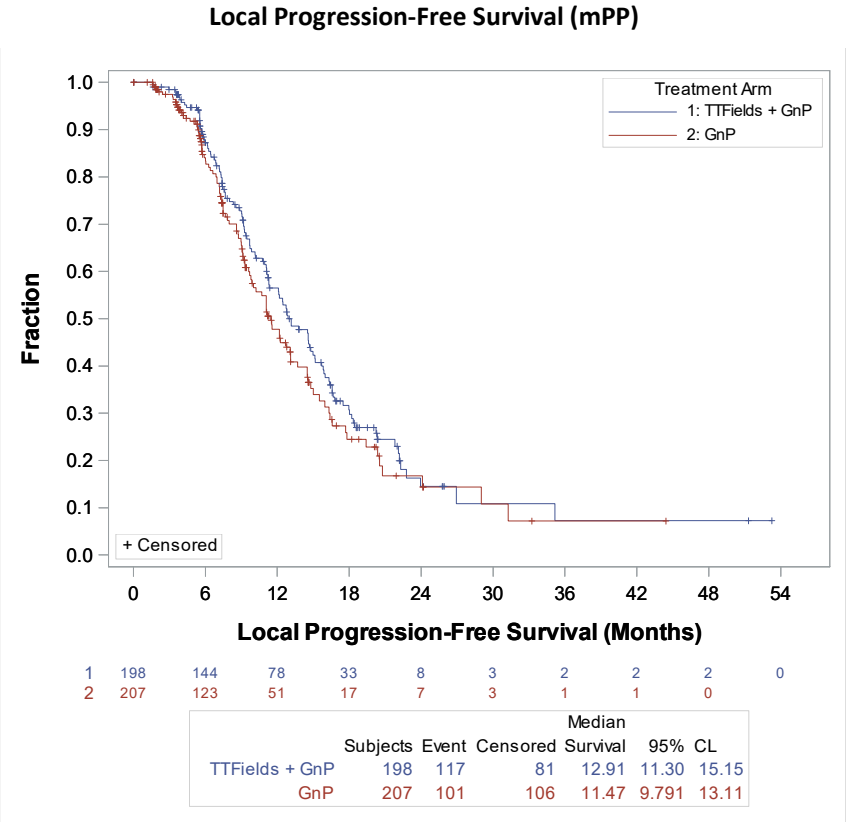
Local Progression Free Survival (ITT)*:* Median local PFS according to RECIST v1.1 was 12.5 months (95% CI: 10.7-14.5) in the TTFields+GnP alone arm compared to 10.4 months (95% CI: 9.1 – 11.8) in the GnP alone arm; HR 0.84 (95% CI: 0.67 – 1.06).



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Local Progression-Free Rate % (95% CI)			
6 Months	78.7 (72.8, 83.4)	76.0 (69.8, 81.1)	3.5
9 Months	66.1 (59.3, 72.0)	59.5 (52.2, 66.1)	11.0
12 Months	51.9 (44.8, 58.6)	41.8 (34.2, 49.2)	24.2
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Hazard Ratio (95% CI)	0.84 (0.67, 1.06)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Local Progression Free Survival (mPP): Treatment with TTFields + GnP resulted in a median local PFS of 12.9 months (95% CI: 11.3 – 15.1) compared to 11.5 months (95% CI: 9.8 – 13.1) with GnP Alone (HR 0.84 [95% CI 0.64 – 1.10].



	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Local Progression-Free Survival Rate % (95% CI)			
6 Months	87.2 (81.4, 91.3)	84.1 (77.6, 88.8)	3.7
9 Months	72.8 (65.4, 78.9)	66.2 (58.0, 73.2)	9.9
12 Months	56.5 (48.3, 63.9)	47.8 (39.0, 56.0)	18.3
24 Months	14.5 (7.8, 23.1)	16.7 (9.1, 26.3)	NE
36 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
42 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
48 Months	7.2 (1.8, 18.0)	0	NE
Hazard Ratio (95% CI)	0.845 (0.64, 1.10)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

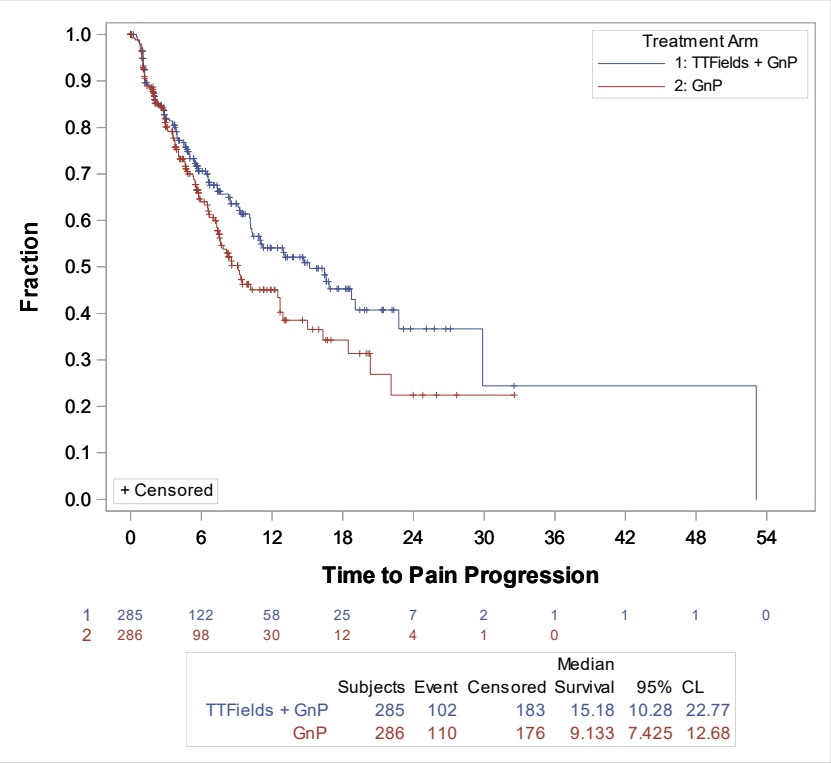
Objective Response Rate (ITT and mPP)*:* Analysis of the ORR was performed based on disease evaluation by the investigator according to RECIST v1.1. In the ITT population, which included 244 participants in the TTFields+GnP Arm and 243 participants in the GnP Alone Arm who had at least one evaluable CT scan after baseline, complete and partial responses in the TTFields+GnP Arm were observed in 3 (1.2%) and 85 (34.8%) participants, respectively, compared to 0 (0%) and 73 (31%) participants, respectively in the GnP Alone Arm. The ORR was 36.1% in the TTFields+GnP Arm compared to 30.0% in the GnP Alone Arm.

In the mPP population, which included 196 participants in the TTFields+GnP Arm and 202 participants in the GnP Alone Arm who had at least one evaluable post-baseline CT scan, complete and partial responses in the TTFields+GnP arm were observed in 3 (1.5%) and 77 (39.8%) participants, respectively, and 0 (0%) and 68 (33.7%), respectively, in the GnP Alone Arm. The ORR was 41.3% in the TTFields+GnP Arm compared to 33.7% of the GnP Alone Arm.

Time to Pain Progression (ITT): Time to pain progression was defined as the duration between the time of randomization until a greater than or equal to twenty-point increase from baseline in a patient self-reported visual analogue scale (VAS) was recorded or death, whichever occurred first. In accordance with the study protocol, patients who experienced local disease progression were no longer followed for pain progression (67/285 patients in the TTFields + GnP arm and 56/286 patients in the GnP alone arm).

The following estimate treats missing evaluations due to discontinued assessment as censored (i.e, pain progression or death are considered as independent of local disease progression) in Kaplan Meier estimate. Median time to pain progression was 15.2 months [95% CI: 10.3-22.8] in the TTFields+GnP arm and 9.1 months [95% CI: 7.4-12.7] in the GnP alone arm. Because a large number of patients stopped pain assessments after local disease progression, this censoring approach can lead to an overestimation, as evidenced below at timepoints beyond 30 months, where the pain progression rates (estimated to be above 20%) are higher than the 10% overall survival observed in both arms at the same timepoint.

Time to Pain Progression (ITT)



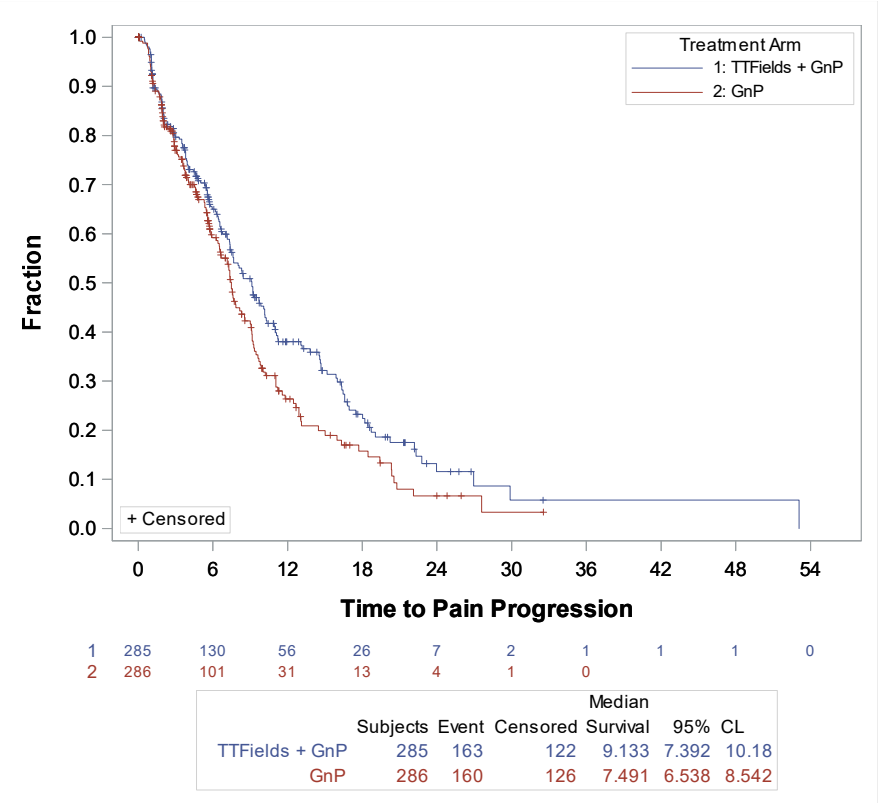
	Subjects	Event	Censored	Median Survival	95% CL	
TTFields + GnP	285	102	183	15.18	10.28	22.77
GnP	286	110	176	9.133	7.425	12.68

	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	70.6 (64.1, 76.1)	64.0 (57.0, 70.2)	10.3
9 Months	63.6 (56.5, 69.8)	50.3 (42.4, 57.7)	26.4
12 Months	54.1 (46.2, 61.3)	45.1 (36.8, 53.0)	20.0
24 Months	36.6 (25.2, 48.2)	22.4 (11.1, 36.2)	NE
36 Months	24.4 (7.4, 46.5)	0	NE
42 Months	24.4 (7.4, 46.5)	0	NE
48 Months	24.4 (7.4, 46.5)	0	NE
Hazard Ratio (95% CI)	0.74 (0.56, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

When local disease progression and death are treated as an event in the Kaplan Meier estimate, median time to pain progression before local progression or death was 9.1 months [95% CI: 7.4 – 10.2] in the TTFields+GnP arm and 7.5 months [95% CI: 6.5 – 8.5] in the GnP alone arm. Although the difference in median values was smaller, the overall pattern showed a delay in pain progression in patients treated with TTFields+GnP compared with GnP alone (HR=0.76, 95% CI: 0.61–0.95).

Time to Pain Progression (ITT) Including Local Disease Progression



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	65.0 (58.4, 70.8)	59.2 (52.3, 65.5)	9.7
9 Months	50.9 (43.9, 57.4)	42.3 (35.1, 49.3)	20.3
12 Months	38.0 (31.2, 44.8)	26.4 (19.7, 33.5)	44.2
24 Months	11.6 (6.1, 18.9)	6.7 (2.7, 13.1)	73.4
36 Months	5.8 (1.5, 14.7)	0	NE
42 Months	5.8 (1.5, 14.7)	0	NE
48 Months	5.8 (1.5, 14.7)	0	NE
Hazard Ratio (95% CI)	0.76 (0.61, 0.95)		

Puncture Free Survival (ITT):

Patients who experienced local disease progression were not evaluated for this endpoint post-progression (93/285 and 70/286 subjects in TTFields+GnP and GnP alone arms). In the puncture-free survival analysis, patients who discontinued assessments following local disease progression were censored at the time of discontinuation. Using this approach, median puncture-free survival was 22.8 months [95% CI: 15.5-NE] in the TTFields+GnP arm and 16.6 months [95% CI: 13.1-NE] in the GnP alone arm. However, because patients who discontinued the study due to local progression were no longer followed, resulting in reduced follow-up time and incomplete capture of subsequent puncture events, this analysis approach can lead to an overestimation, as evidenced at timepoints beyond 30 months, where puncture-free survival rates are 40% and 30% in the TTFields+GnP and GnP alone arms, respectively, while the estimated median puncture free survival times (22.8 in TTFields + GnP arm and 16.6 in GnP arm) are much higher than median Overall Survival times (16.2 months in TTFields + GnP arm and 14.2 in GnP arm). When local disease progression is also treated as an event in the Kaplan-Meier estimate, the median puncture-free survival is 12.75 months [95% CI: 10.7-14.5] in the TTFields+GnP arm and 11.07 months [95% CI: 9.3-12.7] in the GnP alone arm.

