SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Tumor Treatment Fields
Device Trade Name:	Optune Lua™
Device Product Code:	SDA
Applicant's Name and Address:	Novocure GmbH Business Village D4 Park 6/Platz 10 Root 6039, Switzerland
Date(s) of Panel Recommendation:	Not Applicable
Premarket Approval Application (PMA) Number:	P230042
Date of FDA Notice of Approval:	October 15, 2024

II. INDICATIONS FOR USE

Optune Lua concurrent with PD-1/PD-L1 inhibitors or docetaxel is indicated for adult patients with metastatic non-small cell lung cancer who have progressed on or after a platinum-based regimen.

III. CONTRAINDICATIONS

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

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Optune Lua Instructions for Use (IFU) and Patient Information and Operation Manual (PIOM).

V. DEVICE DESCRIPTION

A. Overview

Optune Lua 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 transducer arrays that are placed on the patient's chest and connected to the device. TTFields physically disrupt the rapid cell division exhibited by cancer cells.

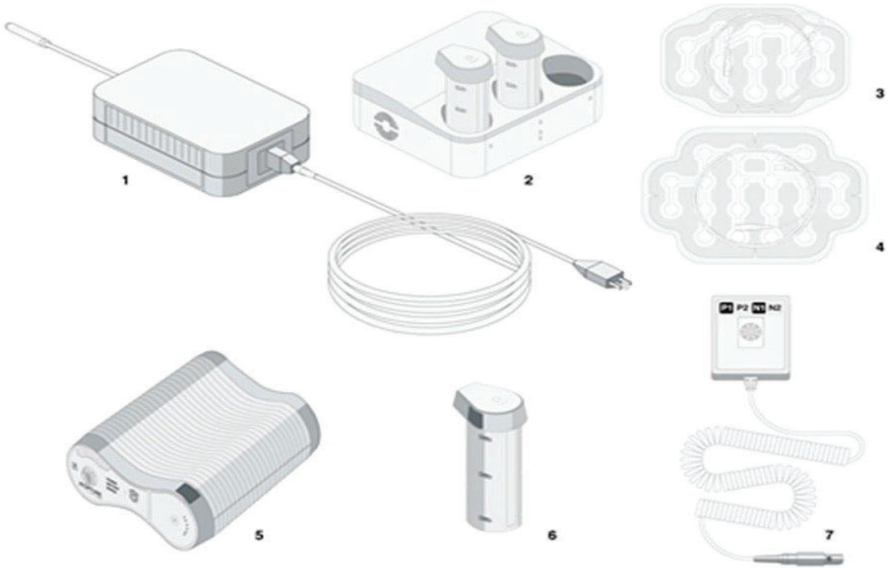
Optune Lua delivers TTFields at 150 kHz to the entire chest cavity. The device's treatment parameters are preset by Novocure. No adjustments can be made to the device by the physician or patient. Patients are initially trained on the use of the device by a Novocure device support specialist (DSS). The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

Optune Lua 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 provided as part of the treatment kit, to receive continuous TTFields treatment without changing their daily routine.

During treatment, the Optune Lua device records and stores technical information in an internal log file, including usage time as well as any errors or technical issues that might have occurred during treatment (e.g., inadequate contact of the transducer arrays to the torso of the patient).

B. Technological Characteristics

Optune Lua is comprised of an Electric Field Generator (the device), Insulated Transducer Arrays (transducer arrays), and several additional components, including a power supply, battery, battery charger, connection cable and carrying bag, that together comprise the Optune Lua Treatment Kit. An illustration of the Treatment Kit is provided in **Figure 1**, below.



1. Power Supply
2. Battery Charger
3. ITE Transducer Arrays -small
4. ITE Transducer Arrays - Large
5. Optune Lua™ Electric Field Generator (the device)
6. Battery
7. Connection Cable

Figure 1. Optune Lua Treatment Kit

Electric Field Generator: The Electric Field Generator produces TTFields per the pre-set output parameters presented below. The intensity and frequency of the TTFields, as well as the maximum allowable temperature of the transducer arrays, are controlled by two microcontrollers that run on the embedded Novocure software.

Table 1. Electric Field Generator Output Parameters

	Output Parameter
Output Frequency	150 kHz
Output Current	1.414 A_{RMS}
Treatment Field Intensity *(average in the lungs, mediastinum, liver)*	0.7 V_{RMS}/cm

The front panel of the Electric Field Generator is a simple user interface consisting of a socket to connect the CAD, a few simple visual indicators for Device, Battery and Error status and a TTFields ON/OFF button and Battery Test button. The back panel of the device houses the Power Supply Port and the Power switch for the device.

During treatment, the device records and stores technical information in log files, for review by Novocure personnel, including usage time of the device as well as any errors or technical issues that might have occurred during treatment. These log files can be downloaded directly by a Novocure device technician by physically connecting the Electric Field Generator to a Novocure laptop with dedicated software. Alternatively, patients can download and transmit the log files to Novocure's secure servers via a cellular network, using MyLink, an optional data transfer unit.

Transducer Arrays: To deliver TTFields therapy, two sets of transducer arrays (4 in total) are placed on the skin of a patient's torso and connected to the Electric Field Generator. Transducer arrays are available in two sizes to accommodate different torso sizes. Large arrays contain 20 ceramic discs, while small arrays contain 13 discs. The size of the arrays chosen for a particular patient is at the physician's discretion, based upon patient size and other considerations.

