LUNAR-2: Pivotal, Randomized, Open-Label Study of Tumor Treating Fields (TTFields, 150 kHz) Concomitant with Pembrolizumab and Platinum Based Chemotherapy for the Treatment of Metastatic Non-Small Cell Lung Cancer

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Objectives: To test the effectiveness and safety of TTFields, delivered using the NovoTTF-200T device, concomitant with pembrolizumab and platinum-based chemotherapy in subjects with metastatic non-small cell lung cancer (NSCLC)

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON56988

Source
ToetsingOnline

Brief title
LUNAR-2

Condition

- Other condition

Synonym
Lung cancer, NSCLC

Health condition

longkanker

Research involving
Human

Sponsors and support

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

Intervention

Keyword: LUNAR-2, TTFields

Outcome measures

Primary outcome

• Overall survival (OS), in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy compared to OS of those treated with pembrolizumab and platinum-based chemotherapy alone.

• Progression-Free Survival (PFS), per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by Blinded Independent Central Review (BICR), in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy compared to PFS of those treated with pembrolizumab and platinum-based chemotherapy alone.

Secondary outcome

• PFS per RECIST v1.1 as assessed by BICR, in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy and of those treated with pembrolizumab and platinum-based chemotherapy alone according to histology.

• OS in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy and of those treated with pembrolizumab and

platinum-based chemotherapy alone according to histology.

• PFS per RECIST v1.1 as assessed by BICR, in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy and of those treated with pembrolizumab and platinum-based chemotherapy alone according to PD-L1 Tumor Proportion Score (TPS).

• OS in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy and of those treated with pembrolizumab and platinum-based chemotherapy alone according to PD-L1 TPS.

• PFS per RECIST v1.1 as assessed by BICR at 6 (PFS6), 12 (PFS12), 24 (PFS24), and 36 (PFS36) months in subjects treated with TTFields concomitant with pembrolizumab and platinum-based chemotherapy and of those treated with pembrolizumab and platinum-based chemotherapy alone.

Study description

Background summary

Worldwide, lung cancer is the leading cause of cancer death with an estimated 1.8 million deaths in 20201. In the United States, there are over 230,000 new cases of lung cancer and 130,000 deaths annually. Approximately 84% of patients with lung cancer have NSCLC and about 60% of them have distant metastases by the time of diagnosis (stage IV).
Substantial improvements in general understanding of disease biology, application of predictive biomarkers, and refinements in treatment have led to remarkable progress and transformed outcomes for many patients. Yet, as the majority of patients unfortunately are metastatic upon diagnosis, the cure rates are low and all stages are at a high risk of relapse and progression despite modern therapy.

TTFields are a non-invasive, loco-regional treatment for solid tumors that is well tolerated and has been approved for the treatment of recurrent and newly diagnosed glioblastoma (GBM) and for unresectable malignant pleural mesothelioma by the Food and Drug Administration (FDA) and has obtained a CE

mark in Europe for the same indication.
TTFields are delivered to the tumor site via a portable medical device that consists of a field generator and arrays that are placed on the patient*s skin. TTFields target cancer cells via multipole mechanisms, disrupting processes important for cancer cells (e.g. division and movement), which can ultimately lead to cell death over time. The functional disruption of polar cellular components (e.g. the microtubule spindle during mitosis) by TTFields ultimately leads to aberrant mitotic effects, cellular stress, and immunogenic forms of cancer cell death over time.

Additionally, TTFields have been shown to enhance antitumor immune responses, downregulate DNA damage response genes in cancer cells, interfere with cancer cell motility via disruption of the organization and dynamics of the microtubule network.
The ability of TTFields to disrupt multiple processes in cancer cells highlights the potential of TTFields to be used with existing cancer therapies. The magnitude of the anticancer effects of TTFields is dependent on the frequency, intensity, time, and direction of TTFields delivery, and can be modified to target a diverse range of solid tumors. The anti-mitotic effect of TTFields has been shown in multiple cell lines when the appropriate frequency was utilized. This includes but is not limited to the following tumor models: GBM at 200 kHz, NSCLC at 150kHz; breast carcinoma at 150kHz; melanoma at 100kHz. The effect of TTFields is directional, i.e., TTFields are most effective when applied in the direction of the division axis of the dividing cell. To increase the efficacy of TTFields, two sequential field directions can be applied to tumors by using two perpendicular pairs of transducer arrays. Using two-directional TTFields in pilot clinical testing demonstrated TTFields to be biologically active in human tumors.

Study objective

Objectives: To test the effectiveness and safety of TTFields, delivered using the NovoTTF-200T device, concomitant with pembrolizumab and platinum-based chemotherapy in subjects with metastatic non-small cell lung cancer (NSCLC)

Study design

Randomized (1:1), open-label, two-arm, multi-center study evaluating TTFields concomitantly with pembrolizumab and platinum-based chemotherapy in subjects with metastatic NSCLC.
Stratification factors:
1. Histology - Squamous vs. non-squamous
2. PD-L1 expression level - TPS <1% vs. TPS 1-49% vs. TPS >=50%
3. Prior treatment with immunotherapy - yes vs. no

Intervention

Mild to moderate dermatitis is the most common adverse event seen in subjects treated with the NovoTTF-200T Treatment Kit. In order to prevent and treat this condition, prophylaxis and intervention recommendations are described in appendix 2 of the study protocol.