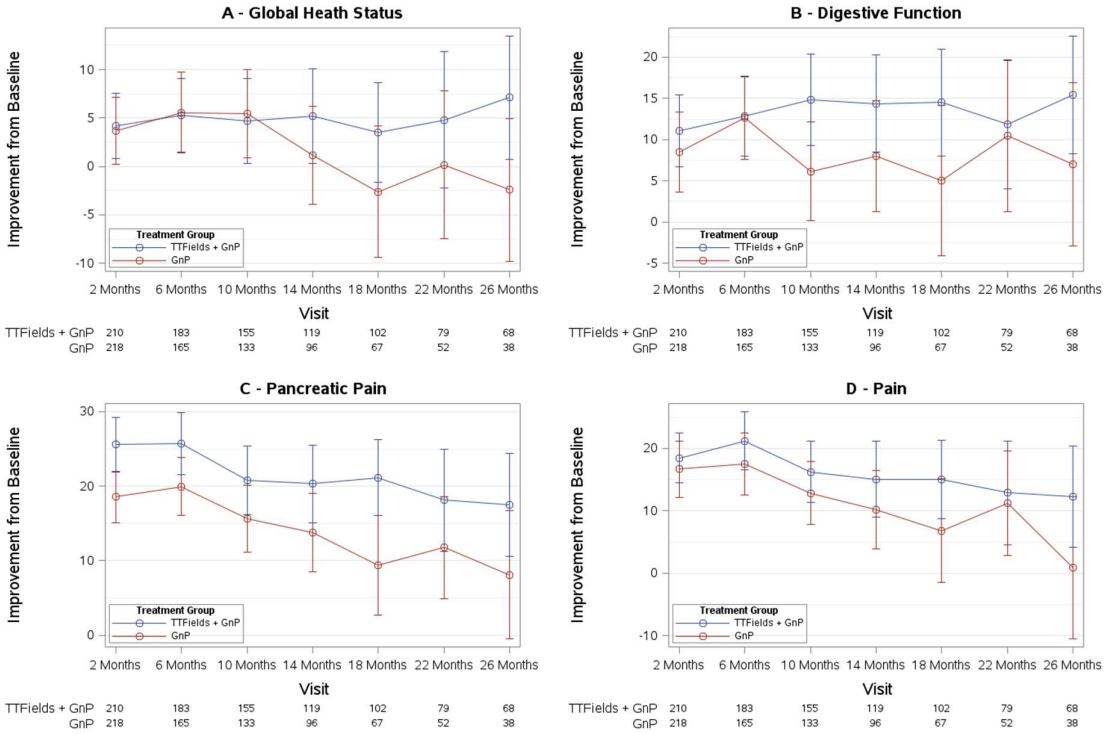
Resectability Rate (ITT): The resectability rates were 7.0% and 10.1% in the TTFields+GnP Arm and GnP Alone Arm, respectively.

Quality of Life (ITT): Quality of Life (QoL) was measured at baseline and every 8 weeks using the EORTC QLQ C-30 questionnaire and PAN26 module (Pancreatic Cancer), and compared between groups for each scale from the questionnaire.

Mean and median baseline QoL scores were comparable between the two arms for all scales/items. The deterioration free survival (DFS) in health-related quality of life or death (defined as the time between randomization and first deterioration in HRQoL score ≥ 10-point with no further improvement in HRQoL score ≥ 10 points), was estimated by Kaplan-Meier methodology using a two-sided stratified Cox Proportional Hazard model. The addition of TTFields to GnP resulted in longer DFS in global health status, pain, pancreatic pain and most of the digestive problems. Similar trends were observed for emotional function and fatigue/lack of energy.

Subjects who experienced local disease progression were not evaluated for Quality of Life endpoints following progression. Consequently, these results do not capture the quality of life status of patients with local disease progression. Notably, analyses that accounted for local disease progression showed consistent trends across the same QoL domains.

Improvement from Baseline Health-Related Quality of Life (ITT)

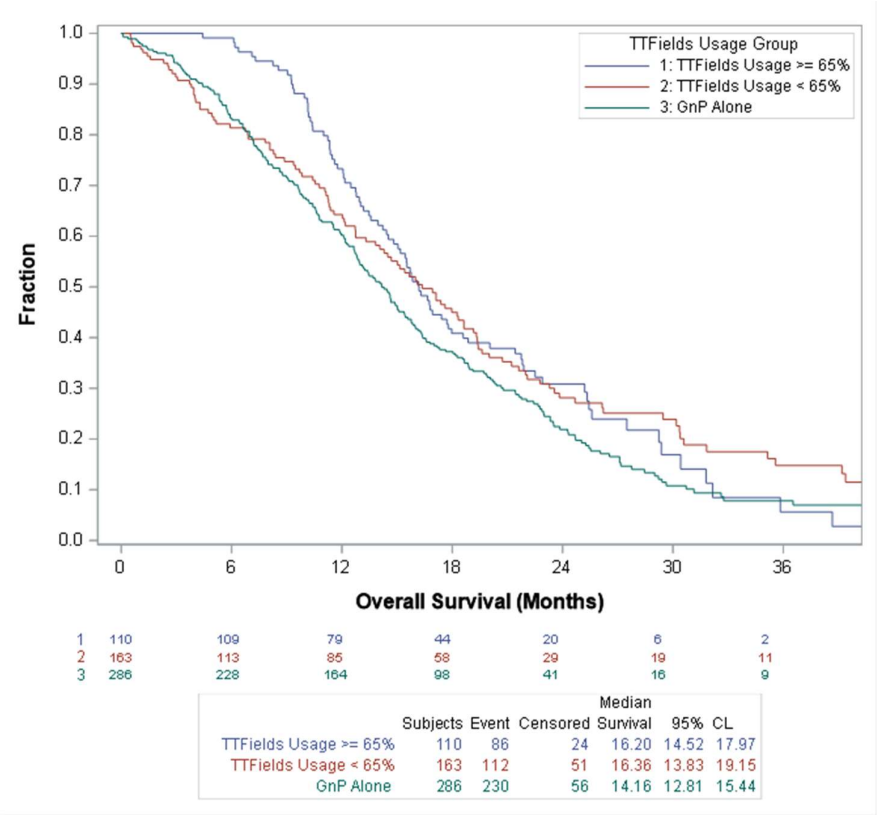


Pain Medication Use (ITT) (Post-Hoc): The pain medication consumption analysis found that overall pain medication use (in terms of type of medications and grade of impact on pain) was similar between study arms, with approximately half of all subjects receiving pain medications of meaningful grade. However, a longer time to first use of pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

Opioid Medication Use (ITT) (Post Hoc): The opioid medication consumption analysis found that overall opioid medication exposure (in terms of opioid types and frequency of exposure) was similar between study arms, with approximately half of all subjects receiving at least one dose of an opioid throughout the study. However, a trend of longer time to first use of opioid pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

TTFields Therapy Usage: The impact of TTFields usage on OS was explored for participants with TTFields usage of ≥65% vs <65% during the first 3 months of treatment. The HR for participants using TTFields therapy ≥65% compared to the GnP Alone was 0.79 (95% CI 0.6157-1.03).

OS by TTFields Usage in the First 3 Months (ITT)



	TTFields Usage ≥ 65% (N=110)	GnP Alone (N=286)	% Improvement*
Survival Rate % (95% CI)			
6 Months	99.1 (93.7, 99.9)	83.3 (78.3, 87.2)	19.0
9 Months	92.7 (86.0, 96.3)	71.6 (65.9, 76.5)	29.5
12 Months	73.3 (63.9, 80.6)	60.2 (54.2, 65.7)	21.7
24 Months	30.9 (22.1, 40.0)	21.9 (16.9, 27.3)	40.8
36 Months	5.6 (1.2, 15.7)	7.8 (4.4, 12.5)	NE
Hazard Ratio (95% CI)	0.79 (0.61; 1.03)		

NE – not estimated. * - improvement was not calculated for groups with N < 10

Safety Results: Overall, TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

AEs by Severity Per CTCAE Version 4.03 or Modified Grading for Skin AEs (Safety)

Severity	TTFields +GnP (N=274) n (%)	GnP Alone (N=273) n (%)	Overall (N=547) n (%)
Number of Subjects with at least one AE	268 (97.8)	270 (98.9)	538 (98.4)
Subjects with AE by Maximum CTCAE Grade			
Grade 1	4 (1.5)	4 (1.5)	8 (1.5)
Grade 2	21 (7.7)	36 (13.2)	57 (10.4)
Grade 3	164 (59.9)	151 (55.3)	315 (57.6)
Grade 4	62 (22.6)	63 (23.1)	125 (22.9)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Study Device-related AE	222 (81.0)	NA	222 (40.6)
Subjects with Study Device-related AE by Maximum Severity			
Grade 1	79 (28.8)	NA	79 (14.4)
Grade 2	117 (42.7)	NA	117 (21.4)
Grade 3	25 (9.1)	NA	25 (4.6)
Grade 4	1 (0.4)	NA	1 (0.2)
Grade 5	0 (0)	NA	0 (0)
Subjects with Gemcitabine or Nab-paclitaxel related AE	258 (94.2)	263 (96.3)	521 (95.2)
Subjects with Gemcitabine or Nab-paclitaxel related AE by Maximum Severity			
Grade 1	4 (1.5)	11 (4.0)	15 (2.7)
Grade 2	50 (18.2)	61 (22.3)	111 (20.3)
Grade 3	155 (56.6)	142 (52.0)	297 (54.3)
Grade 4	46 (16.8)	48 (17.6)	94 (17.2)
Grade 5	3 (1.1)	1 (0.4)	4 (0.7)
Device-related AE Leading to Device Discontinuation	23 (8.4)	NA	23 (4.2)
Systemic Therapy related AE Leading to Systemic Therapy Discontinuation	47 (17.2)	43 (15.8)	90 (16.5)
Subjects with SAE	147 (53.6)	131 (48.0)	278 (50.8)
Subjects with SAE by Maximum CTCAE Grade			
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	4 (1.5)	1 (0.4)	5 (0.9)
Grade 3	104 (38.0)	92 (33.7)	196 (35.8)
Grade 4	22 (8.0)	22 (8.1)	44 (8.0)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Device related SAE	1 (0.4)	NA	1 (0.2)
Subjects with SAE related to Gemcitabine or Nab-paclitaxel	59 (21.5)	56 (20.5)	115 (21.0)
Subjects with SAE Leading to Death	17 (6.2)	16 (5.9)	33 (6.0)
Device-related SAE Leading to Death	0 (0)	NA	0 (0)
Systemic Therapy related SAE Leading to Death	3 (1.1)	1 (0.4)	4 (0.7)
Device-related SAE Leading to Device Discontinuation	0 (0)	NA	0 (0)
Systemic Therapy Related SAE Leading to Systemic Therapy Discontinuation	10 (3.6)	8 (2.9)	18 (3.3)

Conclusions: The PANOVA-3 study met its primary endpoint, demonstrating that TTFields therapy added to GnP resulted in statistically significant improvement in overall survival in patients with locally advanced pancreatic cancer compared to GnP alone (logrank test p = 0.039). In the ITT population, median overall survival (OS) was 16.2 months (95% CI 0.68 – 0.99) with TTFields + GnP compared with 14.2 months (95% CI 12.8 – 15.4) for GnP alone (HR 0.82; p=0.039).

It cannot be concluded from the data that TTFields therapy added to GnP improves PFS compared with using GnP alone. Radiographic response rates were directionally aligned with the survival findings, increasing from 30.0% to 36.1% in ITT.

TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE rates between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with only 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

7 PREVENTIVE SKIN CARE AND PROPHYLAXIS FOR TREATMENT-RELATED REACTIONS UNDER THE TRANSDUCER ARRAYS

To reduce the incidence and severity of device-related dermatologic AEs, advise your patient to adopt proactive skin care, emphasizing prevention and early identification.