Each transducer array is comprised of serially interconnected, insulated ceramic discs that are soldered to a flexible printed circuit board (PCB). The discs are housed between a layer of adhesive tape on one side (the side that adheres to the skin), and on the other, conductive hydrogel and a foam pad layer. In addition, each array contains eight thermistors that measure skin temperature beneath the array throughout treatment. At the set parameters, the discs do not cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue. As an additional safety feature, if the thermistors detect a temperature beyond 41° C, the device will automatically shut off.

Optune Lua is compatible with two array models: ILE Arrays and ITE Arrays. The key features of both models are identical, including the materials, location of the discs and thermistors, performance specifications and availability in two sizes (small and large). The main difference is that the shape of the ITE model's medical tape and PCB are slightly different to allow for more flexibility when on the torso.

The location of placement of transducer arrays on the torso is provided to the patient as an array layout map, which is specific to each patient and based on the considerations presented in Novocure's Clinical Practice Guidelines and the treating physician's medical judgement. Layout maps can be presented in paper-based form, or digital form, via Novocure's TorsoMAX software.

Additional Components and Accessories: Together with the Electric Field Generator and Transducer Arrays, the following components make up the Optune Lua Treatment Kit: Batteries, Battery Charger, Power Supply, and Connection Cable and Box (CAD). In addition, a Carrying Bag and Transducer Array Applicator are provided to patients for use with Optune Lua.

C. Mechanism of Action

Optune Lua produces TTFields within the human body through transducer arrays placed on the chest. TTFields physically disrupt the rapid cell division exhibited by cancer cells. 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 non-small cell lung cancer, NSCLC).

In contrast, the 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 the 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 chest, 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. 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 in temperature.

TTFields have been shown to inhibit cancer cell replication through interference with the proper formation of the mitotic spindle and the cytokinetic contractile band during anaphase and by causing dielectrophoretic intracellular dislocation of macromolecules and organelles during late telophase. Acting together, these two processes, which are specific only to dividing cells, lead to a mitotic catastrophe and apoptosis and can result in tumor arrest of regression *in vivo*.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Conventional procedures used in the treatment of patients with metastatic non-small cell lung cancer who have progressed following platinum failure include chemotherapy, immunotherapy, or some combination of these modalities.

VII. MARKETING HISTORY

Optune Lua for the treatment of non-small cell lung cancer (NSCLC) has not been marketed in the United States or any foreign country. Optune Lua for the

treatment of malignant pleural mesothelioma (MPM) has been available commercially in the U.S. under a humanitarian device exemption (HDE) since 2019 (H180002).

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects associated with the use of Optune Lua include:

- Treatment related skin toxicity
- Allergic reaction to the adhesive or to the gel
- Overheating of the array, leading to pain and/or local skin burns
- Infection at the site where the array makes contact with the skin
- Local warmth and tingling sensation beneath the arrays
- Medical device site reaction
- Muscle twitching
- Skin breakdown / skin ulcer

Please see **Section X** for the specific adverse events that occurred in the pivotal clinical study.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The objective of these studies was to validate the effect of TTFields at 150 kHz on cancer cells *in vitro*. These studies formed the basis for Optune Lua's output frequency for NSCLC.

Table 2. ***In Vitro Studies***

Test/Setup	Purpose	Results	Conclusion
The inhibitory effect of TTFields was tested in various cultures at a range of frequencies between 50 - 500kHz.	Investigate whether there is an optimal frequency for the antimitotic effect of TTFields and identify the main parameters that may affect treatment.	The effect of TTFields is frequency-dependent with frequency inversely related to cell size.	Optimal frequency for NSCLC cells is 150 kHz.
Cancer cell cultures were exposed to TTFields of increasing intensities and a dose-response curve constructed for each cell type.	Test whether the effect of TTFields is intensity dependent and the threshold for inhibition of mitosis.	The effects of TTFields are dose-dependent.	Effective inhibition of NSCLC cell culture growth seen at an IC50 (inhibitor concentration where the response is reduced by half) intensity of 1.7 V/cm.
Kinetic modeling of compartmental tumor growth kinetics.	Test the time needed to achieve tumor growth reversal using TTFields.	Tumor growth reversal is seen only if TTFields are applied continuously for several weeks.	Tumor growth reversal is not immediate.

Test/Setup	Purpose	Results	Conclusion
Effects of combined TTFields with chemotherapeutic agents.	Assess effects of TTFields when combined with chemotherapy commonly used to treat mesothelioma.	Simultaneous application of TTFields with each one of several chemotherapeutic agents enhances probable benefit of treatment as compared to the chemotherapy alone.	TTFields have an additive effect to chemotherapy in NSCLC cell *lines in vitro*.

B. Animal Studies

Novocure has conducted numerous *in vivo* animal studies to investigate the effectiveness of TTFields against orthotropic, syngeneic primary tumors, including three studies of TTFields and concomitant checkpoint inhibitors in treating mice bearing Lewis lung carcinomas and subcutaneous colon carcinomas; a study of TTFields effect on inhibiting metastatic spread of VX-2 tumors in New Zealand white rabbits and metastatic melanomas in mice; several studies of TTFields and concomitant chemotherapies in treating mice bearing Lewis lung carcinomas, mice with ovarian tumors, mice and rats bearing MPM tumors, and mice bearing VX 2 kidney tumors; a study of TTFields and concomitant chemotherapy in treating hamsters bearing pancreatic tumors; and a study of TTFields in treating mice bearing Lewis lung carcinomas and squamous cell lung carcinomas. In all of these studies, TTFields were delivered to animals through specially-designed transducer arrays that could be placed on the body surfaces of these animals. Control animals were treated with sham arrays, delivering heat comparable to that generated by the TTFields transducer arrays. In all studies, TTFields effectiveness was demonstrated in the respective animal and tumor models.

