ENGOT-ov50 / INNOVATE-3: Pivotal, Randomized, Open-Label Study of Tumor Treating Fields (TTFields, 200kHz) Concomitant with Weekly Paclitaxel for the Treatment of Recurrent Ovarian Cancer

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Primary objective:- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients prolongs the overall survival of patients, compared to weekly paclitaxel treatment alone....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52844

Source
ToetsingOnline

Brief title
EF-28 / ENGOT-ov50 / INNOVATE-3

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
ovarian cancer; recurrent ovarian cancer

Research involving

Human

Sponsors and support

Primary sponsor: Novocure GmbH
Source(s) of monetary or material Support: Novocure GmbH

Intervention

Keyword: Ovarian Neoplasms, Recurrent Ovarian Cancer, TTFields, Tumor Treating Fields

Outcome measures

Primary outcome

Primary endpoint:

- Overall survival (OS) of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to overall survival of patients treated with weekly paclitaxel alone, measured from randomization.

Secondary outcome

Secondary endpoint:

- Progression-free survival (PFS) of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to progression-free survival of patients treated with weekly paclitaxel alone, measured as the time interval between randomization and the date of disease progression (based on CT or MRI scans collected during the study, using the RECIST V1.1 Criteria1 and the GCIG guidelines2).

- Objective response rate (ORR) of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer,

compared to the objective response rate of patients treated with weekly paclitaxel alone, based on CT or MRI scans collected during the study, using the RECIST V1.1 Criteria, and the GCIG guidelines2.

- Next progression-free survival (PFS2) of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to the next progression-free survival of patients treated with weekly paclitaxel alone, measured from the time of randomization to tumor progression based on investigator*s assessment, and preferrably based on RECIST V1.1 Criteria1 (as long as radiological data are available at this stage of the study follow up), on next-line treatment46.

- Toxicity profile in patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly
paclitaxel for recurrent ovarian cancer, compared to the toxicity profile of patients treated with weekly paclitaxel alone, measured by the rate of patients with treatment-emergent toxicities in both arms based on the Common Terminology Criteria for Adverse Events (CTCAE) V5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

- Time until definitive deterioration in HRQoL (TUDD) or death of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to the TUDD of patients

treated with weekly paclitaxel alone, measured as the time interval between randomization and the first decrease in HRQoL score >= 10-point with no further improvement in HRQoL score >= 10 points or any further HRQoL data, based on the EORTC QLQ-C30 questionnaire47,48.

- Time to first and second subsequent therapy or death (TFST & TSST) of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to the TFST & TSST of patients treated with weekly paclitaxel alone, measured as the time from the date of randomization to the clinical decision made by the investigator to initiate a first and second subsequent lines of treatment, respectively, or death date49.

- Quality of life of patients treated with TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel for recurrent ovarian cancer, compared to the quality of life of patients treated with weekly paclitaxel alone, assessed using the EORTC QLQ C30 quality of life questionnaire with the ovarian cancer symptom OV28 module.

Study description

Background summary

Novocure, sponsor of this clinical study, has previously developed the experimental device NovoTTF-100A for use in treating glioblastoma multiform, a type of brain cancer. A randomized study that included 695 patients with glioblastoma which has been recently diagnosed has been conducted to evaluate

TTFields in this disease. It was shown that adding TTFields at a specific frequency to the standard chemotherapy used to treat patients after their initial therapy led to a longer survival time in these patients.

The effect of TTFields on ovarian cancer has been tested in the laboratory in cell cultures and animal studies. In these studies, TTFields treatment resulted in decreased ovarian cancer cell growth. When combined with chemotherapy there was an even greater decrease in ovarian cancer cell growth.

TTFields have also been evaluated in a clinical study in ovarian cancer patients. In this pilot study, 31 patients suffering from recurrent platinum-resistant ovarian cancer applied the NovoTTF-100L(O) System to the abdomen and pelvis. At the same time, subjects received weekly drug called paclitaxel. Paclitaxel is a chemotherapy used in subjects with platinum resistant ovarian cancer. This NovoTTF-100L(O) system, used also in the current trial, delivers TTFields at a specific frequency. This frequency was demonstrated to kill ovarian cancer cells in the lab more effectively.

Patients treated with TTFields using the NovoTTF-100L(O) combined with weekly paclitaxel as part of this trial tolerated the treatment well. Mild to moderate skin irritation was the most common adverse event related to the device. In most cases, creams or ointments applied to the skin improved the skin irritation. If case skin irritation occurs, study doctor will provide you with appropriate treatment.

Ovarian cancer is the second most common gynecologic malignancy and the most common cause of gynecologic cancer death in the United States. Most patients are diagnosed at an advanced, unresectable stage and receive palliative therapy. PROC, developed ultimately in almost all patients, remains a condition with poor prognosis and little advancement in prolonging survival over the last decade.