General guidance

Effective monitoring and prompt management of device-related dermatologic AEs prevent the progression of minor irritations into more severe skin complications and support treatment continuity.

General skin care guidelines are provided to the patient in the "Patient Information and Operation Manual", aiming to preserve skin intactness and minimize irritation. The recommended routine measures include the following:

- Cleanse skin daily with lukewarm water and mild, fragrance-free soap or bodywash
- Avoid products containing alcohol, fragrances, solvents, petroleum-based products or harsh disinfectants
- Minimize sun exposure and apply appropriate sun protection when outdoors
- Avoid friction and abrasion. Do not rub skin with towels and avoid tight-fitting clothing
- Moisturize regularly
- Choose loose-fitting clothing when possible, to allow air circulation around the abdomen/arrays.
- Avoid clothing made of materials that can irritate the skin (e.g., coarse wool), as these materials may cause itching
- Avoid clothing made of materials that are not breathable (e.g., some synthetic fabrics), as these materials may cause excessive sweating around the abdomen and arrays.

Consider prescribing

- Routine prophylaxis using water- or silicone-based (e.g., dimethicone-based films or non-petroleum-based wipes)
- Skin barrier films
- Topical corticosteroids, or nonsteroidal immunomodulators

Monitoring and Evaluation

- Monitor the patient closely for skin issues, especially during the first 25 days of TTFields treatment, by scheduling periodic follow-up visits.
- Whenever feasible, patients should be asked to attend follow-up visits with the arrays temporarily removed, allowing direct skin inspection by the clinical team.

Recommended Treatment of Skin Adverse Events

Skin adverse events (AEs) related to TTFields therapy are consistent in nature with those observed in other dermatologic conditions.

The table below outlines standard severity grading, clinical descriptions, and recommended dermatologic management strategies, based on *Haanen et al., and* adapted from *Lacouture et al, 2020 and Anadkat et al. 2023*.

Where a referral to a dermatologist is indicated in the table, it is recommended to refer to a dermatologist with expertise in oncology.

Severity	Description	Recommended management	TTFields guidance	Dermatology referral
Grade 1	• Asymptomatic or mild skin changes (e.g. erythema, dryness, pruritic) • No functional impact	• Initiate or optimize use of water-based moisturizers • Add barrier film or dimethicone-based protectant, if needed • Low-potency topical corticosteroids, if needed (e.g. hydrocortisone 1%) • Preference for non-occlusive, alcohol-free, fragrance-free products	• Continue TTFields uninterrupted	Not required unless symptoms persist or diagnosis is unclear
Grade 2	• Symptomatic erythema, localized erosions, or pruritus interfering with daily activities	• Moderate-potency corticosteroids (e.g. triamcinolone 0.1%) • Topical antibiotics for suspected secondary infection • Antihistamines or anti-pruritic as needed	• Continue TTFields if tolerable • Consider brief treatment break (2-7 days) for recovery	Recommended if symptoms do not resolve or diagnosis is uncertain
Grade 3	• Skin ulceration, bleeding, or widespread erosions	• Wound care with hydrogels or hydrocolloid dressings • Topical and/or systemic antibiotics based on culture • Short-course systemic corticosteroids if topical therapy is inadequate	• Interrupt treatment with TTFields • Resume once lesion is re-epithelialized and resolves to Grade ≤1	Strongly recommended to seek dermatologist or wound care specialist
Grade 4	Full thickness ulceration, systemic infection, or necrosis	• Hospital-based wound care • IV antibiotics • Multidisciplinary care including dermatology and infectious disease	Discontinue TTFields temporarily or permanently based on clinical judgement. Reinitiate only after full resolution and multidisciplinary approval.	Mandatory multidisciplinary referral

8 ADDITIONAL INFORMATION

Information for physicians on determining the optimal array layout for patients

- Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies)

Detailed information for patients on the use of Optune Pax can be found in the following documents:

- Optune Pax® Patient Information and Operation Manual (ILE Transducer Arrays) – QSD-QR-914

9 GLOSSARY

AE – Adverse event

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune Pax – A portable, battery, or power supply, operated device for delivering 150 kHz TTFields to the abdomen of patients with pancreatic adenocarcinoma

OS – Overall survival

PFS – Progression free survival

Radiological Response Rate - sum of complete and partial radiological response rates

Disease Control Rate – sum of stable disease, complete and partial radiological response rates

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

10 CONTACT INFORMATION

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Manufacturer information:
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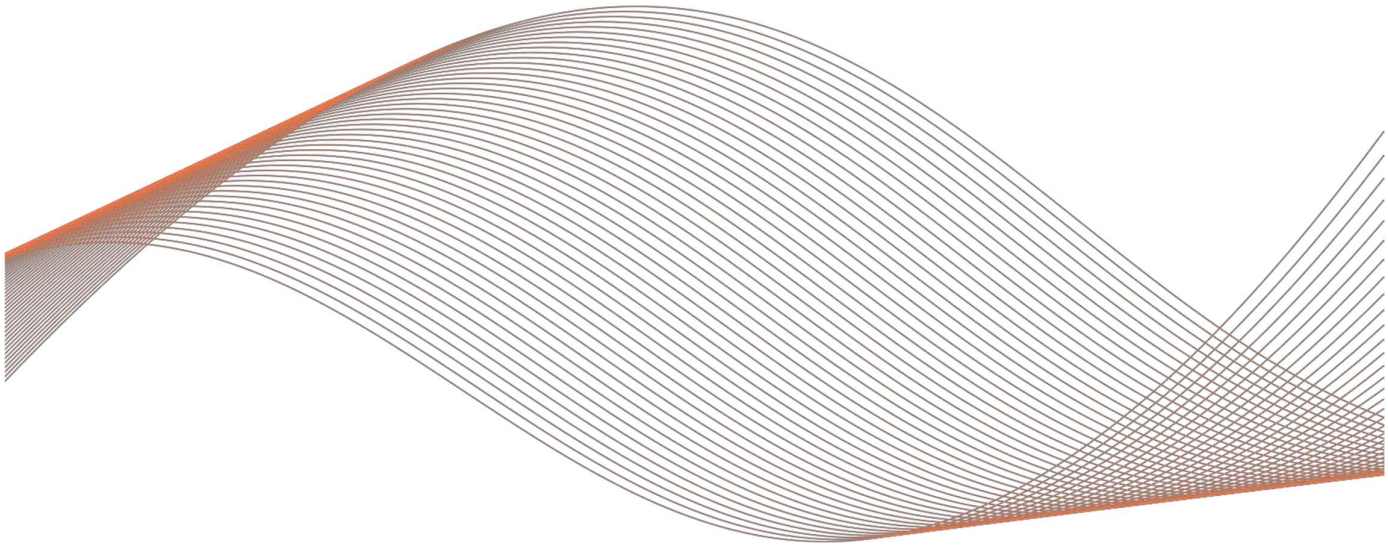
QSD-QR-915 US(EN)

Optune Pax® for Locally Advanced Pancreatic Cancer

Physician Instructions for Use



This manual is intended for physicians prescribing the use of Optune Pax® for Locally Advanced Pancreatic Cancer

Caution: Federal law restricts this device to sale by or on the order of a physician

TABLE OF CONTENTS

1 INDICATION FOR USE

Optune Pax is intended for the treatment of adult patients with locally advanced pancreatic cancer, concomitant with gemcitabine and nab-paclitaxel.

2 CONTRAINDICATIONS, WARNINGS, PRECAUTIONS & NOTICES

Contraindications

Do not use Optune Pax if you have an electrical implant. Use of Optune Pax together with electrical implants has not been tested and may lead to malfunctioning of the implanted device.

Do not use Optune Pax if you are known to be sensitive to gels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the gel used with Optune Pax may commonly cause increased redness and itching and rarely may even lead to severe allergies such as a fall in blood pressure and breathing difficulty.

Warnings

Warning – Use Optune Pax only after receiving training from Novocure or other qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Your training will include a detailed review of the patient user manual and practice in the use of the device. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune Pax without receiving this training can result in breaks in treatment and may rarely cause increased skin irritation, open sores on your abdomen or back, or allergic reactions or even an electric shock.

Warning - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), contact your doctor who will prescribe you high potency topical steroids (hydrocortisone cream) to use when replacing the transducer arrays. Using this cream will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin breakdown, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals.

Warning - All device servicing must be performed by qualified and trained personnel. No modification of this equipment is allowed. If you attempt to open and service the device yourself, you may cause damage to the device. You could also get an electric shock by touching the inner parts of the device.

Warning - The transducer arrays are for single use and should not be taken off your body and then put back on again. If you put a used transducer array back on again, it may not stick well to your skin and the device could turn off. The transducer arrays should not be re-used. Re-use of transducer arrays can lead to poor contact with the skin and may cause the device to alarm and stop working. Re-use of transducer arrays can lead to worsening of the skin inflammation and rarely even to local infection. If you suffer from an infection on your skin (pus, swelling and warmth) consult with your doctor immediately

Precautions

Caution - Do not use Optune Pax with any parts that did not come with the device, that were not sent to you by the device manufacturer, or that were not given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment.

Caution - Do not use Optune Pax if any parts look damaged (such as torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case, opening in power supply). Use of damaged components can damage the device and cause a break in treatment.

Caution - Do not get the device, transducer arrays or other parts wet. Getting the device wet may damage it, preventing you from receiving treatment. Getting the transducer arrays very wet is likely to cause them to come loose from your skin. If this happens, the device will turn off and you will need to change the transducer arrays.

Caution - Before connecting or disconnecting the transducer arrays, make sure that Optune Pax power switch is in the OFF position. Disconnecting transducer arrays with the power switch in the ON position may cause a device alarm to go off and could damage the device.

Caution - If you have an underlying serious skin condition on the abdomen, discuss with your doctor whether this may prevent or temporarily interfere with Optune Pax treatment.

Caution - Do not use Optune Pax if you are pregnant, you think you might be pregnant or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Pax was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant, or if it will be effective.

Caution – There is a hazard of falling due to entanglement in the connection cable. You may consider clipping the cable to your belt.

Caution – The device dropping on the user may result in injury.

Notices

Notice - Optune Pax and transducer arrays will activate metal detectors.

Notice - If you plan to be away from home for more than 1 hour, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply, you may have a break in your treatment.

Notice - Make sure you have at least 12 extra transducer arrays at all times. This will last until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays on time, you may have a break in your treatment.

Notice - Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1 hour from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment.

Notice - You should carry the Troubleshooting Guide from the Patient Information and Operation Manual at all times. This guide is necessary to ensure Optune Pax works properly. If you do not work the device correctly, you may have a break in your treatment.

Notice - Do not block the device vents located on the front and back of the device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this

happens, unblock the vents, wait 5 minutes and restart the device. In case the vents are blocked with pet hair/dust, return the device to the manufacturer for service.

Notice - Do not block the battery charger vents located on the sides of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging. In case the vents are blocked with pet hair/dust, return the battery charger to the manufacturer for service.

Notice - Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

Notice - Keep the device out of the reach of children and pets.

Notice – The device has a cord that may cause tripping when connected to an electric socket.

Notice – Do not cover the device or power supply. This can lead to overheating of the device and cause superficial thermal injury.

3 DEVICE DESCRIPTION

Optune Pax is a portable, battery-powered or mains-powered device that produces alternating electrical fields, called tumor treating fields ("TTFields") within the body. TTFields are applied to the patient by non-invasive, electrically-insulated surface transducer arrays that are placed on the patient's abdomen and connected to the Electric Field Generator. TTFields physically disrupt the rapid cell division exhibited by cancer cells.

Optune Pax is comprised of two main components: (1) an Electric Field Generator (the Optune Pax device) and (2) Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included: power supply, battery, battery charger, connection cable and carrying bag.

Optune Pax delivers TTFields at 150 kHz to the entire abdominal cavity. The device's treatment parameters are preset by Novocure. No adjustments can be made to the device by the physician or patient. Patients are initially trained on the use of the device by a Novocure device support specialist (DSS). The patient should learn to switch out and recharge depleted device batteries, connect to an external power supply and replace the transducer arrays every 3-4 days according to the array layout recommended by you, their physician.

The physician should follow the *Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies*) to select the optimized layout for their patient. However, at their discretion, the physician may select an alternative configuration tailored to the patient's needs or may include more than one recommended layout in the prescription (For example, substituting large arrays with smaller ones for patients who prefer them).

Optune Pax is designed to accompany the patient throughout their daily activities for continuous treatment, with short breaks for personal needs, such as to shower or replace the arrays. Patients can carry the device and battery in the specially designed bag to receive continuous treatment without changing their daily routine.

Optune Pax should be used for at least 12 hours per day, on average.