Novocure has also conducted several safety studies in healthy rabbits and rats, including a safety study of 150 kHz TTFields applied to rat torsos, and safety studies of 150 kHz TTFields applied to rabbit torsos with concomitant chemotherapies. These studies found no treatment-related side effects when TTFields were applied alone or together with concomitant chemotherapies, thus supporting the safety of TTFields. The reasons for the low toxicity of TTFields treatment can be explained in the light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated transducer arrays.

C. Additional Studies

Simulations of Field Intensity Distributions*:* Simulations were performed to evaluate the safety and effectiveness of Optune Lua when delivering Tumor Treating Fields to the torso. A virtual representation of the Optune Lua was used to deliver TTFields to the lungs of three (3) different human computational models – a female model, a male model, and an obese male model with a range of body mass index (BMI) values from normal to obese. The simulations showed that for all models, Optune Lua delivers therapeutic intensities of over 0.7 V/cm RMS to over at least 76% of the lungs. Thermal safety threshold levels were determined by

current density and specific absorption rate (SAR). Current density within the models was below the safety threshold of 100 mA/cm^2. SAR values within the internal organs were below the levels at which thermal damage occurs. In the superficial body layers, higher SAR values were observed. However, Optune Lua incorporates temperature control that prevents the skin from heating to levels at which thermal damage can occur. Thus, the numerical simulations support the observations that Optune Lua delivers TTFields to the lungs at therapeutic levels and that the device is safe for use with adequate mitigation measures.

Electrical Safety and Electromagnetic Compatibility Tests*:* Novocure commissioned an independent laboratory to evaluate the electrical safety and electromagnetic compatibility of Optune Lua. The laboratory tested the device according to IEC 60601-1, IEC 60601-1-11, and IEC 60601-1-2, and found it to be free from safety hazards and in compliance with the requirements of that standard.

Table 3. Electrical Safety and EMC Testing

Test	Purpose	Standard	Results
Safety-general	Equipment when transported, stored, installed, operated in normal use, and maintained according to the instructions of the manufacturer, causes no safety hazard which could reasonably be foreseen and which is not connected with its intended application in normal condition (NC) and in single fault condition (SFC).	IEC-60601-1	Pass
Safety-classification	Type of protection against electric shock. Internally powered equipment.	IEC 60601-1	Pass
Safety-degree of protection against electric shock	Type BF applied part.	IEC 60601-1	Pass
Safety-mode of operation	Continuous operation.	IEC 60601-1	Pass
Safety-use in the home environment	Home environment use.	IEC 60601-1-11	Pass
Emissions	Radiated RF emissions, Class B.	EN/IEC 60601-1-2	Pass
Immunity	Immunity to electrostatic discharge (ESD). Radiated immunity to radio frequency electromagnetic field. Conducted immunity to electrical fast transients/bursts (EFT/ B). Conducted immunity to disturbances induced by radio frequency field. Radiated immunity to power frequency magnetic field, 50/60 1 Hz.	EN/IEC 60601-1-2	Pass

Software Verification and Validation Testing: Novocure provided software information for Optune Lua in accordance with the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" issued on May 11, 2005. Optune Lua software was deemed major level of concern, with documentation of appropriate controls and testing provided,

including: Level of Concern, Software Description, Device Hazard Analysis, Software Requirements Specifications, Architecture Design Chart, Software Design Specification, Traceability, Software Development Environment Description, Verification and Validation Documentation, Revision Level History, Unresolved Anomalies, and Run-Time Error Detection.

Optune Lua incorporates embedded device software comprised of two independent modules. The main device software module is embedded in the Electric Field Generator and controls the intensity of the tumor treating fields, the frequency of the waves, and the temperature of the transducer arrays via micro-controllers. The CAD software module is embedded within the CAD component and provides communication from the transducer arrays to the Electric Field Generator. The device software has been fully verified and validated to meet its predefined specifications, by engineers who were not involved in the development of the software or software accessories.

In addition to the embedded device software are the NovoTerminal software, MyLink software, and TorsoMAX software. The NovoTerminal software resides on a Novocure computer and is used by Novocure employees to extract logfile data from devices. MyLink is used to download Optune Lua device log files and transmit them to Novocure's secure servers via a cellular network. TorsoMAX is used by medical professionals to prepare a digital copy of the paper-based transducer array layout reports.

Cybersecurity risk management was performed in accordance with the FDA Draft Guidance, "Content of Premarket Submissions for Management of Cybersecurity in Medical Devices" and "Postmarket Management of Cybersecurity in Medical Devices". The system's software has an overall low level of complexity, and its use presents low likelihood of harm due to cybersecurity risk.

Biocompatibility: The transducer arrays are the only patient-contacting component of the device and have been tested for biocompatibility in GLP-certified laboratories according to ISO 10993-1, ISO 10993-5, and ISO 10993-10. The company performed biocompatibility endpoint assessments for cytotoxicity, skin irritation/intracutaneous reactivity, and sensitization for the transducer arrays. The tests result clearly showed that no leachable substances were released in cytotoxic concentrations from the transducer arrays. Furthermore, the tests show that the arrays have no sensitizing properties and do not cause skin irritation. Based on this testing, the materials that may encounter the patient are safe and biocompatible considering the biocompatibility requirements, the nature of contact and duration.

Sterilization: The transducer arrays are sterilized per EN 556-1 standard for sterilization of medical devices and comply with EN/ISO 11137-1, EN/ISO 11137-2, EN/ISO 11137-3, EN/ISO 11737-1 and EN/ISO 11737-2 standards. Sterilization process validation for the ITE transducer arrays follows the same sterilization process that has been previously validated, and already approved for the ILE transducer arrays (under H180002). The tolerability of the transducer arrays to high

dose gamma irradiation limit was determined to be 40 kGY for one irradiation cycle and the compatibility of materials with this dose was validated. Package integrity was validated and found in full compliance with ISO 11607-1, "Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems" and ISO 11607-2, "Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes."