TTFields have been demonstrated to reduce the proliferative capacity of multiple cancers in preclinical models, predominantly by inhibiting the normal polymerization process of the mitotic spindle at metaphase. TTFields increased survival when added to temozolomide in a phase 3 in newly diagnosed glioblastoma. It also showed to have a mild safety profile with preliminary promising efficacy in pilot studies in NSCLC, mesothelioma and pancreatic cancer. TTFields is a loco-regional anti-mitotic therapy, which can be applied to the abdominal and pelvic regions. Simulations have demonstrated that therapeutic level TTFields could be delivered to common sites of disease in ovarian cancer, including malignant ascites.

The efficacy of TTFields in ovarian cancer has been shown using in vitro and in vivo models. The addition of taxanes to TTFields was synergistic in preclinical ovarian models, potentially resulting from the mitotic spindle being a common target for both treatments. In the INNOVATE pilot clinical study, TTFields at

200 kHz to the abdomen and pelvis were used in combination of weekly paclitaxel for the treatment of 31 PROC patients, who had good compliance on TTFields and promising PFS outcomes. The only TTFields-related adverse event was dermatitis underneath the transducer arrays in most patients, which was CTCAE grade 1-2 in the vast majority of cases.

Taken together, there is a strong rationale for testing TTFields at 200 kHz to the abdomen and pelvis in combination with weekly paclitaxel as a potentially safe and effective treatment in PROC.

The hypothesis of this study is that the use of TTFields concommitant to weekly paclitaxel in subjects with recurrent ovarian cancer will increase overall survival compared to subjects treated with weekly paclitaxel alone.

Study objective

Primary objective:

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients prolongs the overall survival of patients, compared to weekly paclitaxel treatment alone.

Secondary objectives:

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients prolongs the progression-free survival (PFS) of patients, compared to weekly paclitaxel treatment alone.

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients increases the rate of objective response rate (ORR) of patients, compared to weekly paclitaxel treatment alone.

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients prolongs the next progression-free survival (PFS2) of patients, compared to weekly paclitaxel treatment alone.

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients is a safe treatment compared to weekly paclitaxel treatment alone.

- To determine if TTFields at 200 kHz to the abdomen and pelvis with weekly paclitaxel in the treatment of recurrent ovarian cancer patients prolongs the time until definitive deterioration in HRQoL (TUDD) or death of patients,

compared to weekly paclitaxel treatment alone.

Study design

Pivotal, randomized (1:1), open-label, two-arm, multi-center study of the NovoTTF-100L(O) system.

Stratification factors:
1. Prior Therapy - 1) No prior systemic therapy following platinum resistance 2) One prior line of systemic therapy following platinum resistance 3) Two prior lines of systemic therapies following platinum resistance

2. Prior bevacizumab use - 1) bevacizumab was used prior to enrollment in the study 2) bevacizumab was not used prior to enrollment in the study

3. BRCA Status - 1) mutated BRCA 2) wild type BRCA / unknown

Intervention

Patients will be centrally randomized using an IxRS system at a 1:1 ratio to 2 treatment arms within 28 days of signing the ICF, using variable blocked randomization:

1. Treatment arm I: Patients receive TTFields at 200 kHz to the abdomen and pelvis using the
NovoTTF-100L(O) System together with weekly paclitaxel.

2. Treatment arm II: Patients receive weekly paclitaxel alone.

The NovoTTF-100L(O) System is an investigational medical device delivering 200 kHz TTFields to the abdomen and pelvis for the treatment of patients at the age of 18 years or older with platinum-resistant ovarian, primary peritoneal or fallopian tube carcinomas, in combination with weekly paclitaxel. It is intended to be used for at least 18 hours per day on a monthly average and exclusively by patients in a clinical trial.

The device is a portable, battery operated system which delivers TTFields at 200 kHz to the abdomen and pelvis by means of insulated Transducer Arrays. The NovoTTF-100L(O) produces electric forces intended to disrupt cancer cell division.

Paclitaxel will be administered per institutional practice with appropriate pre-medications and will be supplied from commercial sources as concentrate for reconstitution and administered weekly intravenously over 1 hour. The starting dose for all patients will be 80 mg/m2. Paclitaxel will be administered via intravenous infusion weekly for 8 weeks and then for all subsequent cycles on

days 1, 8 and 15 of each subsequent 28 day cycle. Paclitaxel will be administered until radiological progression per RECIST V1.1 and the GCIG guidelines2, clear clinical disease progression per study investigator or unacceptable toxicity based on investigator assessment. Hematologic toxicities will be assessed prior to each paclitaxel dose with a complete blood count (CBC) including differential and platelet count.