4 PRINCIPLES OF OPERATION

Optune Pax produces TTFields within the human body through transducer arrays placed on the abdomen. TTFields physically disrupt the rapid cell division exhibited by cancer cells.[1] TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. TTFields technology takes advantage of the special characteristics and geometrical shape of dividing cells, which make them susceptible to the effects of the TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 150 kHz for pancreatic cancer).

In contrast, TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult cells proliferate very slowly, if at all, they are hypothesized to be little affected by TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the lungs), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. It is noted that, because TTFields are only applied to the abdomen, they have no effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any meaningful increase in tissue temperature.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. In addition, various in vitro experiments have demonstrated abnormal mitotic process outcomes following TTFields application, which can lead to different forms of cellular death. Specifically, the abnormal chromosome segregation induced by TTFields can lead to mitotic cell death, or to the formation of abnormal daughter cells experiencing endoplasmic reticulum (ER) stress and autophagy, leading them to downstream immunogenic cell death. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature (Kirson et al. 2004; Giladi et al 2015).

5 PRECLINICAL DATA

TTFields have been shown in vitro to inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to inhibit different cancer cell types, due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase.[2]

Specifically, TTFields have been shown to inhibit pancreatic cancer cells in vitro at a frequency of 150 kHz and an intensity of 1 V/cm. Based on realistic finite element mesh simulations, Novocure has concluded that therapeutic TTFields intensities can be generated in the abdomen of large animals and humans.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for TTFields has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

6 CLINICAL DATA

Pilot Clinical Study in Locally Advanced Pancreatic Cancer

The PANOVA study was a multicenter, non-randomized, open-label pilot study designed to assess the safety and preliminary effectiveness of TTFields therapy when used together with gemcitabine or gemcitabine + nab-paclitaxel (GnP) in advanced pancreatic adenocarcinoma (a mix of locally-advanced and metastatic patients). The primary endpoint was safety. Secondary endpoints were progression free survival (PFS), overall survival (OS) and usage rates of TTFields therapy. Forty (40) patients with advanced pancreatic cancer were enrolled. All patients had unresectable tumors, an ECOG performance score of 0-1, and no prior therapy. Study subjects received continuous daily TTFields at 150 kHz (18 hours per day recommended) to the abdomen together with standard doses of either gemcitabine or GnP per their approved package inserts. TTFields treatment continued until radiological disease progression, death or unacceptable device-related adverse events. Chemotherapy continued until disease progression, death or unacceptable toxicity.

The results of the pilot PANOVA study demonstrated the safety and effectiveness of TTFields therapy in an advanced pancreatic cancer population.

- Safety: In the TTFields + gemcitabine cohort, fourteen patients (70%) had serious adverse events (AEs) during the study period. Ten patients (50%) had treatment-related skin toxicity, of which only 2 were grade 3, and both resolved with appropriate treatment. No TTFields-related serious AEs were reported. In the TTFields+GnP cohort, ten patients (50%) had serious AEs during the study period. Eleven patients (55%) had treatment-related skin toxicity, of which 5 had grade 3 toxicity. No TTFields-related serious AEs were reported.

- Preliminary Efficacy: In the TTFields+gemcitabine cohort, the median PFS was 8.3 months (95% CI 4.3, 10.3). In locally-advanced patients specifically, the median PFS was 10.3 months. The median OS was 14.9 months (95% CI 6.2, NA) in the TTFields+gemcitabine cohort; 1-year survival rate was 55% (95% CI 29, 75). In locally-advanced patients specifically, the 1-year survival rate was 86%. In the TTFields+GnP cohort, the median PFS was 12.7 months (95% CI 5.4, NA). In locally-advanced patients specifically, the median PFS was not reached (PFS6 was 87.5%). Median OS was not reached for the TTFields+GnP cohort; the 1-year survival rate was 72% (95% CI 44, 88). In locally-advanced patients specifically, the 1-year survival rate was 87.5%.

- Device Usage: In the TTFields+GnP group, the median TTFields usage rate was 12.2 hours per day. The median TTFields usage rate in the gemcitabine alone cohort was 14 hours per day. In patients experiencing a grade 3 skin toxicity, there was a median decrease in daily usage of the device of 12.5% (3 hours).

Pivotal Clinical Study in Locally Advanced Pancreatic Cancer – The PANOVA-3 Study

Study Design: The PANOVA-3 study was a pivotal, randomized, open-label, two-arm, multi-center study evaluating the effectiveness and safety of Optune Pax concomitant with gemcitabine and nab-paclitaxel (GnP) for front-line treatment of locally advanced pancreatic cancer. GnP is approved for the treatment of pancreatic cancer, and is one of only a few accepted treatments for patients with locally-advanced pancreatic cancer. Gemcitabine and nab-paclitaxel were administered according to their approved package inserts in both study arms. Subjects in the study were randomized in a 1:1 ratio to receive TTFields together with GnP (TTFields+GnP Arm) or GnP (GnP Alone Arm). A total of 138 sites enrolled 571 subjects globally (285 in the TTFields+GnP Arm; 286 in the GnP Alone Arm).

Eligibility Criteria: The inclusion and exclusion criteria were as follows:

Inclusion Criteria

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 (per Al-Hawary MM, et al., Radiology 201413; NCCN Clinical Practice Guidelines in Oncology))*
    a. *Head/uncinate process:*
        i. *Solid tumor contact with SMA>180°*
        ii. *Solid tumor contact with the CA>180°*
        iii. *Solid tumor contact with the first jejunal SMA branch*
        iv. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
        v. *Contact with most proximal draining jejunal branch into SMV*
    b. *Body and tail:*
        i. *Solid tumor contact of >180° with the SMA or CA*
        ii. *Solid tumor contact with the CA and aortic involvement*
        iii. *Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)*
    c. *No distant metastasis, including non-regional lymph node metastasis*
    d. *No borderline resectable (per Al-Hawary MM, et al., Radiology 201413)*
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 independently or with the help of a caregiver*
8. *Signed informed consent form for the study protocol*

Exclusion Criteria

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 nonmelanomatous 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 109/L and platelet count <100 x 109/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. Subjects 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 subject to receive protocol therapy*
f. *History of any psychiatric condition that might impair subject'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 subjects 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 subjects 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*

Study Procedures:

TTFields+GnP Arm: Participants received Optune Pax together with gemcitabine and nab-paclitaxel (GnP). TTFields therapy was initiated within 7 days of randomization, and ± 3 days of administering GnP. Participants received uninterrupted multiple single month courses of continuous TTFields therapy. Treatment was to be stopped in cases of intolerable toxicity or disease progression in the abdomen ("local disease progression"). The recommended transducer array layout was determined by the investigator for each participant using the *Clinical Practice Guidelines-Layout Optimization in Pancreatic Malignancies*, which was developed to maximize TTFields intensity in the area of maximal disease burden in the abdomen (based on the patient's baseline CT scan). After being trained on how to use the device and place the arrays, participants continued TTFields therapy at home. Participants were instructed to replace the arrays two to three times per week. At array replacement, the skin was re-shaved if needed, and treated using topical steroids or antibiotic creams, if recommended. The concomitant chemotherapy, GnP, was administered as described below.

GnP Alone Arm: Participants received gemcitabine and nab-paclitaxel according to their approved package inserts. Gemcitabine was administered as follows: 1000 mg/m^2 over 30-minute infusion administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment. Nab-paclitaxel was administered as follows: 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle, until radiological progression per RECIST V1.1, or unacceptable toxicity based on investigator assessment.

Follow-Up: During the treatment period, participants were seen ever four weeks until local disease progression, with the following assessments performed: concomitant medication recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry including CA-19-9, AE and device deficiency collection and recording, documentation of ascitic fluid drainage (if applicable), pain assessment using VAS and device usage time assessment (only for subjects in the TTFields+GnP Arm). In addition, every eight weeks, the following assessments were performed until local disease progression: CT/MRI scan of the chest and

abdomen, assessment of local and distant disease status per RECIST v1.1. Furthermore, EORTC QLQ C30 questionnaires with the PAN26 addendum were completed by the participating subjects. In addition, bone scan and/or CT/MRI of the brain were performed if clinically indicated. One month following treatment discontinuation, the following assessments were performed: concomitant medications recording, ECOG performance status, physical examination (including vital signs), complete blood count including differential, serum chemistry panel including CA-19-9, AE and device deficiency collection and recording and documentation of ascitic fluid drainage were performed during this visit. In addition, following local disease progression, telephone follow-up was conducted every four weeks for survival status until study completion or death.

Analyses: Primary and secondary effectiveness endpoints were analyzed in the ITT (Intent-to-Treat) and modified Per Protocol (mPP)[1] populations. The ITT population includes all 571 randomized participants (285 in the TTFields+GnP arm and 286 in the GnP Alone arm). The mPP population includes only those participants who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms), and for the TTFields+GnP Arm, also received at least 4 weeks (28 days) of TTFields therapy (198 in the TTFields+GnP arm and 207 in the GnP Alone arm). Safety endpoints were analyzed in the Safety population, which included all 547 randomized participants who received any amount of TTFields or GnP treatment (274 participants in the TTFields+GnP arm, and 273 participants in the GnP Alone arm).

Protocol Deviations: Protocol deviations were categorized per the definitions set forth in the ICH E3 Guideline. Of the deviations categorized as "Major and Important", eleven were identified as deviations with the potential to impact study outcomes and/or subject safety, and involved either enrollment of patients who did not meet the eligibility criteria or incorrect dose or administration timing of a study treatment. Following a careful evaluation, it was determined that these deviations did not impact study outcomes and/or subject safety. Overall, protocol deviations were generally balanced between the two arms. The majority of protocol deviations involved failure to report SAEs within 24 hours or missed/out of window assessments that in many cases were included at future visits, allowing for an appropriate clinical and safety evaluation during the study period.

Participant Demographics and Baseline Characteristics: Demographics and baseline characteristics were well balanced between treatment groups. Overall, participants' median age was 67 years (range: 31-90 years), with 3.9% ECOG performance score of 2, 57.6% with score of 1 and 38.5% with score of 0. The median time from diagnosis to study enrollment was 3.6 weeks (range: 0.1- 53.7).

[1] *Referred to as the Modified Intent-to-Treat (mITT) population in the PANOVA-3 protocol and SAP.*

Demographics and Baseline Characteristics – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Age (Years) Median (range)	67 (31, 90)	67.5 (40, 88)	67 (31, 90)
Gender, n (%)			
Male	147 (51.6)	125 (43.7)	272 (47.6)
Female	138 (48.4)	161 (56.3)	299 (52.4)
Race, n (%)			
American Indian or Alaska Native	9 (3.2)	4 (1.4)	13 (2.3)
Asian	44 (15.4)	44(15.4)	88 (15.4)
Black or African American	16 (5.6)	14 (4.9)	30 (5.3)
Native Hawaiian or Other Pacific Islander	0	0	0
White	202 (70.9)	204 (71.3)	406 (71.1)
Other	3 (11)	5 (1.7)	8 (1.4)
Not Reported	11 (3.9)	15 (5.2)	26 (4.6)
Ethnicity, n (%)			
Hispanic or Latino	32 (11.2)	22 (7.7)	54 (9.5)
Not Hispanic or Latino	238 (83.5)	247 (86.4)	485 (84.9)
Not Reported/Unknown	15 (5.3)	17 (5.9)	32 (5.6)
Region, n (%)			
North America	123 (43.2)	125 (43.7)	248 (43.4)
Eastern Europe	43 (15.1)	42 (14.7)	85 (14.9)
Western Europe and Israel	62 (21.8)	61 (21.3)	123 (21.5)
Rest of the World	57 (20.0)	58 (20.3)	115 (20.1)
ECOG Performance Status, n (%)			
0	109 (38.2)	111 (38.8)	220 (38.5)
1	166 (58.2)	163 (57.0)	329 (57.6)
2	10 (3.5)	12 (4.2)	22 (3.9)
BMI Group, n (%)			
< 25 kg/m^2	166 (58.2)	174 (60.8)	340 (59.5)
≥ 25 kg/m^2	117 (41.1)	108 (37.8)	225 (39.4)
CA-19.9, n (%)			
Low (≤37 U/mL)	48 (16.8)	44 (15.4)	92 (16.1)
Moderate (38-1,000 U/mL)	140 (49.1)	152 (53.1)	292 (51.1)
High (>1,000 U/mL)	88 (30.9)	79 (27.6)	167 (29.2)
Untested	9 (3.2)	11 (3.8)	20 (3.5)
Target Lesion Site, n (%)			
Head of Pancreas	164 (57.5)	160 (55.9)	324 (56.7)
Body of Pancreas	82 (28.8)	81 (28.3)	163 (28.5)
Tail of Pancreas	9 (3.2)	19 (6.6)	28 (4.9)
	55 (19.3)	49 (17.1)	104 (18.2)
Other			
Multiple regions in pancreas	26 (9.1)	22 (7.7)	48 (8.4)
Extra-pancreatic	29 (10.2)	27 (9.4)	56 (9.8)

Pancreatic Cancer History – ITT Population

	TTFields + GnP (N=285)	GnP Alone (N=286)	Overall (N=571)
Time Since Initial Pathological Diagnosis (weeks) Median (range)	3.7 (0.1, 53.7)	3.6 (0.1, 21.4)	3.6 (0.1, 53.7)

Histologic Subtype at Baseline – ITT Population

Histology at Baseline	TTFields + GnP (N=285)	GnP Alone (N=286)
	n (%)	
Pancreatic Adenocarcinoma, Not Otherwise Specified	251 (88)	258 (90)
Adenosquamous carcinoma	2 (1)	1 (0.3)
Ductal adenocarcinoma	27 (9)	24 (8)
Histology not further specified	5 (2)	3 (1)

Treatment exposure to GnP was similar between the two arms, both in terms of number of cycles received and duration of exposure. Median duration of TTFields exposure was similar, at 27.6 weeks, with average daily usage 59.3%, and median daily usage 62.1%. The most common reason for discontinuation of concomitant treatments in both arms was disease progression or clinical deterioration. The most common reason for TTFields discontinuation was local disease progression.