Table 4. Biocompatibility, Sterilization, and Shelf Life – Transducer Arrays

Test	Standard/Method	Result	Conclusion
Biocompatibility testing, including cytotoxicity, skin irritation, intracutaneous reactivity, and sensitization	FDA Guidance Document: Use of International Standard ISO 10993-1 FDA recognized consensus standard ISO 10993-1:2009/(R) 2013	Pass: Test results showed that no leachable substances released in cytotoxic concentrations from arrays. Furthermore, the tests show that the arrays have no sensitizing properties and do not cause skin irritation.	The materials that may come in contact with the patient are safe and biocompatible considering the biocompatibility requirements, the nature of contact, and duration.
Gamma irradiation sterilization validation	Arrays sterilized per EN 556-1 and comply with EN/ISO-11137-1, EN/ISO 11137-2, EN/ISO 11137-3, EN/ISO 11737-1, and EN/ISO 11737-2	Pass	Arrays are sterile.
Shelf-Life validation	Test whether electrical and mechanical properties of the arrays remain within their specifications at the end of their shelf life.	Pass	Shelf life for the arrays is 9 months

Table 5. Hardware, Functional and Usability Testing

Test	Methods / Acceptance Criteria	Results

Electric Field Generator Testing	• Functional/durability testing:
	  ○ Device interface buttons (36,500 cycles);
	  ○ Power supply cable connection/disconnection (3650 cycles);
	  ○ CAD connection/disconnection (3650 cycles);
	  ○ Watchdog circuit
	  ○ Overvoltage and overcurrent
	• Device temperature measurements across functional range to ensure accuracy of temperature measurements of ±2°C
	• Signal waveform testing over a range of loads, with/without battery power
	• Low power hardware protection testing
		PASS

Test	Methods / Acceptance Criteria	Results
Battery / Battery Charger Testing	• Battery Testing o Performance testing of the fuel gage buttons/indicator on the Battery o Performance testing of Battery physical features o Performance/durability testing of Battery docking (750 cycles) o Charge carrying performance of the Battery (in the context of treatment time) and low battery error/visual indications functionality o Battery temperature testing o Electrical specifications testing o Safety testing (e.g., inclusion of a protection circuit) • Battery Charger Testing o Mechanical/physical testing o User interface visual inspection/functional testing (including indicators functional testing) o Performance testing (e.g., Battery voltage overtime during charging, charge current) o Battery detection testing (including faulty Battery detection)	PASS
Power Supply Testing	• Functional testing of the connections and indicators on the Power Supply • Electrical performance testing	PASS
Array Thermistor Testing	• Temperature measurements made by the thermistors are accurate to ±1°C within the range of 30 – 40°C (ILE Transducer Arrays) • Temperature measurements thermistors were accurate to ±1°C within the range of 36 – 42°C (ITE Transducer Arrays) • Temperature measurements are made every 10±1 seconds • Over-temperature alarm is triggered at temperature values greater than 41°C	PASS
Array Testing	• Verification/Validation Testing o Array capacitance (i.e., between 20 – 60 nF) and resistance to DC (direct current) is within specification (i.e., less than 1OMD) o Array impedance values at 30.6°C and 43.4°C are less than or equal to 19.94D o Measured leakage current values are less than < 1OμA with no damage to ceramic discs after applying 400VDC o Measured current at each ceramic disc is greater than 230mA during 1 minute of therapy o Array strain relief and cable / connection cable box (CAD) compatibility (ITE arrays) o Adhesive strength of the adhesive tape and ability to peel the liner o Lack of mechanical/electrical damage due to bending	PASS

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study (EF-24 / LUNAR) to establish a reasonable assurance of safety and effectiveness of Optune Lua in the treatment of adult patients with metastatic NSCLC following platinum failure in the US under IDE G170238. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

Pilot Clinical Study in NSCLC

The use of TTFields together with chemotherapy was tested in a single arm, pilot study involving 42 subjects with inoperable stage 3B or stage 4 NSCLC who had tumor progression after at least one line of prior chemotherapy. Subjects received continuous daily TTFields at 150 kHz (12 hours per day) to the chest and upper

abdomen together with pemetrexed (500mg/m2 intravenously every 3 weeks), until disease progression. Median time to in-field progression was 28 weeks. Median time to progression was 22 weeks. Median overall survival (OS) was 13.8 months (compared to a historical control of 8.3 months reported in a phase III study of pemetrexed alone compared to docetaxel). The 1-year survival rate was 57% (compared to the historical control of 30%). The use of TTFields together with pemetrexed was well-tolerated. There was no increase in the adverse event (AE) rate, GI toxicity or hepatic toxicity as compared to the historical control. No device related cardiac arrhythmias were reported in the study, and there were no TTFields-related serious AEs. The only device-related AE was mild to moderate skin irritation in 14 participants. Duration of TTFields usage therapy was very good, with 85% of participants achieving the recommended 12 hours per day.

Pivotal Clinical Study in Stage 4 NSCLC – The LUNAR Study

A. Study Design

The LUNAR study was a prospective, randomized, open-label, multicenter study comparing the use of Optune Lua concurrent with standard of care (SOC) therapies (PD- 1/PD-L1 inhibitors or docetaxel) ("TTFields+SOC") versus SOC therapies alone ("SOC"), in patients with stage 4 advanced/metastatic NSCLC who have progressed on or after a platinum-based regimen. At the time of study initiation, the approved SOC in the U.S. for metastatic NSCLC following platinum failure included the chemotherapy docetaxel, and PD-1/PD-L1 inhibitors nivolumab, pembrolizumab and atezolizumab. These SOC therapies were used in the study and were administered according to their approved labeling.