Study burden and risks

Patients will come to the study site two times for baseline evaluation / screening and then every 4 weeks for until disease progression. If the study treatment is discontinued, another visit will be scheduled for approximately one month after discontinuation. Following local disease progression, patients will be followed monthly for survival by telephone call to the patient or caregiver appointed in the informed consent process (unless a clinical visit is performed). Information on survival status, treatment for ovarian cancer and disease progression therapy will be collected.
Additionally, patients will receive weekly paclitaxel infusion as per institutional practice.

A CT scan or MRI scan of chest, abdomen and pelvis is performed 28 days prior to randomization. Additionally bone scan, another MRI or the CT scan of the brain can be performed if clinically indicated. Within 14 days prior to randomization following examinations will be performed: Medical history, physical examinations, vital signs (blood pressure, heart rate, respiratory rate, temperature, size and weight), concomitant medication recording, performance status (ECOG Score), serum pregnancy test (if applicable), blood draws (for complete blood count, serum chemistry panel including CA-125, coagulation tests), EORT QLQ C30 questionnaire + OV28 module questionnaire.

All patients will come to the hospital every 4 weeks after randomization for physical examination including vital signs assessment and performance status determination, blood draws (serum chemistry, complete blood count,). Additionally every other visit, a CT Scan and/or MRI Scan is performed to evaluate the tumour assessment (same modality through entire follow-up period). CT/MRI of the brain and a bone scan can be performed if indicated. A paper-based Quality of Life Questionnaire (total of 4 pages) is to be completed by the patient every other visit (every 8 weeks).

Patients assigned to the treatment arm with TTFields together with weekly paclitaxel will be trained on the use of the NovoTTF-100L(O) device and the array placement onto the skin.

The NovoTTF-100L(O) System is comprised of two main components: The NovoTTF-100L(O) device which generates TTFields and the transducer arrays - sticky pads- which attach around the abdominal region and deliver TTFields to the ovary/ovaries. The device can be used with minimal change to the daily

routine. The device is designed to allow normal social life with minimal discomfort:
Patients are able to carry the portable, battery operated device in a dedicated backpack. .For sleeping or times where the patient stays in the same place, the device is plugged into a standard wall outlet.

Patients will replace the transducer arrays twice to three times per week with the help of a caregiver. A device technician (Novocure Device Support Specialist) is assisting the patient in the functionality of the device and re-training of the transducer array placement.

Patients assigned to NovoTTF arm will have to use NovoTTF-100L(O) for at least 18 hours a day on average. Patients may take breaks for personal needs (e.g. showering, array exchange) as long as the average treatment remains 18 hours per day (monthly average). TTFields may be continued as long as there is no progression in the abdominal or pelvic regions (*local disease progression*) per RECIST V1.11 or any of the treatment discontinuation conditions.

Risks:

Paclitaxel:
The most common side effects are:
Low number of blood cells, including white (leucocytes) and red (erythrocytes) blood cells and platelets, infections and fever; bleeding; hypersensitivity reactions, including an itchy skin rash, swelling of the throat and tongue; shortness of breath, swelling of the hands, face or feet; hives; slow heartbeat; low blood pressure; injury to the peripheral nervous system (the part of the nervous system outside the brain and spinal cord), leading to weakness, numbness, pain and changes in the sensitivity of the hands and feet (the hands and feet are less sensitive or completely insensitive to the effects of stimulants such as temperature, touch, vibrations, pain, changes in position, and pressure). This is frequently associated with the sensation of tingling or a feeling of numbness); joint and muscle pain; nausea; vomiting; diarrhea; intestinal inflammation; hair loss; reduced liver function; skin reactions at the paclitaxel injection site, such as increased skin pigmentation, redness, tenderness, swelling, heat or dryness of the skin; a feeling of weakness or fatigue.

TTFields:
We do not expect treatment with the NovoTTF-100L(O) to cause any severe adverse reactions. However, it is possible that treatment may cause localized skin irritation, skin issues, or infection where the electrodes come into contact with your skin, as well as pain. If these symptoms occur, however, they shall be assessed and treated by the investigator, and should be completely healed as soon treatment with the device ends. The device may also cause a local sensation of heat and tingling, as well as falls and fatigue (tiredness and

exhaustion). The treatment may also have no effect on tumor progression or regression.
Apart from the expected skin irritation, it has not been reported in animal studies nor in the pilot study in ovarian cancer patients described above that the use of TTFields was associated with damage to healthy tissues, which are not related to the tumor. Nevertheless, since the NovoTTF-100L(O) intends to interfere with the cell division process, there is a potential risk of such damage to healthy tissues in the region of the tumor.
The other possible risks of any electrical device, including the NovoTTF-100L(O), are the risk of a power cut or mechanical problems, an electric shock and electromagnetic interference. However, the device manufacturer has taken appropriate measures to minimize the probability of these risks appearing.