Exposure to GnP by Study Arm (Safety Population)

	TTFields + GnP (N=274)	GnP Alone (N=273)
Gemcitabine Number of Cycles Received Median (range)	6.0 (1.0, 57.0)	6.0 (1.0, 30.0)
Duration of Exposure (weeks) Median (range)	24.1 (0.1, 232.4)	22.1 (0.1, 134.1)
Nab-paclitaxel Number of Cycles Received Median (range)	6.0 (1.0, 57.0)	5.0 (1.0, 30.0)
Duration of Exposure (weeks) Median (range)	23.0 (0.1, 232.4)	21.4 (0.1, 134.1)

TTFields Therapy Usage Duration (Safety Population)

	TTFields + GnP (N=274)
Duration of Exposure (weeks)	
Median (range)	27.6 (0.1, 234.4)
Average Usage	
Mean (SD)	59.3 (21.2)
Median (range)	62.1 (0, 99)
Average Usage, (%)	
≤75%	200 (73.0)
>75%	74 (27.0)

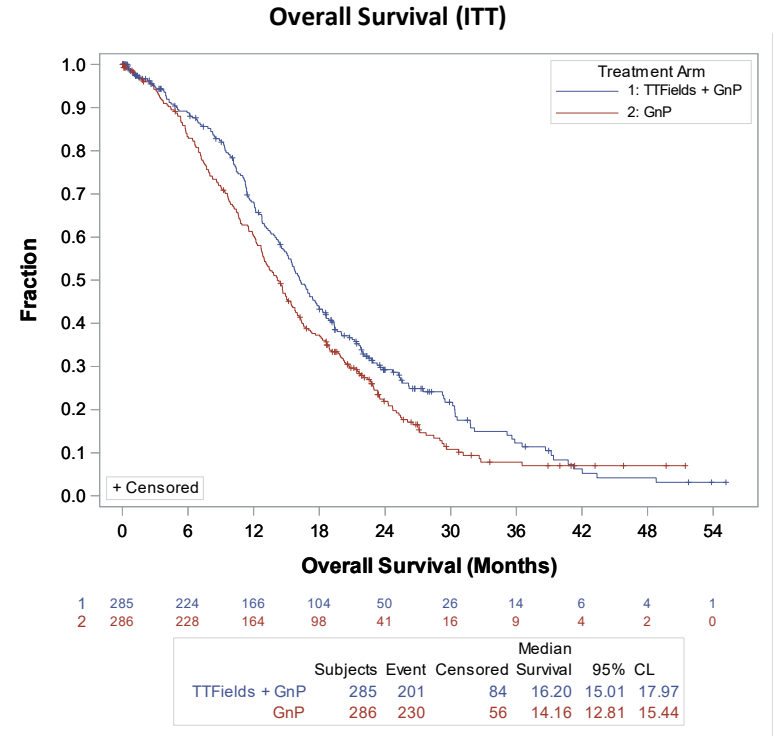
Effectiveness Results:

Analysis Populations

- Intent to Treat (ITT): All randomized patients, regardless of whether the treatment was received. The ITT population consists of 285 patients in the TTFields+GnP arm and 286 patients in the GnP Alone arm.
- Modified Per Protocol (mPP): All patients who received at least one cycle of GnP (as defined in the approved Package Inserts) (both arms) and at least 4 weeks (28 days) of TTFields therapy (in the TTFields+GnP arm). The mPP population consists of 198 patients in the TTFields+GnP arm and 207 patients in the GnP Alone arm.

Primary Endpoint – Overall Survival (OS)

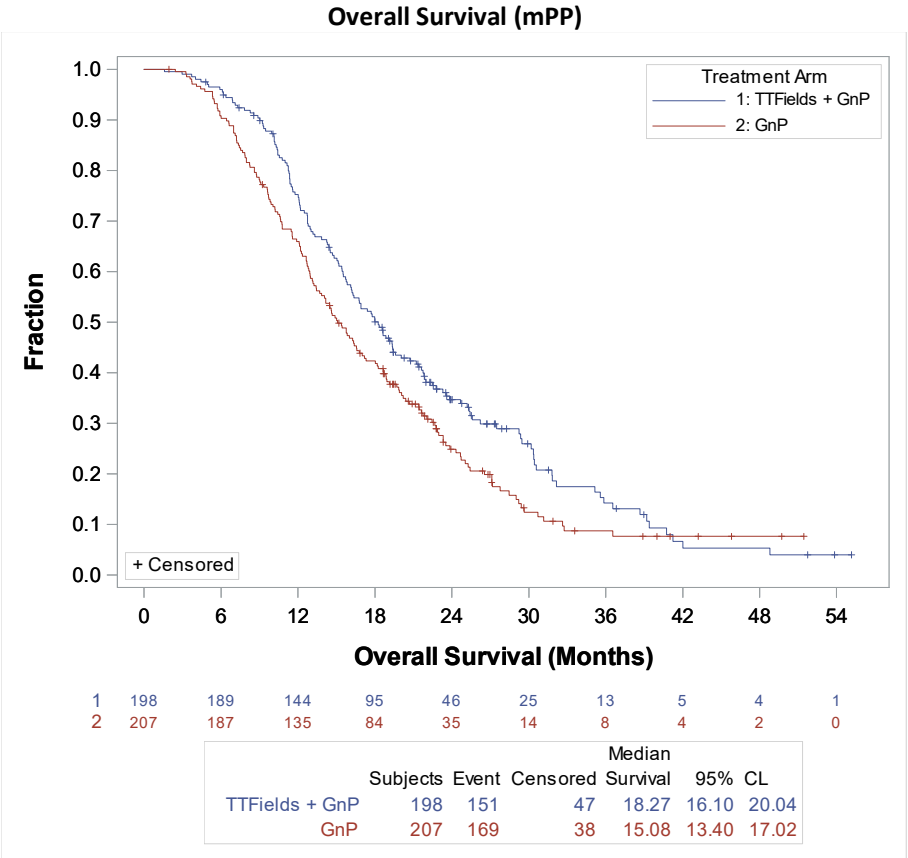
***Overall Survival (ITT)*:** Overall survival was measured from the date of randomization to the date of death (in months). At the time of analysis, patients lost to follow-up or still on protocol follow-up were censored at the last date when they were known to be alive. The OS at the final analysis in the ITT population met the threshold for statistical significance which was pre-defined as p=0.04794. A statistically significant difference in the OS distribution between study arms was observed (log-rank P=0.039). The median OS in the TTFields+GnP arm was 16.2 months (95% CI 15.0-18.0) compared to 14.2 months (95% CI 12.8-15.4) in the GnP Alone arm. A 2-month improvement in median OS was observed in favor of the TTFields+GnP arm. The hazard ratio (HR) for OS was 0.82 (95% CI 0.68 – 0.99). A descriptive analysis of the Kaplan-Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	88.8 (84.3, 92.1)	83.3 (78.3, 87.2)	6.6
9 Months	82.4 (77.1, 86.6)	71.6 (65.9, 76.5)	15.1
12 Months	68.1 (62.0, 73.5)	60.2 (54.2, 65.7)	13.1
24 Months	29.2 (23.4, 35.2)	21.9 (16.9, 27.3)	33.3
36 Months	12.3 (7.6, 18.2)	7.8 (4.4, 12.5)	NE
42 Months	6.3 (2.8, 11.7)	7.0 (3.7, 11.6)	NE
48 Months	4.2 (1.5, 9.2)	7.0 (3.7, 11.6)	NE
54 Months	3.1 (0.9, 7.8)		NE
Log Rank P-value	0.039		
Hazard Ratio (95% CI)	0.82 (0.68, 0.99)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Overall Survival (mPP): OS was also analyzed in the mPP population. The median OS in the TTFields+GnP Arm was 18.3 months (95% CI 16.1-20.0) compared to 15.1 months (95% CI 13.4-17.0) in the GnP Alone Arm. A statistically significant difference in the overall survival distribution between treatment arms was observed (log-rank P=0.023). A 3.2 months improvement in median OS was observed in favor of the TTFields+GnP arm. The HR for OS was 0.77 (95% CI 0.62-0.97). A descriptive analysis of the Kaplan–Meier overall survival curves showed an early separation between the TTFields+GnP and GnP Alone arms, which was maintained at multiple time points.



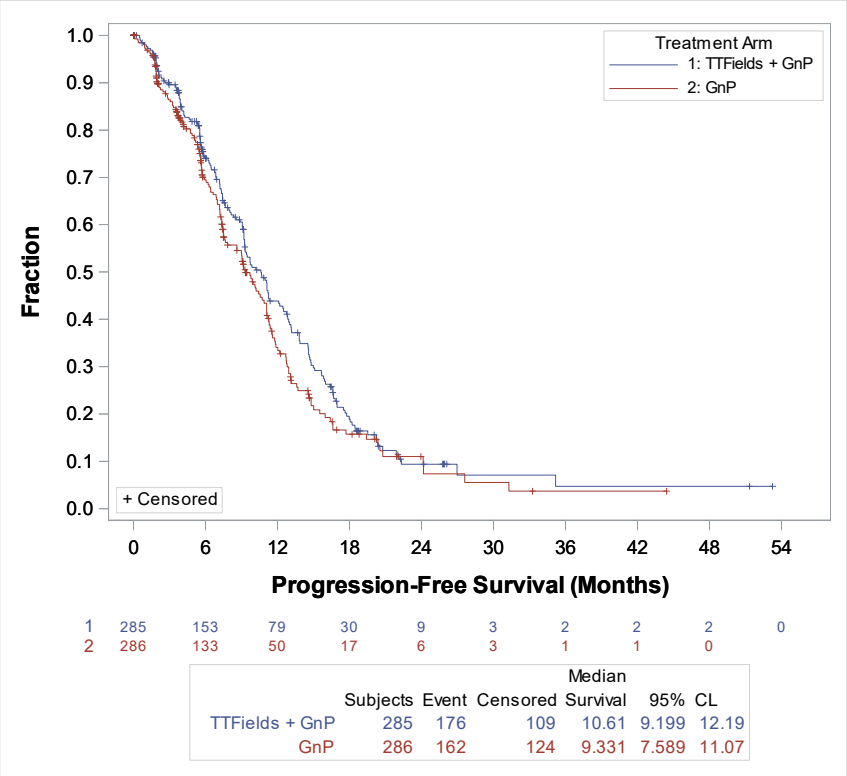
	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Overall Survival Rate % (95% CI)			
6 Months	96.0 (92.1, 98.0)	90.8 (85.9, 94.0)	5.7
9 Months	90.3 (85.3, 93.7)	78.2 (71.9, 83.2)	15.6
12 Months	75.2 (68.5, 80.7)	65.9 (59.0, 72.0)	14.0
24 Months	34.7 (27.8, 41.7)	24.8 (18.8, 31.3)	39.7
36 Months	14.2 (8.5, 21.3)	8.7 (4.6, 14.3)	NE
42 Months	6.6 (2.7, 13.0)	7.6 (3.8, 13.2)	NE
48 Months	5.3 (1.9, 11.4)	7.6 (3.8, 13.2)	NE
54 Months	4.0 (1.1, 9.8)		NE
Log Rank 2-sided P-value	0.023		
Hazard Ratio (95% CI)	0.77 (0.62, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Key Secondary Endpoint – Progression Free Survival (PFS)

***Progression Free Survival (ITT)*:** Treatment with TTFields+GnP. showed no statistically significant improvement in PFS compared to GnP Alone (logrank test p = 0.137). The hazard ratio was 0.85 (95% CI 0.68 – 1.05). Median PFS was 10.6 months (95% CI: 9.2 – 12.2) with TTFields+GnP compared to 9.3 months (95% CI: 7.6 – 11.1) with GnP Alone.