Patients were centrally randomized in a 1:1 ratio to the TTFields+SOC arm or the SOC arm, with randomization stratification factors of geographic region, SOC therapy (PD-1/PD-L1 inhibitors or docetaxel) and tumor histology (squamous versus non-squamous). A total of sixty-eight (68) sites enrolled patients in the United States, Europe, China and Canada. The LUNAR study objectives were as follows:

- To prospectively compare OS of metastatic NSCLC patients treated with TTFields+SOC (PD-1/PD-L1 inhibitors or chemotherapy) versus those treated with SOC;
- To prospectively compare OS of metastatic NSCLC patients treated with TTFields+docetaxel versus those treated with docetaxel;
- To prospectively compare OS of metastatic NSCLC patients treated with TTFields+PD-1/PD-L1 inhibitors versus those treated with PD-1/PD-L1 inhibitors; and
- To collect evidence of the safety of TTFields+SOC in metastatic NSCLC patients.

Patient enrollment began in February 2017, with last patient last visit in December 2022. A total of 291 subjects were enrolled in the LUNAR study at 68 sites globally

(34 sites in the US; 28 sites in Europe; 5 sites in China; 1 site in Canada). The PMA reflects data collected through October 3, 2023.

Participant accrual was originally planned to last 30 months, with follow-up to last for an additional 18 months. To detect a hazard ratio (HR) of <0.75 of TTFields therapy-treated participants compared to the control group, the study needed to accrue 240 subjects per arm to achieve 80% power. When allowing for 10% loss to follow-up, the total sample size was 534 participants (267 in each arm).

An interim analysis was performed at month 48 of active patient accrual. Based on a review of the interim analysis and safety data, the Data and Monitoring Committee (DMC) recommended accrual to 276 subjects total with a minimum follow-up of 12 months. The protocol was so amended and approved. A total of 291 subjects were ultimately randomized, reflecting enrollment of potential subjects who were in screening at the time the target enrollment number (276) was met.

Study Arms

The LUNAR study included two arms, as follows:

TTFields+SOC Arm:

Patients received Optune Lua together with SOC therapies (PD-1/PD-L1 inhibitors or docetaxel) until disease progression in the thorax and/or liver, or intolerable toxicity. TTFields therapy was initiated within 7 days of randomization, and ± 3 days of administration of the SOC therapy. Patients received multiple one-month courses of continuous TTFields therapy applied to the thorax (recommended target was 18 hours/day on average). TTFields therapy was to be stopped in cases of device-related intolerable toxicity or disease progression in the thorax and/or liver. In cases where TTFields therapy participants stopped SOC therapy due to intolerable toxicity of the SOC therapy, they were allowed to continue TTFields therapy either alone or with a next line of treatment according to local practice (per investigator's judgement and the patient's wishes). The SOC therapy was administered as described below.

SOC Arm:

Patients received either docetaxel or PD-1/PD-L1 inhibitor (physician-choice) until disease progression in the thorax and/or liver, or intolerable toxicity. Docetaxel was administered at 75 mg/m2 IV over 1 hour every 3 weeks until disease progression according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria or unacceptable toxicity. Nivolumab (240 mg every 2 weeks or 480 mg every 4 weeks or as a weight-based dose), pembrolizumab (200 mg every 3 weeks or 400 mg every 6 weeks as an intravenous infusion over 30 minutes, or as a weight-based dose) and atezolizumab (840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks, as an intravenous infusion over 60 minutes) were administered until disease progression according to Immune-related RECIST (irRECIST) or unacceptable toxicity.

1. Clinical Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for the trial were as follows:

Inclusion Criteria:

1. 22 years of age and older
2. Life expectancy of > 3 months
3. Histological or cytological diagnosis of squamous or non-squamous, inoperable, metastatic NSCLC
4. Diagnosis of radiological progression while on or after first platinum-based systemic therapy administered for advanced or metastatic disease.
    a. Patients who received adjuvant or neoadjuvant platinum-based chemotherapy (after surgery and/or radiation therapy) and developed metastatic disease within 6 months of completing therapy are eligible.
    b. Patients with metastatic disease more than 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum- based regimen given to treat the advanced or metastatic disease, are eligible.
    c. Patients should not receive any systemic therapy after platinum failure before enrollment into the study. Maintenance therapy after platinum-based therapy and prior to progression is allowed.
5. Eastern Cooperative Oncology Group (ECOG) Score of 0-2
6. Assigned by the physician to receive either docetaxel or immune checkpoint inhibitor per standard of care regimens
7. Able to operate the NovoTTF-200T device independently or with the help of a caregiver
8. Signed informed consent for the study protocol

Exclusion Criteria:

1. Metastases to central nervous system (CNS) with clinical symptoms or evidence of new metastases to CNS during screening. Patients who previously

received treatments for the metastases to CNS, are stable and meet the following requirements are allowed to be enrolled:

a. The patients are neurologically returned to baseline (except for residual signs or symptoms related to CNS treatment).
b. No treatment for the metastases to CNS during the screening period (e.g. surgery, radiotherapy, corticosteroid therapy- prednisone > 10 mg/day or equivalent).
c. No progress in CNS lesions as indicated by MRI within 14 days prior to randomization.
d. No meningeal metastasis or spinal cord compression.