Taking blood:
The risks associated with taking a blood sample include mild pain when the needle is inserted into the arm, the formation of hematoma at the injection site, a low risk of venous inflammation, nerve lesions (nerve injuries) and a risk of fainting. There is also a risk of infection. Up to 10 ml of blood (2 teaspoons) may be taken for each scheduled laboratory test. Approximately 220 mL of blood (1 cup) will be drawn during the entire duration of the study. If necessary, the investigator may test blood more frequently.
The blood samples will be examined at the hospital. Blood samples will not be sent outside the hospital for examination.

Computed tomography (CT):
CT imaging is a painless procedure that is safe for most people. People with fear of confined spaces may feel anxious during the procedure. Nausea, headaches, hot flushes, palpitations and allergic reactions (anaphylactic shock included) may happen as a reaction to the contrast agent. The increased dose of radiation may lead to cancer and other diseases.

Magnetic Resonance Imaging (MRI):
Some people feel anxious or are fearful in small spaces (claustrophobia). The MRI scanner makes loud knocking noises during measurements, which may be uncomfortable.
Gadolinium-based contrast agents in patients with pre-existing, severe hepatic dysfunction, or who have recently (within the last 4 weeks) had a kidney or liver transplant, is associated with a rare occurrence of nephrogenic systemic fibrosis (NSF), however kidney function will be checked for in medical history.

Intravenous infusion:
The risks associated with the intravenous cannulas are similar to those associated with taking a blood sample (see above).

Contacts

Public
Novocure GmbH

Park 6
Root D4 6039
CH
Scientific
Novocure GmbH

Park 6
Root D4 6039
CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. 18 years of age and older
2. Epithelial histology of ovarian/primary peritoneal or fallopian tube carcinoma at the time of diagnosis
3. Life expectancy of >= 12 weeks
4. Maximum two prior lines of systemic therapy following diagnosis of platinum-resistance
a. Platinum resistance is defined as tumor progression per RECIST V1.1 within 6 months of the last administration of a platinum agent
b. *Line of systemic therapy* includes the following:
(i) Any targeted therapy
(ii) Any change to a new family of systemic therapy following toxicity (regardless of radiological status)
c. *Line of systemic therapy* does NOT include the following:

(i) Maintenance therapy (started prior to progressive disease per RECIST V1.1)
(ii) Therapy replaced with another agent of the same family (i.e. due to toxicity)
5. Maximum total of 5 prior lines of systemic therapy
6. Amenable to receive weekly paclitaxel and able to operate the NovoTTF-100L(O) System
7. ECOG 0-1
8. Evaluable (measurable or non-measurable) disease in the abdominal/pelvic region per RECIST
V1.1
9. Signed informed consent form for the study protocol

Exclusion criteria

1. Primary platinum-refractory disease (progression per RECIST V1.1 during or within 1 month after first line therapy), while secondary platinum-refractory disease is allowed
2. Prior disease progression on a weekly paclitaxel for recurrent disease
3. Brain metastasis or leptomeningeal spread of the tumor
4. Albumin level <25 gram/liter (subjects should not receive total parenteral nutrition or albumin within 2 weeks of the test)
5. CTCAE V5.0 Grade 3 or higher peripheral neuropathy
6. Implantable electrical medical devices
7. Known allergies to medical adhesives or hydrogel
8. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to paclitaxel or drugs similar or related to paclitaxel, except for cases that were able to undergo desensitization per investigator
9. Prior malignancies treated primarily or for recurrence within 2 years prior to inclusion in this study, except for completely resected non-melanomatous skin carcinoma, or successfully treated in situ carcinoma of the skin, breast or cervix of the uterus,
10. Serious co-morbidities:
a. 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, as long as they are determined clinically significant by the investigator.
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 not adequately controlled. Specifically, patients with atrial fibrillation or flutter controlled by

medication are not excluded from participation in the trial.
d. History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable.
e. Active infection or serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.
f. Unable to follow the protocol for medical, psychological, familial, geographic or other reasons, or comply with the requirements of the study or to provide consent.
11. Concurrent anti-tumor therapy beyond weekly paclitaxel, excluding hormonal therapy for breast cancer.
12. Concurrent active treatment in another clinical trial. However prior participation in clinical trials is allowed as well as participation during survival follow-up.
13. 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.
14. Admitted to an institution by administrative or court order.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-09-2021
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	NovoTTF-100L(O) System
Registration:	No

Ethics review

Approved WMO Date:	03-03-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	05-05-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03940196
CCMO	NL74118.041.20