Effect of Tumor Treating Fields (TTFields, 150 kHz) as Front-Line Treatment of Locally-advanced Pancreatic Adenocarcinoma Concomitant With Gemcitabine and Nab-paclitaxel (PANOVA-3)

**NCT-Nummer:**
NCT03377491

**Studienbeginn:**
Mai 2018

**Letztes Update:**
24.05.2019

**Wirkstoff:**
nab paclitaxel, Gemcitabine

**Indikation (Clinical Trials):**
Adenocarcinoma

**Geschlecht:**
Alle

**Altersgruppe:**
Erwachsene (18+)

**Phase:**
Phase 3

**Sponsor:**
NovoCure Ltd.

**Collaborator:**
-

**Studien-Informationen**

**Detailed Description:**

PAST PRE-CLINICAL AND CLINICAL EXPERIENCE:

The effect of the electric fields (TTFields, TTF) has demonstrated significant activity in in vitro and in vivo pancreatic adenocarcinoma pre-clinical models both as a single modality treatment and in combination with chemotherapies. TTFields have been demonstrated to act synergistically with taxanes and have been shown to be additive when combined with other chemotherapies.
including gemcitabine. In addition, TTFields have shown to inhibit metastatic spread of malignant melanoma in in vivo experiment.

In a pilot study, 40 patients with locally advanced or metastatic pancreatic adenocarcinoma received gemcitabine together with TTFields (150 kHz) or gemcitabine and nab-paclitaxel together with TTFields (150 kHz) applied to the abdomen until disease progression. The combination was well tolerated and the only device-related adverse event was contact dermatitis.

In addition, a phase III trial of Optune® (200 kHz) as monotherapy compared to active chemotherapy in recurrent glioblastoma patients showed TTFields to be equivalent to active chemotherapy in extending survival, associated with minimal toxicity, good quality of life, and activity within the brain (14% response rate) (Stupp R., et al., EJC 2012). Finally, a phase III trial of Optune® combined with maintenance temozolomide compared to maintenance temozolomide alone has shown that combined therapy led to a significant improvement in both progression free survival and overall survival in patients with newly diagnosed glioblastoma without the addition of high grade toxicity and without decline in quality of life (Stupp R., et al., JAMA 2017).

DESCRIPTION OF THE TRIAL:

All patients included in this trial are patients with locally advanced pancreatic adenocarcinoma. In addition, all patients must meet all eligibility criteria.

Eligible patients will be randomly assigned to one of two groups:

1. Patients receive gemcitabine and nab-paclitaxel in combination with TTFields using the NovoTTF-100L(P) System.

2. Patients receive gemcitabine and nab-paclitaxel without TTFields.

Patients will be randomized at a 1:1 ratio. Baseline tests will be performed in patients enrolled in both arms. If assigned to the NovoTTF-100L(P) group, the patients will be treated continuously with the device until progression in the abdomen. On both arms, patients who have progression outside the abdomen will switch to a second line treatment according to local practice.

SCIENTIFIC BACKGROUND:

Electric fields exert forces on electric charges similar to the way a magnet exerts forces on metallic particles within a magnetic field. These forces cause movement and rotation of electrically charged biological building blocks, much like the alignment of metallic particles seen along the lines of force radiating outwards from a magnet.

Electric fields can also cause muscles to twitch and if strong enough may heat tissues. TTFields are alternating electric fields of low intensity. This means that they change their direction repetitively many times a second. Since they change direction very rapidly (150 thousand times a second), they do not cause muscles to twitch, nor do they have any effects on other electrically activated tissues in the body (brain, nerves and heart). Since the intensities of TTFields in the body are very low, they do not cause heating.

The breakthrough finding made by Novocure was that finely tuned alternating fields of very low intensity, now termed TTFields (Tumor Treating Fields), cause a significant slowing in the growth
of cancer cells. Due to the unique geometric shape of cancer cells when they are multiplying, TTFields cause electrically-charged cellular components of these cells to change their location within the dividing cell, disrupting their normal function and ultimately leading to cell death. In addition, cancer cells also contain miniature building blocks which act as tiny motors in moving essential parts of the cells from place to place. TTFields interfere with the normal orientation of these tiny motors related to other cellular components since they are electrically-charged as well. As a result of these two effects, tumor cell division is slowed, results in cellular death or reverses after continuous exposure to TTFields.

Other cells in the body (normal healthy tissues) are affected much less than cancer cells since they multiply at a much slower rate if at all. In addition TTFields can be directed to a certain part of the body, leaving sensitive areas out of their reach. Finally, the frequency of TTFields applied to each type of cancer is specific and may not damage normally dividing cells in healthy tissues.

In conclusion, TTFields hold the promise of serving as a brand new treatment for pancreatic adenocarcinoma with very few side effects.

Ein-/Ausschlusskriterien

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:
   - Head/uncinate process:
     1. Solid tumor contact with SMA>180°
     2. Solid tumor contact with the CA>180°
     3. Solid tumor contact with the first jejunal SMA branch
     4. Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland thrombus)
   - Body and tail
     1. Solid tumor contact of >180° with the SMA or CA
     2. Solid tumor contact with the CA and aortic involvement
     3. Unreconstructible SMV/PV due to tumor involvement or occlusion (can be d/t tumor or bland
- No distant metastasis, including non-regional lymph node metastasis
- No borderline resectable (per Al-Hawary MM, et al., Radiology 201414)

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-100L(P) System 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 non-melanomatous skin cancer.