Study burden and risks

- The study lasts a total of approximately 2 years for patients.
- Additional hospital visits, additional physical tests, including a pregnancy test.
-Possible discomforts and risks associated with the study procedures:
• Blood samples: Taking blood may cause faintness and/or swelling, pain, redness, bruising, bleeding, or infection (infection rarely happens) at the site where the needle is inserted.
• Scans: Skin irritation is very rare but could occur from the gel that is used.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. a. >=22 years of age in the USA b. >=18 years of age outside of the USA.
2. Histologically or cytologically diagnosis of stage 4 (according to Version 8 of the American Joint Committee on Cancer [AJCC] criteria) non-squamous or squamous NSCLC.
3. Evaluable (measurable or non-measurable) disease in the thorax per RECIST v1.1.
4. Have not received prior systemic treatment for their metastatic NSCLC. Subjects who received adjuvant, neoadjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease are eligible if the therapy was completed at least 12 months prior to the development of metastatic disease.
5. Have provided tumor tissue from locations not radiated prior to biopsy; formalin - fixed specimens after the subject has been diagnosed with metastatic disease will be preferred for determination of PD-L1 status assessed locally prior to randomization.
6. ECOG Performance Status (PS) of 0-1.
7. Adequate hematologic and end-organ function, defined by the following laboratory test results, obtained within 14 days prior to randomization:
o ANC >= 1.5 x 109/L (1500/µL) without granulocyte colony-stimulating factor support
o Platelet count >= 100 x 109/L (75,000/µL) without transfusion
o Hemoglobin >= 90 g/L (9 g/dL)
Subjects may be transfused to meet this criterion.
o AST, ALT <=2.5 × ULN (<=5 × ULN for participants with liver metastases)
o Serum bilirubin <= 1.5x ULN
o Serum creatinine <= 1.5 x ULN
For subjects not receiving therapeutic anticoagulation: INR or aPTT <= 1.5 x ULN (unless participant is receiving anticoagulant therapy as long as INR or aPTT is within therapeutic range of intended use of anticoagulants).
8. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
a. Not a woman of childbearing potential (WOCBP)
b. A WOCBP who agrees to use two adequate barrier methods or a barrier method plus a hormonal method during the treatment period and for at least 120 days after the last dose of study therapy. Such methods of contraception, or true abstinence from heterosexual activity, when this is in line with the preferred and usual lifestyle of the subject, are required (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception).
9. If male subject with a female partner(s) of child-bearing potential, must agree to use an effective contraception method based on the recommendation of

the investigator or a gynecologist, starting with the first dose of study therapy through 120 days after the last dose of study therapy. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.
Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
10. All subjects must sign written informed consent.
11. Able to operate the NovoTTF-200T system independently or with the help of a caregiver.

Exclusion criteria

1. Mixed small cell and NSCLC histology.
2. EGFR sensitizing mutation and/or ALK translocation, and/or ROS1 and/or RET targetable gene rearrangement, and/or METex14 skipping mutation, and/or NTRK1/2 gene fusion directed therapy is indicated or planned for other targeted therapy, where such testing and therapy is locally approved and available. Source documentation of the applicable driver mutations should be available at the site. Note: For subjects enrolled who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR mutation, ALK translocation and ROS1 and/or RET gene rearrangements, and/or METex14 skipping mutation, and/or NTRK1/2 gene fusion will not be required as this is not standard of care and is not part of current diagnostic guidelines.
3. Has received systemic therapy for metastatic disease.
4. Had major surgery <3 weeks prior to randomization
5. Received radiation therapy to the lung that is > 30 Gy within 6 months of randomization.
6. Has received prior radiotherapy within 2 weeks of randomization. Subjects must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<=2 weeks of radiotherapy) to non-CNS disease.
7. Is expected to require any other form of antineoplastic therapy while on study.
8. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
9. Has untreated or symptomatic Central Nervous System (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they were treated before randomization and are clinically stable and without requirement of steroid treatment for at least 3 days prior to randomization.
10. Has active autoimmune disease that has required systemic treatment in past

2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior randomization. Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
12. Had prior treatment with any other anti-PD-1, or PD-L1 or PD-L2 agent or an antibody or a small molecule targeting other immuno-regulatory receptors or mechanisms in the 12 months prior to randomization. Examples of such antibodies include (but are not limited to) antibodies against IDO, PD-L1, IL-2R, GITR.
13. Participation in another clinical study with an investigational agent or device during the 4 weeks prior to randomization.
Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
14. Concurrent treatment with other experimental treatments for NSCLC while in the study.
15. Significant comorbidity which is expected to affect the subject*s prognosis or ability to receive the study therapy:
a) 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).
b) 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.
c) Any serious underlying medical condition (including active infection) that would impair the ability of the subject to receive protocol therapy.
d) History of any psychiatric condition that might impair the subject*s ability to understand or comply with the requirements of the study or to provide consent.
e) Known medical condition that, in the investigator*s opinion, would increase the risk associated with study participation or study drug administration or interfere with the interpretation of safety results.
16. Implanted pacemaker, defibrillator, or other electrical medical devices in the torso.
17. Known allergies or hypersensitivity to medical adhesives, hydrogel.
18. Has a known sensitivity to any component of the planned systemic therapies (pembrolizumab, cisplatin/carboplatin, pemetrexed/paclitaxel/nab-paclitaxel) .
19. Pregnant or breastfeeding (all subjects of childbearing potential must use effective contraception method based on the recommendation of the investigator

or a gynecologist for up to 120 days after the last dose of pembrolizumab and through 180 days after last dose of chemotherapy).
20. Admitted to an institution by administrative or court order.
21. Any medical contraindication to treatment with platinum-based doublet chemotherapy or pembrolizumab as listed in the local labelling.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-08-2024
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Generic name:	NovoTTF-200T
Registration:	No

Ethics review

Approved WMO

Date:	29-08-2024
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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
CCMO	NL86318.000.24