Progression Free Survival (ITT)

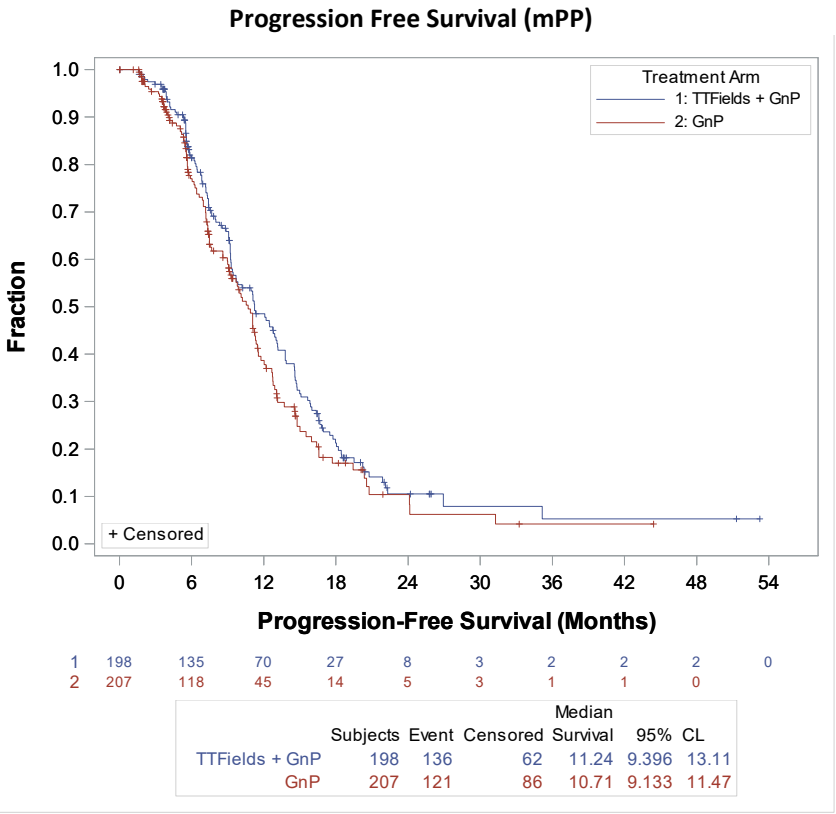


	Subjects	Event	Censored	Median Survival	95% CL	
TTFields + GnP	285	176	109	10.61	9.199	12.19
GnP	286	162	124	9.331	7.589	11.07

	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Progression-Free Rate % (95% CI)			
6 Months	74.0 (67.9, 79.2)	69.5 (63.0, 75.1)	6.5
9 Months	60.5 (53.7, 66.7)	54.0 (46.9, 60.5)	12.2
12 Months	43.9 (36.9, 50.6)	34.1 (27.1, 41.2)	28.8
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Log Rank 2-sided P-value	0.137		
Hazard Ratio (95% CI)	0.85 (0.68, 1.05)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

***Progression-Free Survival (mPP)*:** In the mPP population, the median progression-free survival (PFS) per RECIST v1.1 was 11.2 months (95% CI: 9.4–13.1) in participants treated with TTFields + GnP, compared to 10.7 months (95% CI: 9.1–11.5) with GnP Alone (HR: 0.84; 95% CI: 0.66–1.08; log-rank P = 0.183).

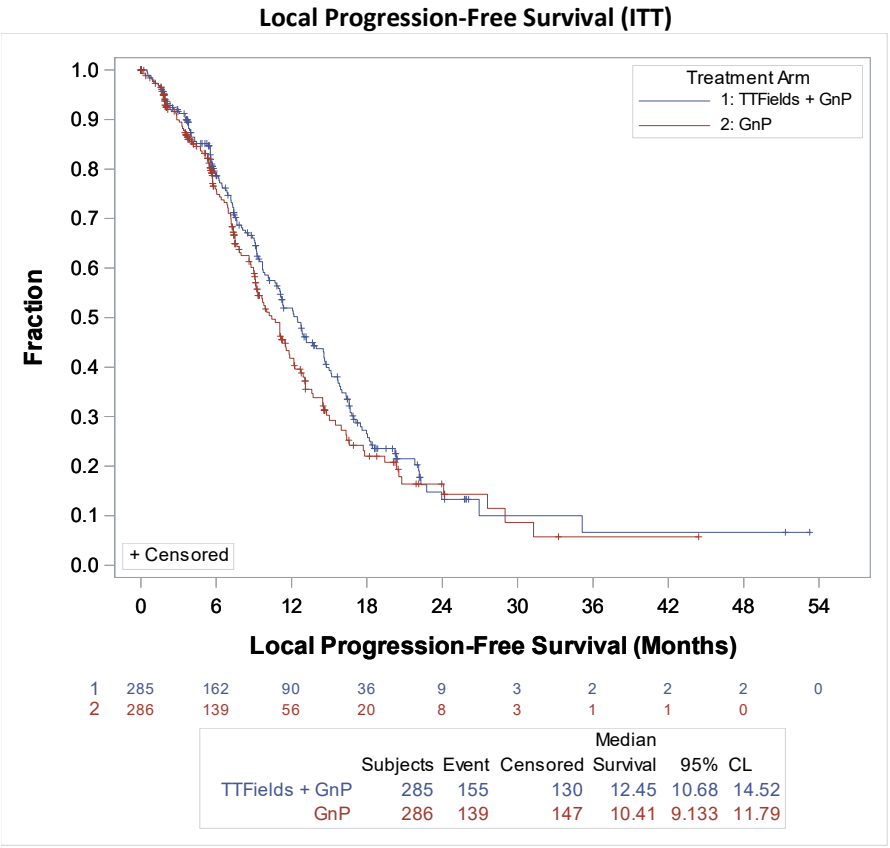


	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
PFS Survival Rate % (95% CI)			
6 Months	81.4 (74.9, 86.3)	77.0 (70.0, 82.6)	5.7
9 Months	65.9 (58.2, 72.5)	59.6 (51.5, 66.8)	10.5
12 Months	48.5 (40.5, 56.0)	38.7 (30.5, 46.8)	25.4
24 Months	10.5 (5.6, 17.1)	10.4 (4.9, 18.2)	NE
36 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
42 Months	5.2 (1.3, 13.3)	4.2 (0.9, 11.7)	NE
48 Months	5.2 (1.3, 13.3)	0	NE
Log Rank 2-sided P-value	0.183		
Hazard Ratio (95% CI)	0.84 (0.66, 1.08)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Additional Secondary Effectiveness Endpoints

Local Progression Free Survival (ITT)*:* Median local PFS according to RECIST v1.1 was 12.5 months (95% CI: 10.7-14.5) in the TTFields+GnP alone arm compared to 10.4 months (95% CI: 9.1 – 11.8) in the GnP alone arm; HR 0.84 (95% CI: 0.67 – 1.06).

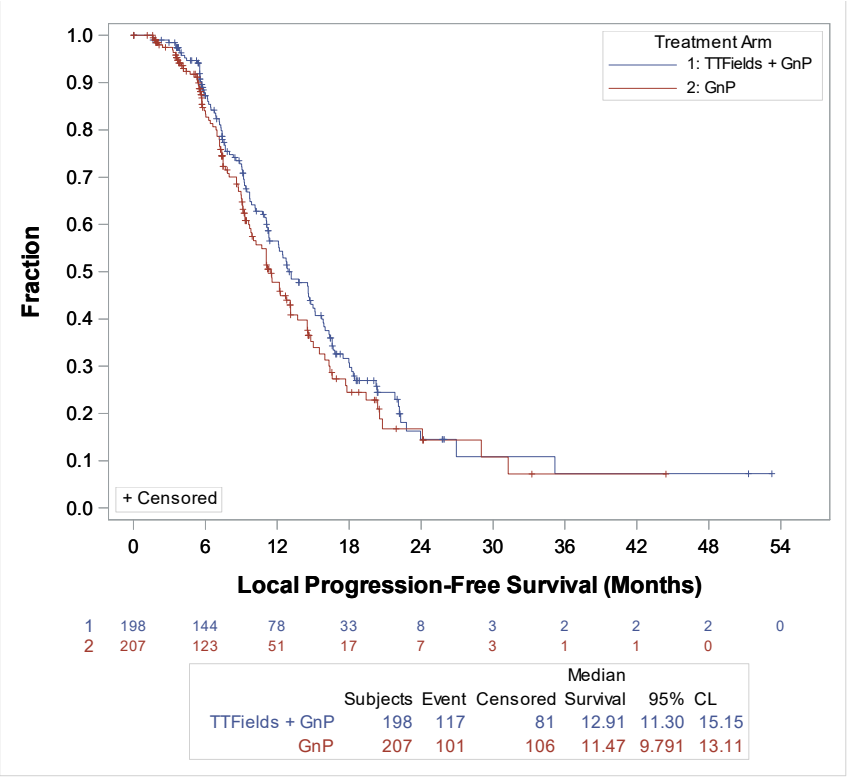


	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Local Progression-Free Rate % (95% CI)			
6 Months	78.7 (72.8, 83.4)	76.0 (69.8, 81.1)	3.5
9 Months	66.1 (59.3, 72.0)	59.5 (52.2, 66.1)	11.0
12 Months	51.9 (44.8, 58.6)	41.8 (34.2, 49.2)	24.2
24 Months	13.3 (7.6, 20.7)	16.4 (9.9, 24.3)	NE
36 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
42 Months	6.7 (1.7, 16.4)	5.7 (1.3, 15.2)	NE
48 Months	6.7 (1.7, 16.4)	0	NE
Hazard Ratio (95% CI)	0.84 (0.67, 1.06)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

Local Progression Free Survival (mPP): Treatment with TTFields + GnP resulted in a median local PFS of 12.9 months (95% CI: 11.3 – 15.1) compared to 11.5 months (95% CI: 9.8 – 13.1) with GnP Alone (HR 0.84 [95% CI 0.64 – 1.10].

Local Progression-Free Survival (mPP)



	Subjects	Event	Censored	Median Survival	95%	CL
TTFields + GnP	198	117	81	12.91	11.30	15.15
GnP	207	101	106	11.47	9.791	13.11

	TTFields + GnP (N=198)	GnP Alone (N=207)	% Improvement*
Local Progression-Free Survival Rate % (95% CI)			
6 Months	87.2 (81.4, 91.3)	84.1 (77.6, 88.8)	3.7
9 Months	72.8 (65.4, 78.9)	66.2 (58.0, 73.2)	9.9
12 Months	56.5 (48.3, 63.9)	47.8 (39.0, 56.0)	18.3
24 Months	14.5 (7.8, 23.1)	16.7 (9.1, 26.3)	NE
36 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
42 Months	7.2 (1.8, 18.0)	7.2 (1.7, 18.2)	NE
48 Months	7.2 (1.8, 18.0)	0	NE
Hazard Ratio (95% CI)	0.845 (0.64, 1.10)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

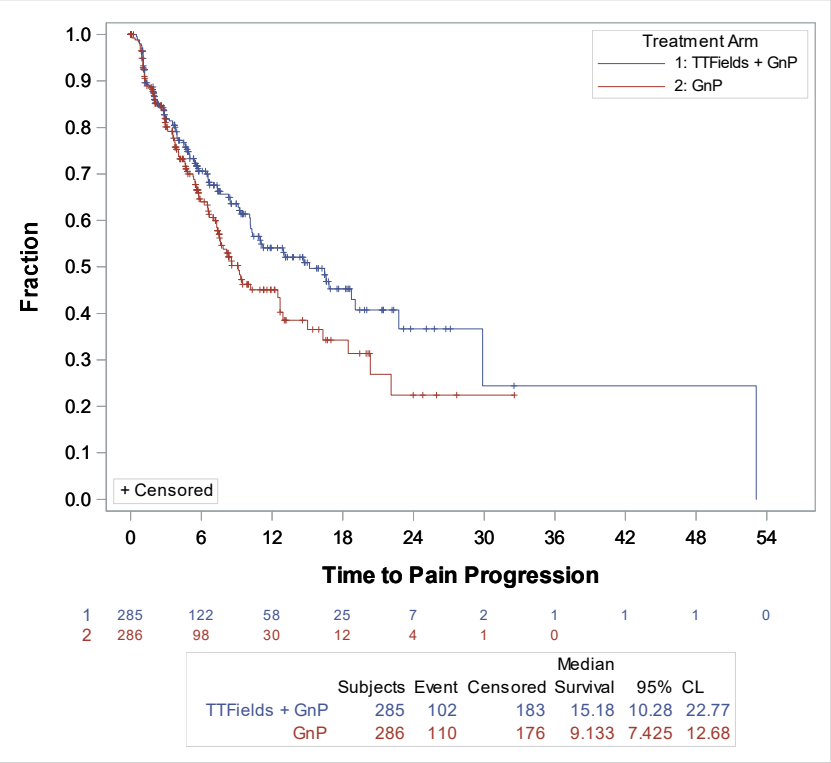
Objective Response Rate (ITT and mPP)*:* Analysis of the ORR was performed based on disease evaluation by the investigator according to RECIST v1.1. In the ITT population, which included 244 participants in the TTFields+GnP Arm and 243 participants in the GnP Alone Arm who had at least one evaluable CT scan after baseline, complete and partial responses in the TTFields+GnP Arm were observed in 3 (1.2%) and 85 (34.8%) participants, respectively, compared to 0 (0%) and 73 (31%) participants, respectively in the GnP Alone Arm. The ORR was 36.1% in the TTFields+GnP Arm compared to 30.0% in the GnP Alone Arm.