3. Serious co-morbidities:

1. Clinically significant (as determined by the investigator) hematological, hepatic and renal dysfunction, defined as: Neutrophil count < 1.5 x 10^9/L and platelet count < 100 x 10^9/L; bilirubin > 1.5 x Upper Limit of Normal (ULN); AST and/or ALT > 2.5 x ULN; and serum creatinine > 1.5 x ULN.

2. 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).

3. History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the trial.

4. History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable.

5. Active infection or serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.

6. History of any psychiatric condition that might impair patient's ability to understand or comply with the requirements of the study or to provide consent.

4. Concurrent anti-tumor therapy beyond gemcitabine and nab-paclitaxel

5. Implantable electronic medical devices in the torso, such as pacemakers
6. Known severe hypersensitivities to medical adhesives or hydrogel, or to one of the chemotherapies used in this trial.

7. Pregnancy or breast-feeding (female patients with reproductive potential and their partners must accept to use effective contraception throughout the entire study period and for 3 months after the end of treatment). All patients who are capable of becoming pregnant must take a pregnancy test which is negative within 72 hours before beginning treatment. 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.

**Studien-Rationale**

**Primary outcome:**

1. Overall survival (Time Frame - 4 years)

**Secondary outcome:**

1. Progression-free survival (Time Frame - 4 years)

2. Local progression-free survival (Time Frame - 4 years)

3. Objective response rate (Time Frame - 4 years)

4. One-year survival rate (Time Frame - 4 years)

5. Quality of life (Time Frame - 4 years): 

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

6. Pain-free survival (Time Frame - 4 years):

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

7. Puncture-free survival (Time Frame - 4 years)

8. Resectability rate (Time Frame - 4 years)

9. Toxicity profile (Time Frame - 4 years):

   *Toxicity profile in patients treated with TTFIELDS in combination with gemcitabine and nab-paclitaxel compared to the toxicity profile of patients treated with chemotherapy alone, measured by the rate of treatment-emergent toxicities in both arms. Adverse events will be collected and recorded based on the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.*
Studien-Arme

- Experimental: NovoTTF-100L(P)
  Patients receive TTFIELDS using the NovoTTF-100L(P) System together with gemcitabine and nab-Paclitaxel
- Active Comparator: Best Standard of Care
  Patients receive best standard of care with gemcitabine and nab-Paclitaxel

Geprüfte Regime

- NovoTTF-100L(P) (TTFIELDS):
  Patients receive continuous TTFIELDS treatment using the NovoTTF-100L(P) device. TTFIELDS treatment will consist of wearing four electrically insulated electrode arrays on the torso. The treatment enables the patient to maintain regular daily routine.
- Gemcitabine:
  Gemcitabine 1000 mg/m^2 over 30 minute infusion will be administered immediately after nab-paclitaxel on Days 1, 8 and 15 of each 28-day cycle.
- nab paclitaxel:
  nab-paclitaxel 125 mg/m^2 administered as an intravenous infusion over 30-40 minutes on Days 1, 8 and 15 of each 28-day cycle.

Kontakt

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Studienlocations (3 von 64)

Banner MD Anderson Cancer Center
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Status: Rekrutierend
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| <strong>Pacific Cancer Medical Center</strong> | 92801 Anaheim | United States | <strong>Status:</strong> Rekrutierend |
| <strong>Dignity Health - Mercy Cancer Centers</strong> | 95816 Sacramento | United States | <strong>Status:</strong> Rekrutierend |
| <strong>Associated Neurologists of Southern CT, P.C.</strong> | 06460 Bridgeport | United States | <strong>Status:</strong> Rekrutierend |
| <strong>Florida Cancer Specialists - South</strong> | 33901 Fort Myers | United States | <strong>Status:</strong> Rekrutierend |
| <strong>Mount Sinai Medical Center</strong> | 33140 Miami Beach | United States | <strong>Status:</strong> Rekrutierend |
| <strong>BRCR Medical Center INC</strong> | 33324 Plantation | United States | <strong>Status:</strong> Rekrutierend |
| <strong>Florida Cancer Specialists</strong> | | | |</p>
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United States

**Status: Rekrutierend**

**Ochsner Medical Center**  
70121 New Orleans  
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**Maryland Oncology Hematology, P.A - US Oncology Research**  
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United States

**Karmanos Cancer Institute**  
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**Cancer and Hematology Centers of Western Michigan, PC**  
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**University of Minnesota**  
55455 Minneapolis  
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| **Nebraska Methodist Hospital**  
68114 Omaha  
United States |
| **Comprehensive Cancer Centers of Nevada**  
89619 Las Vegas  
United States |
| **Renown Regional Medical Center, Institute for Cancer**  
89502 Reno  
United States |
| **New York-Presbyterian/Queens**  
11355 Flushing  
United States |
| **NYU Langone Arena Oncology**  
11042 Lake Success  
United States |
| **Novant Health Clinical Research**  
27103 Winston-Salem  
United States |
| **University of Oklahoma Health Sciences Center**  
73104 Oklahoma City  
United States |
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<td>75246 Dallas</td>
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<td>West Virginia University Cancer Institute</td>
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Quelle: ClinicalTrials.gov