Effect of Tumor Treating Fields (TTFields) (150 kHz) Concurrent With Standard of Care Therapies for Treatment of Stage 4 Non-small Cell Lung Cancer (NSCLC) Following Platinum Failure (LUNAR)

NCT-Nummer:
NCT02973789

Studienbeginn:
Dezember 2016

Letztes Update:
07.08.2019

Wirkstoff:
Immune checkpoint inhibitors or docetaxel

Indikation (Clinical Trials):
Lung Neoplasms, Carcinoma, Non-Small-Cell Lung

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 NSCLC pre-clinical models both as a single modality treatment and in combination with chemotherapies and PD-1 inhibitors. TTFields have been demonstrated to act synergistically with taxanes and have been shown to be additive when combined with PD-1 inhibitors. In addition,
TTFields have shown to inhibit metastatic spread of malignant melanoma in in vivo experiment.

In a pilot study, 42 patients with advanced NSCLC who had had tumor progression after at least one line of prior chemotherapy, received pemetrexed together with TTFields (150 kHz) applied to the chest and upper abdomen until disease progression (Pless M., et al., Lung Cancer 2011). The combination was well tolerated and the only device-related adverse event was mild to moderate contact dermatitis. Efficacy endpoints were remarkably high compared to historical data for pemetrexed alone.

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 2015).

DESCRIPTION OF THE TRIAL:

All patients included in this trial are patients with squamous or non-squamous, stage 4 NSCLC who had disease progression on or after receiving platinum based chemotherapy. In addition, all patients must meet all eligibility criteria.

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

Patients receive docetaxel or immune checkpoint inhibitor in combination with TTFields using the NovoTTF-100L System.

Patients receive docetaxel or immune checkpoint inhibitor 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 group, the patients will be treated continuously with the device until disease progression in the thorax and/or liver according to RECIST or irRECIST (Immune-Related Response Evaluation Criteria In Solid Tumors) (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively).

On both arms, patients who have disease progression according to RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively) will switch to a third 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 NSCLC with very few side effects.

Ein-/Ausschlusskriterien

**Inclusion Criteria:**

1. 22 years of age and older
2. Life expectancy of ≥ 3 months
3. Histological diagnosis of squamous or non-squamous, inoperable, stage 4 NSCLC
4. Diagnosis of radiological progression while on or after first platinum-based systemic therapy
5. Randomization within 28 days of diagnosis of last progression
6. ECOG Score of 0-2
7. Assigned by the physician to receive either docetaxel or immune checkpoint inhibitor per standard of care regimens
8. Able to operate the NovoTTF-100L device independently or with the help of a caregiver
9. Signed informed consent for the study protocol

**Exclusion Criteria:**
1. Presence of brain metastasis or leptomeningeal spread of the disease

2. Patients planned to receive immune checkpoint inhibitor with contra-indications to receive immunotherapy

3. Patients planned to receive docetaxel with contra-indications to receive docetaxel

4. Severe comorbidities:

   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 ULN; AST and/or ALT > 2.5 x ULN or > 5 x ULN if patient has documented liver metastases; 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 pericarditis

   5. History of interstitial lung disease

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

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

   8. 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

   9. Any other malignancy requiring anti-tumor treatment in the past three years, excluding treated stage I prostate cancer, in situ cervical cancer, in situ breast cancer and non-melanomatous skin cancer

   5. Concurrent treatment with other experimental treatments for NSCLC while on the study

   6. Implantable electronic medical devices (e.g. pacemaker, defibrillator) in the upper torso

   7. Known allergies to medical adhesives or hydrogel

   8. Pregnancy or breast-feeding (patients with reproductive potential must use effective contraception methods throughout the entire study period, as determined by their investigator/gynecologist)
Studien-Rationale

**Primary outcome:**

1. Overall survival of patients treated with TTFields + docetaxel or immune checkpoint inhibitors vs. docetaxel or immune checkpoint inhibitors alone (superiority analysis) (Time Frame - 4 years)

**Secondary outcome:**

1. Overall survival of patients treated with TTFields + docetaxel vs. docetaxel alone (superiority analysis) (Time Frame - 4 years)

2. Overall survival of patients treated with TTFields + immune checkpoint inhibitors vs. immune checkpoint inhibitors alone (superiority) (Time Frame - 4 years)

3. Overall Survival of patients treated with TTFields + docetaxel Vs. immune checkpoint inhibitors alone (non-inferiority analysis) (Time Frame - 4 years)

4. Progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors + TTFields vs. docetaxel or immune checkpoint inhibitors alone, based on RECIST Criteria (Time Frame - 4 years)

5. Overall radiological response rate (based on RECIST criteria) of patients treated with docetaxel or Immune checkpoint inhibitors + TTFields vs. docetaxel or immune checkpoint inhibitors alone. (Time Frame - 4 years)

6. Quality of life using the EORTC QLQ C30 questionnaire with LC13 addendum (Time Frame - 4 years)

7. Analyses of the effects of NovoTTF-100L with each type of immune checkpoint inhibitor on overall survival and progression free survival (Time Frame - 4 years)

8. Analysis of the effects of NovoTTF-100L on overall survival and progression free survival within each histological subgroup (squamous and non-squamous) (Time Frame - 4 years)

9. The effect of treatment compliance with NovoTTF-100L on overall survival and progression free survival outcomes (Time Frame - 4 years)

10. Adverse events, severity and frequency based on Common Terminology Criteria for Adverse Events (CTCAE) V4.03 (Time Frame - 4 years)

**Studien-Arme**

- **Experimental: NovoTTF-100L**

  *Patients receive TTFields using the NovoTTF-100L System together with immune checkpoint*
Patients receive best standard of care with immune checkpoint inhibitors or docetaxel

Geprüfte Regime

- NovoTTF-100L (TTFields): Patients receive continuous TTFields treatment using the NovoTTF-100L device. TTFields treatment will consist of wearing four electrically insulated electrode arrays on the chest. The treatment enables the patient to maintain regular daily routine.
- Immune checkpoint inhibitors or docetaxel: Patients receive standard of care with Immune checkpoint inhibitors or docetaxel

Kontakt

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*Quelle: ClinicalTrials.gov*