In the mPP population, which included 196 participants in the TTFields+GnP Arm and 202 participants in the GnP Alone Arm who had at least one evaluable post-baseline CT scan, complete and partial responses in the TTFields+GnP arm were observed in 3 (1.5%) and 77 (39.8%) participants, respectively, and 0 (0%) and 68 (33.7%), respectively, in the GnP Alone Arm. The ORR was 41.3% in the TTFields+GnP Arm compared to 33.7% of the GnP Alone Arm.

Time to Pain Progression (ITT): Time to pain progression was defined as the duration between the time of randomization until a greater than or equal to twenty-point increase from baseline in a patient self-reported visual analogue scale (VAS) was recorded or death, whichever occurred first. In accordance with the study protocol, patients who experienced local disease progression were no longer followed for pain progression (67/285 patients in the TTFields + GnP arm and 56/286 patients in the GnP alone arm).

The following estimate treats missing evaluations due to discontinued assessment as censored (i.e, pain progression or death are considered as independent of local disease progression) in Kaplan Meier estimate. Median time to pain progression was 15.2 months [95% CI: 10.3-22.8] in the TTFields+GnP arm and 9.1 months [95% CI: 7.4-12.7] in the GnP alone arm. Because a large number of patients stopped pain assessments after local disease progression, this censoring approach can lead to an overestimation, as evidenced below at timepoints beyond 30 months, where the pain progression rates (estimated to be above 20%) are higher than the 10% overall survival observed in both arms at the same timepoint.

Time to Pain Progression (ITT)



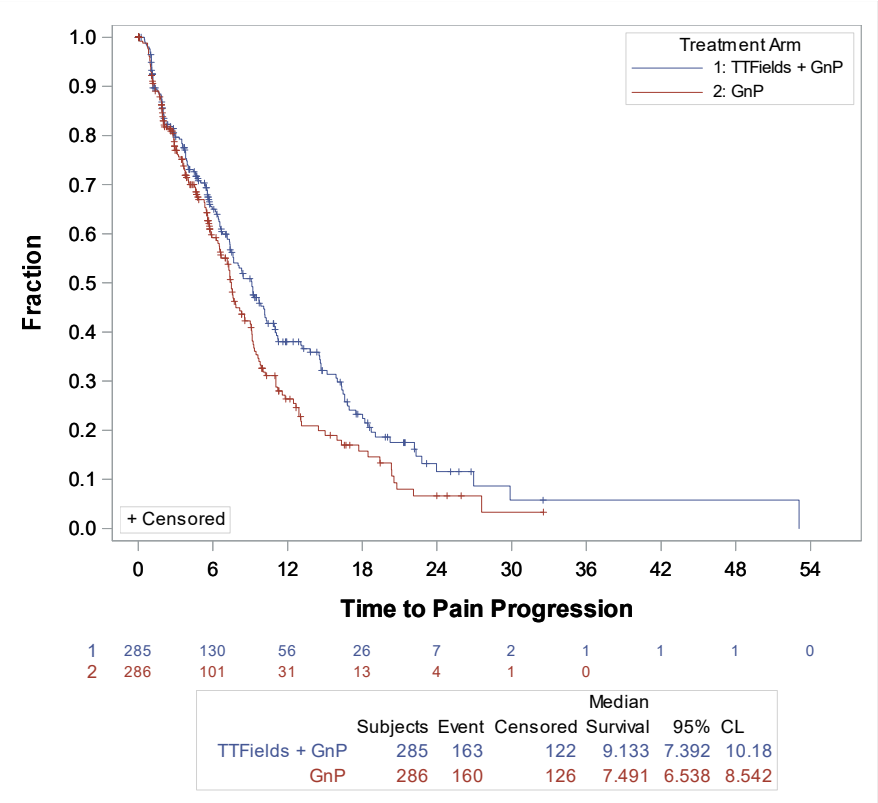
	Subjects	Event	Censored	Median Survival	95% CL	
TTFields + GnP	285	102	183	15.18	10.28	22.77
GnP	286	110	176	9.133	7.425	12.68

	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	70.6 (64.1, 76.1)	64.0 (57.0, 70.2)	10.3
9 Months	63.6 (56.5, 69.8)	50.3 (42.4, 57.7)	26.4
12 Months	54.1 (46.2, 61.3)	45.1 (36.8, 53.0)	20.0
24 Months	36.6 (25.2, 48.2)	22.4 (11.1, 36.2)	NE
36 Months	24.4 (7.4, 46.5)	0	NE
42 Months	24.4 (7.4, 46.5)	0	NE
48 Months	24.4 (7.4, 46.5)	0	NE
Hazard Ratio (95% CI)	0.74 (0.56, 0.97)		

*Improvement not calculated for groups with N < 10; NE = Not Estimated

When local disease progression and death are treated as an event in the Kaplan Meier estimate, median time to pain progression before local progression or death was 9.1 months [95% CI: 7.4 – 10.2] in the TTFields+GnP arm and 7.5 months [95% CI: 6.5 – 8.5] in the GnP alone arm. Although the difference in median values was smaller, the overall pattern showed a delay in pain progression in patients treated with TTFields+GnP compared with GnP alone (HR=0.76, 95% CI: 0.61–0.95).

Time to Pain Progression (ITT) Including Local Disease Progression



	TTFields + GnP (N=285)	GnP Alone (N=286)	% Improvement*
Time to Pain Progression Rate % (95% CI)			
6 Months	65.0 (58.4, 70.8)	59.2 (52.3, 65.5)	9.7
9 Months	50.9 (43.9, 57.4)	42.3 (35.1, 49.3)	20.3
12 Months	38.0 (31.2, 44.8)	26.4 (19.7, 33.5)	44.2
24 Months	11.6 (6.1, 18.9)	6.7 (2.7, 13.1)	73.4
36 Months	5.8 (1.5, 14.7)	0	NE
42 Months	5.8 (1.5, 14.7)	0	NE
48 Months	5.8 (1.5, 14.7)	0	NE
Hazard Ratio (95% CI)	0.76 (0.61, 0.95)		

Puncture Free Survival (ITT):

Patients who experienced local disease progression were not evaluated for this endpoint post-progression (93/285 and 70/286 subjects in TTFields+GnP and GnP alone arms). In the puncture-free survival analysis, patients who discontinued assessments following local disease progression were censored at the time of discontinuation. Using this approach, median puncture-free survival was 22.8 months [95% CI: 15.5-NE] in the TTFields+GnP arm and 16.6 months [95% CI: 13.1-NE] in the GnP alone arm. However, because patients who discontinued the study due to local progression were no longer followed, resulting in reduced follow-up time and incomplete capture of subsequent puncture events, this analysis approach can lead to an overestimation, at timepoints beyond 30 months, where puncture-free survival rates are 40% and 30% in the TTFields+GnP and GnP alone arms, respectively, while the estimated median puncture free survival times (22.8 in TTFields + GnP arm and 16.6 in GnP arm) are much higher than median Overall Survival time (16.2 months in TTFields + GnP arm and 14.2 in GnP arm). When local disease progression is also treated as an event in the Kaplan-Meier estimate, the median puncture-free survival is 12.75 months [95% CI: 10.7-14.5] in the TTFields+GnP arm and 11.07 months [95% CI: 9.3-12.7] in the GnP alone arm.

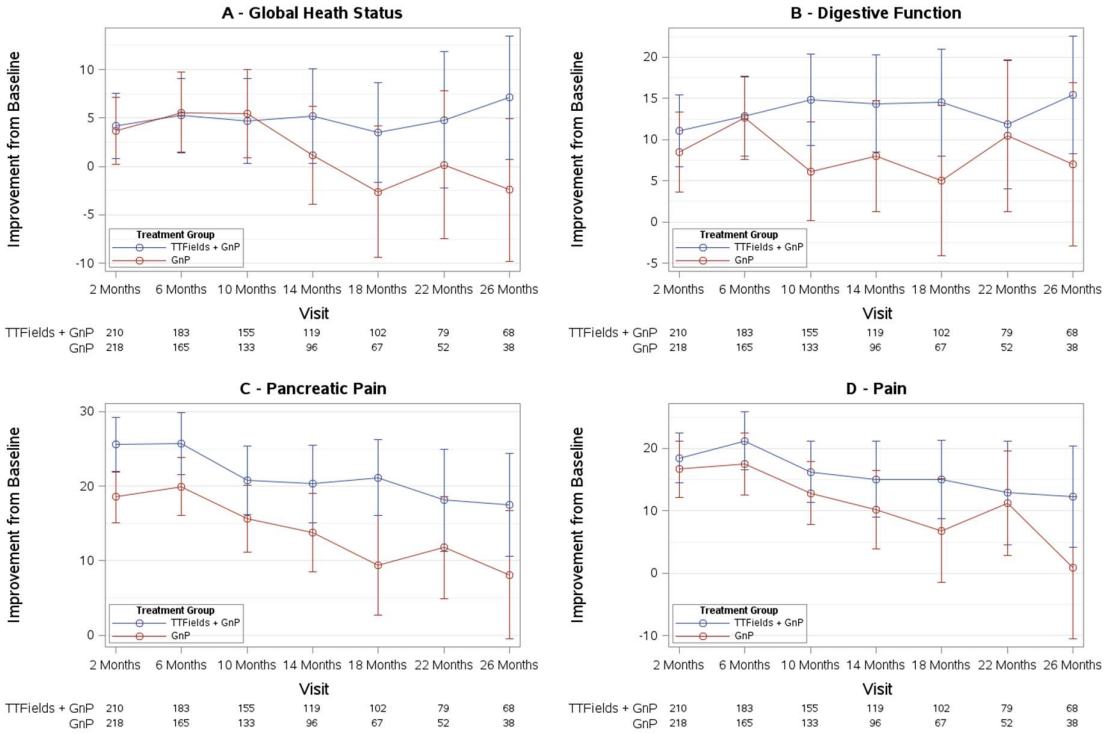
Resectability Rate (ITT): The resectability rates were 7.0% and 10.1% in the TTFields+GnP Arm and GnP Alone Arm, respectively.

Quality of Life (ITT): Quality of Life (QoL) was measured at baseline and every 8 weeks using the EORTC QLQ C-30 questionnaire and PAN26 module (Pancreatic Cancer), and compared between groups for each scale from the questionnaire.

Mean and median baseline QoL scores were comparable between the two arms for all scales/items. The deterioration free survival (DFS) in health-related quality of life or death (defined as the time between randomization and first deterioration in HRQoL score ≥ 10-point with no further improvement in HRQoL score ≥ 10 points), was estimated by Kaplan-Meier methodology using a two-sided stratified Cox Proportional Hazard model. The addition of TTFields to GnP resulted in longer DFS in global health status, pain, pancreatic pain and most of the digestive problems. Similar trends were observed for emotional function and fatigue/lack of energy.

Subjects who experienced local disease progression were not evaluated for Quality of Life endpoints following progression. Consequently, these results do not capture the quality of life status of patients with local disease progression. Notably, analyses that accounted for local disease progression showed consistent trends across the same QoL domains.