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:
   a. 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); alanine transaminase (AST) and/or aspartate transaminase (ALT) > 2.5 x ULN or > 5 x ULN if patient has documented liver metastases; 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. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the study
   d. History of pericarditis
   e. History of interstitial lung disease
   f. History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable
   g. Active infection or serious underlying medical condition that would impair the ability of the patient to receive protocol therapy
   h. 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
   i. 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 in 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)
9. Admitted to an institution by administrative or court order

2. Follow-up Schedule

During the treatment period, subjects were seen every 6 weeks, with the following assessments performed until progression in the thorax and/or liver: CT scan(s) of the chest and abdomen including radiological assessment, concomitant medication recording, performance status, physical examination, complete blood count including differential, serum chemistry, QoL questionnaires, AE collection and device usage time. Bone scans, MRI of the brain and coagulation tests were performed, if clinically relevant. Post-progression follow-up was performed 30 days (±1week), 60 days (±1 week), and 100 days (±1 week) after disease progression in the liver or thorax. Patients could be seen at an outpatient clinic for these visits, with the following performed: concomitant medication recording, performance status, physical examination, complete blood count including differential, serum chemistry and adverse event collection. Survival follow-up was every 4 weeks (±1 week) by telephone (unless a clinical visit was performed). **Table 6** below provides the full schedule of evaluations in the study.

Table 6. Study Evaluation Visit Calendar

	SCREENING / BASELINE		RANDOM-IZATION	FOLLOW UP	POST PD IN THE THORAX AND/OR LIVER	SURVIVAL FOLLOW UP
	T=(-28)-0 days (baseline evaluation)	T=(-14)-0 days (baseline evaluation)	T=Day 0	T=q6 weeks from randomization until PD in the thorax and/or liver (day 42, 84, … ± 7 days)	T= 30 ± 7; 60 ± 7; 100- 107 days after PD in the thorax and/or liver	T= q4 weeks after last visit (day 28, 56, … post last visit +/- 7 days)
Signed ICF	+					
CT scan of chest & Abdomen	+			+		
Bone scan	#			#		
MRI of brain		+				
CT/MRI scan of brain				#		
Medical history		+				
Recording of PD-L1 expression and genetic test results		+				
Concomitant Medications		+		+	+	
ECOG score		+		+	+	
Physical examination		+		+	+	
Serum Pregnancy Test		#				
Complete blood count, including differential		+		+	+	
Serum chemistry		+		+	+	
Coagulation tests		+		#	#	

Quality of life questionnaire		+		+		
Randomization			+			
Adverse Events and device deficiency				+	+	
Review of treatment usage time				+		
Radiological Assessment per irRECIST/RECIST				+		
Telephone Follow up for survival						+

+: Performed during designated visit
#: Performed during designated visit only if clinically relevant/applicable

3. Clinical Endpoints

Primary Effectiveness Endpoint:

- OS of patients treated with TTFields concomitant with SOC (PD-1/PD-L1 inhibitors or docetaxel) compared to patients treated with SOC (superiority)

Key Secondary Effectiveness Endpoints:

- OS of patients treated with TTFields+docetaxel compared to OS of patients treated with docetaxel (superiority)
  - OS of patients treated with TTFields+ PD-1/PD-L1 inhibitors compared to OS of patients treated with PD-1/PD-L1 inhibitors (superiority)

Additional Secondary Endpoints:

- OS of TTFields+docetaxel vs. PD-1/PD-L1 inhibitors (non-inferiority)
- Progression-free survival (PFS) of TTFields+SOC vs. SOC
- Radiological Response Rate (RRR) of TTFields+SOC vs. SOC
- Quality of life (QoL) of TTFields+SOC vs. SOC
- Assessment of the effects of TTFields therapy on OS and PFS for each PD-1/PD-L1 inhibitor used in the study
- Assessment of the effects of TTFields therapy on OS and PFS by histological subgroup (squamous and non-squamous)
- Assessment of the effects of TTFields therapy usage time on OS and PFS

Safety:

- Adverse events, severity and frequency in patients treated with TTFields+docetaxel or PD-1/PD-L1 inhibitors compared to patients treated with docetaxel or PD-1/PD-L1 inhibitors.

4. Study Schema

The study schema for the EF-24/LUNAR study is provided in **Figure 2** below.