Improvement from Baseline Health-Related Quality of Life (ITT)

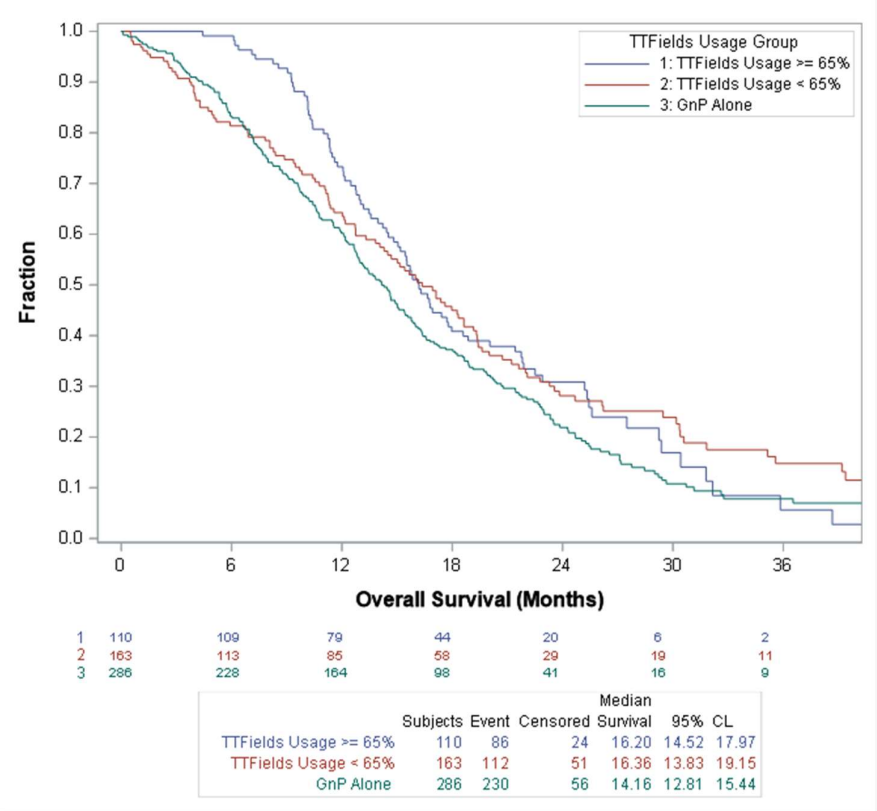


Pain Medication Use (ITT) (Post-Hoc): The pain medication consumption analysis found that overall pain medication use (in terms of type of medications and grade of impact on pain) was similar between study arms, with approximately half of all subjects receiving pain medications of meaningful grade. However, a longer time to first use of pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

Opioid Medication Use (ITT) (Post Hoc): The opioid medication consumption analysis found that overall opioid medication exposure (in terms of opioid types and frequency of exposure) was similar between study arms, with approximately half of all subjects receiving at least one dose of an opioid throughout the study. However, a trend of longer time to first use of opioid pain medication was observed in the TTFields+GnP arm, compared to the GnP Alone arm.

TTFields Therapy Usage: The impact of TTFields usage on OS was explored for participants with TTFields usage of ≥65% vs <65% during the first 3 months of treatment. The HR for participants using TTFields therapy ≥65% compared to the GnP Alone was 0.79 (95% CI 0.6157-1.03).

OS by TTFields Usage in the First 3 Months (ITT)



	TTFields Usage ≥ 65% (N=110)	GnP Alone (N=286)	% Improvement*
Survival Rate % (95% CI)			
6 Months	99.1 (93.7, 99.9)	83.3 (78.3, 87.2)	19.0
9 Months	92.7 (86.0, 96.3)	71.6 (65.9, 76.5)	29.5
12 Months	73.3 (63.9, 80.6)	60.2 (54.2, 65.7)	21.7
24 Months	30.9 (22.1, 40.0)	21.9 (16.9, 27.3)	40.8
36 Months	5.6 (1.2, 15.7)	7.8 (4.4, 12.5)	NE
Hazard Ratio (95% CI)	0.79 (0.61; 1.03)		

NE – not estimated. * - improvement was not calculated for groups with N < 10

Safety Results: Overall, TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

AEs by Severity Per CTCAE Version 4.03 or Modified Grading for Skin AEs (Safety)

Severity	TTFields +GnP (N=274) n (%)	GnP Alone (N=273) n (%)	Overall (N=547) n (%)
Number of Subjects with at least one AE	268 (97.8)	270 (98.9)	538 (98.4)
Subjects with AE by Maximum CTCAE Grade			
Grade 1	4 (1.5)	4 (1.5)	8 (1.5)
Grade 2	21 (7.7)	36 (13.2)	57 (10.4)
Grade 3	164 (59.9)	151 (55.3)	315 (57.6)
Grade 4	62 (22.6)	63 (23.1)	125 (22.9)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Study Device-related AE	222 (81.0)	NA	222 (40.6)
Subjects with Study Device-related AE by Maximum Severity			
Grade 1	79 (28.8)	NA	79 (14.4)
Grade 2	117 (42.7)	NA	117 (21.4)
Grade 3	25 (9.1)	NA	25 (4.6)
Grade 4	1 (0.4)	NA	1 (0.2)
Grade 5	0 (0)	NA	0 (0)
Subjects with Gemcitabine or Nab-paclitaxel related AE	258 (94.2)	263 (96.3)	521 (95.2)
Subjects with Gemcitabine or Nab-paclitaxel related AE by Maximum Severity			
Grade 1	4 (1.5)	11 (4.0)	15 (2.7)
Grade 2	50 (18.2)	61 (22.3)	111 (20.3)
Grade 3	155 (56.6)	142 (52.0)	297 (54.3)
Grade 4	46 (16.8)	48 (17.6)	94 (17.2)
Grade 5	3 (1.1)	1 (0.4)	4 (0.7)
Device-related AE Leading to Device Discontinuation	23 (8.4)	NA	23 (4.2)
Systemic Therapy related AE Leading to Systemic Therapy Discontinuation	47 (17.2)	43 (15.8)	90 (16.5)
Subjects with SAE	147 (53.6)	131 (48.0)	278 (50.8)
Subjects with SAE by Maximum CTCAE Grade			
Grade 1	0 (0)	0 (0)	0 (0)
Grade 2	4 (1.5)	1 (0.4)	5 (0.9)
Grade 3	104 (38.0)	92 (33.7)	196 (35.8)
Grade 4	22 (8.0)	22 (8.1)	44 (8.0)
Grade 5	17 (6.2)	16 (5.9)	33 (6.0)
Subjects with Device related SAE	1 (0.4)	NA	1 (0.2)
Subjects with SAE related to Gemcitabine or Nab-paclitaxel	59 (21.5)	56 (20.5)	115 (21.0)
Subjects with SAE Leading to Death	17 (6.2)	16 (5.9)	33 (6.0)
Device-related SAE Leading to Death	0 (0)	NA	0 (0)
Systemic Therapy related SAE Leading to Death	3 (1.1)	1 (0.4)	4 (0.7)
Device-related SAE Leading to Device Discontinuation	0 (0)	NA	0 (0)
Systemic Therapy Related SAE Leading to Systemic Therapy Discontinuation	10 (3.6)	8 (2.9)	18 (3.3)

Conclusions: The PANOVA-3 study met its primary endpoint, demonstrating that TTFields therapy added to GnP resulted in statistically significant improvement in overall survival in patients with locally advanced pancreatic cancer compared to GnP alone (logrank test p = 0.039). In the ITT population, median overall survival (OS) was 16.2 months (95% CI 0.68 – 0.99) with TTFields + GnP compared with 14.2 months (95% CI 12.8 – 15.4) for GnP alone (HR 0.82; p=0.039).

It cannot be concluded from the data that TTFields therapy added to GnP improves PFS compared with using GnP alone. Radiographic response rates were directionally aligned with the survival findings, increasing from 30.0% to 36.1% in ITT.

TTFields therapy was well-tolerated, with no exacerbation of GnP-related systemic toxicity, no new safety signals, and comparable SAE rates between study arms. Most TTFields-treated patients experienced the expected device-related skin toxicity under the arrays (76.3% of the TTFields-treated participants). The majority of these events were low grade (Grade 1-2), with only 21 (7.7%) experiencing a Grade ≥3 event. The most common device-related AE not related to skin toxicity was fatigue, reported in 14 participants (5.1%). There was one Grade 4 AEs suspected to be related to the device by the investigator, which was a non-serious event of neutrophil count decrease. There were no device-related AEs that led to death, and no unanticipated device-related safety issues during the course of the study.

7 PREVENTIVE SKIN CARE AND PROPHYLAXIS FOR TREATMENT-RELATED REACTIONS UNDER THE TRANSDUCER ARRAYS

To reduce the incidence and severity of device-related dermatologic AEs, advise your patient to adopt proactive skin care, emphasizing prevention and early identification.

General guidance

Effective monitoring and prompt management of device-related dermatologic AEs prevent the progression of minor irritations into more severe skin complications and support treatment continuity.

General skin care guidelines are provided to the patient in the "Patient Information and Operation Manual", aiming to preserve skin intactness and minimize irritation. The recommended routine measures include the following:

- Cleanse skin daily with lukewarm water and mild, fragrance-free soap or bodywash
- Avoid products containing alcohol, fragrances, solvents, petroleum-based products or harsh disinfectants
- Minimize sun exposure and apply appropriate sun protection when outdoors
- Avoid friction and abrasion. Do not rub skin with towels and avoid tight-fitting clothing
- Moisturize regularly
- Choose loose-fitting clothing when possible, to allow air circulation around the abdomen/arrays.
- Avoid clothing made of materials that can irritate the skin (e.g., coarse wool), as these materials may cause itching
- Avoid clothing made of materials that are not breathable (e.g., some synthetic fabrics), as these materials may cause excessive sweating around the abdomen and arrays.

Consider prescribing

- Routine prophylaxis using water- or silicone-based (e.g., dimethicone-based films or non-petroleum-based wipes)
- Skin barrier films
- Topical corticosteroids, or nonsteroidal immunomodulators

Monitoring and Evaluation

- Monitor the patient closely for skin issues, especially during the first 25 days of TTFields treatment, by scheduling periodic follow-up visits.
- Whenever feasible, patients should be asked to attend follow-up visits with the arrays temporarily removed, allowing direct skin inspection by the clinical team.

Recommended Treatment of Skin Adverse Events

Skin adverse events (AEs) related to TTFields therapy are consistent in nature with those observed in other dermatologic conditions.

The table below outlines standard severity grading, clinical descriptions, and recommended dermatologic management strategies, based on *Haanen et al., and* adapted from *Lacouture et al, 2020 and Anadkat et al. 2023*.

Where a referral to a dermatologist is indicated in the table, it is recommended to refer to a dermatologist with expertise in oncology.

Severity	Description	Recommended management	TTFields guidance	Dermatology referral
Grade 1	• Asymptomatic or mild skin changes (e.g. erythema, dryness, pruritic) • No functional impact	• Initiate or optimize use of water-based moisturizers • Add barrier film or dimethicone-based protectant, if needed • Low-potency topical corticosteroids, if needed (e.g. hydrocortisone 1%) • Preference for non-occlusive, alcohol-free, fragrance-free products	• Continue TTFields uninterrupted	Not required unless symptoms persist or diagnosis is unclear
Grade 2	• Symptomatic erythema, localized erosions, or pruritus interfering with daily activities	• Moderate-potency corticosteroids (e.g. triamcinolone 0.1%) • Topical antibiotics for suspected secondary infection • Antihistamines or anti-pruritic as needed	• Continue TTFields if tolerable • Consider brief treatment break (2-7 days) for recovery	Recommended if symptoms do not resolve or diagnosis is uncertain
Grade 3	• Skin ulceration, bleeding, or widespread erosions	• Wound care with hydrogels or hydrocolloid dressings • Topical and/or systemic antibiotics based on culture • Short-course systemic corticosteroids if topical therapy is inadequate	• Interrupt treatment with TTFields • Resume once lesion is re-epithelialized and resolves to Grade ≤1	Strongly recommended to seek dermatologist or wound care specialist
Grade 4	Full thickness ulceration, systemic infection, or necrosis	• Hospital-based wound care • IV antibiotics • Multidisciplinary care including dermatology and infectious disease	Discontinue TTFields temporarily or permanently based on clinical judgement. Reinitiate only after full resolution and multidisciplinary approval.	Mandatory multidisciplinary referral

8 ADDITIONAL INFORMATION

Information for physicians on determining the optimal array layout for patients

- Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (pancreatic malignancies)

Detailed information for patients on the use of Optune Pax can be found in the following documents:

- Optune Pax® Patient Information and Operation Manual (ITE Transducer Arrays) – QSD-QR-916

9 GLOSSARY

AE – Adverse event

ITT – Intent-to-Treat. This analysis population includes all randomized subjects.

kHz – kilo hertz; number of cycles per second

Optune Pax – A portable, battery, or power supply, operated device for delivering 150 kHz TTFields to the abdomen of patients with pancreatic adenocarcinoma

OS – Overall survival

PFS – Progression free survival

Radiological Response Rate - sum of complete and partial radiological response rates

Disease Control Rate – sum of stable disease, complete and partial radiological response rates

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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