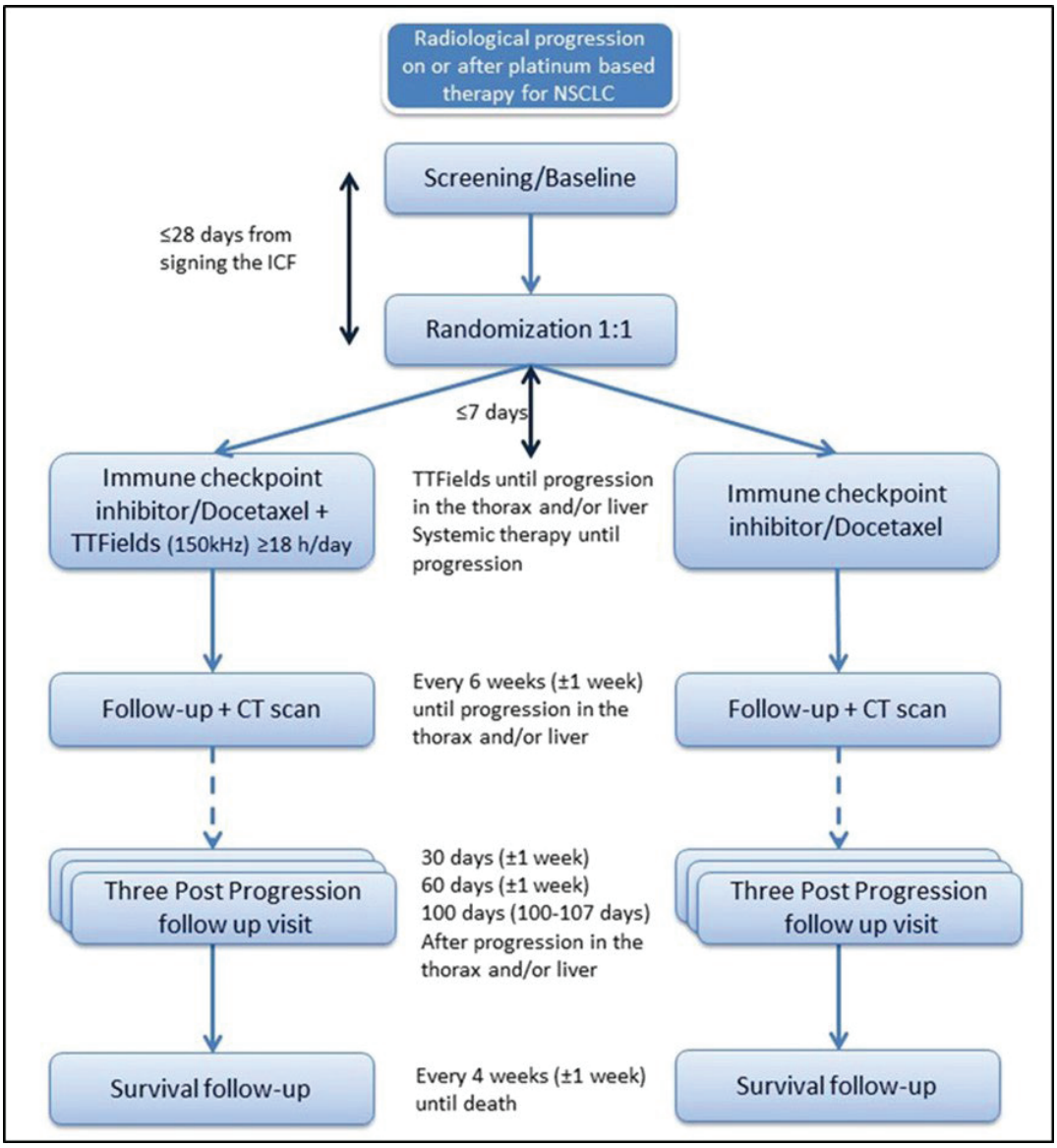


Figure 2. LUNAR Study Schema

5. Statistical Analysis Plan and Analysis Populations

Statistical Hypotheses:

The original sample size estimated to test the superiority hypothesis that TTFields+SOC would significantly increase OS compared to SOC was 534. The primary endpoint of the study would be achieved if OS is significantly greater in the TTFields+SOC arm than in the SOC arm, with OS measured from the time of randomization. The hazard rate for SOC therapies is represented by h_{SOC} and the hazard for TTFields with SOC is represented by $h_{SOC+TTF}$, with the null hypothesis being H_0=1, and the alternate hypothesis being H_Af1. The comparison itself is defined between h_{SOC} and $h_{SOC+TTF}$, as follows:

- H_0: *Hazard Ratio* = $h_{SOC+TTF} / h_{SOC} = 1$
- H_A: *Hazard Ratio* = $h_{SOC+TTF} / h_{SOC} \neq 1$

The primary endpoint would be met if the null hypothesis is rejected.

The key secondary endpoints were to be tested only if the primary endpoint was met ('hierarchical testing' to control the type I error). For the testing of the key secondary endpoints, the SOC treatments used in the LUNAR study were to be grouped by therapeutic class, so there would be only 2 subgroups - immune checkpoint inhibitors or Docetaxel - each tested concurrently at the 0.025 (one-sided) level, as follows:

- H_0: *Hazard Ratio* = $h_{TTFields + Docetaxel} / h_{Docetaxel} \geq 1$
- H_A: *Hazard Ratio* = $h_{TTFields + Docetaxel} / h_{Docetaxel} < 1$

- H_0: *Hazard Ratio* = $h_{TTFields + Immune} / h_{Immune} \geq 1$
- H_A: *Hazard Ratio* = $h_{TTFields + Immune} / h_{Immune} < 1$

Analysis Datasets:

The following pre-specified analysis populations were used to evaluate the study results:

- Intent to Treat Population (Efficacy) - All subjects randomized to the study.

- Safety Population - Includes all patients who received any amount of TTFields or standard of care in the study. Safety subjects are analyzed according to the actual treatment received.

Protocol Deviations:

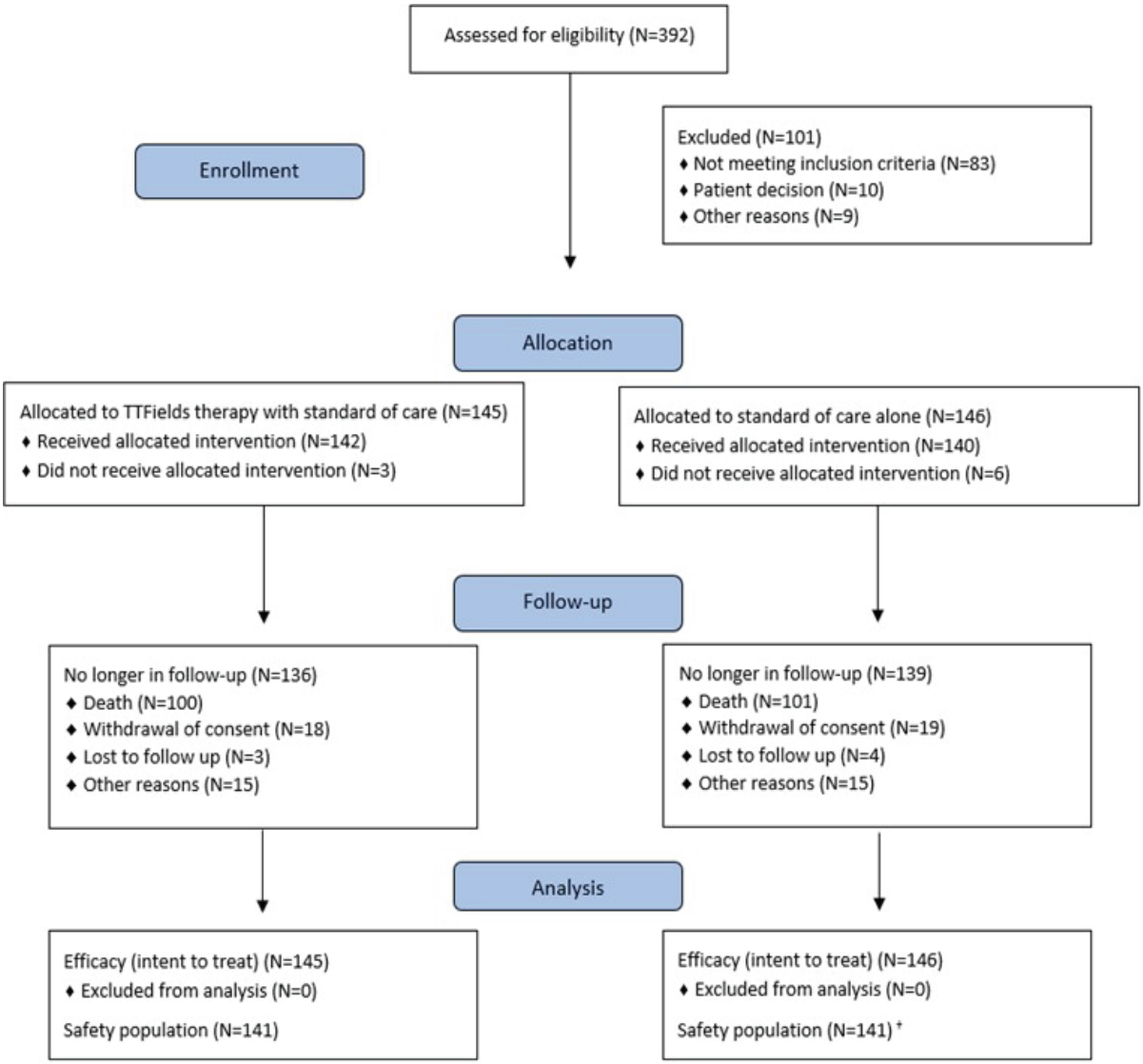
Protocol deviations were categorized per the definitions set forth in the ICH E3 Guideline. Of the deviations categorized, eight were identified as deviations with the potential to impact study outcomes and/or subject safety, and involved either enrollment of patients who did not meet the eligibility criteria or administration of a SOC treatment that was not consistent with the subject's randomization assignment. Following a careful evaluation, it was determined that these deviations did not impact study outcomes and/or subject safety.

Overall, protocol deviations were well-balanced between the two arms. The majority of protocol deviation involved missed or 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.

Patient Disposition:

Of the 392 patients screened and evaluated for eligibility, 291 were found eligible and randomized. The remaining 101 patients were screen failures for various reasons, including not meeting the eligibility criteria, patient decision, or other

reason. Of the 291 randomized participants, 145 were randomized to the TTFields+SOC arm, with 142 of those patients receiving treatment. One hundred and forty-six (146) patients were randomized to the SOC arm, with 140 receiving treatment. Patient disposition is summarized in **Figure 3** below:



†One patient randomized to Tumor Treating Fields (TTFields) with standard of care instead received standard of care alone.

Figure 3. Patient Disposition

B. Accountability of PMA Cohort

The study included 291 patients with a minimal follow-up of 12 months. As seen in **Table 7** below, the number of patients available for survival analysis at each time point is the difference between the expected number of patients and the total

censored until that time point. The number of patients expected is the number expected at the previous time point minus the patients who died during the period. Sixty-nine available patients out of 82 expected (84%) from the TTFields+SOC group, and 60 available patients out of 63 expected patients (94%) had vital status information available at the protocol specified data cutoff of 12 months follow-up.

Table 7. Subject Accountability – ITT Population

	Baseline		6 Months		12 Months	
Treatment Arm	**TTFields + SOC**	**SOC**	**TTFields+ SOC**	**SOC**	**TTFields + SOC**	**SOC**
Expected	145	146	114	103	82	63
Total Censored	0	0	10	2	3	1
Death	0	0	0	0	0	0
Investigator decision	0	0	1	0	1	0
Lost to follow-up	0	0	2	0	0	0
Study closure	0	0	0	0	0	0
Withdrawal of consent	0	0	7	1	2	1
Subject randomized by mistake	0	0	0	1	0	0
Deaths	0	0	31	43	32	40
Available	145	146	104	101	69	60
% Follow-up	100	100	91	98	84	95

C. Study Population Demographics and Baseline Parameters

A total of 291 metastatic NSCLC patients with histological or cytological diagnosis of squamous or non-squamous, inoperable, metastatic NSCLC who had progressed on or after a platinum-based regimen were enrolled in the study.

Demographics and baseline characteristics were well-balanced between the TTFields+SOC arm and the SOC arm, as shown in **Table 8** below. Median age of the study cohort was 64 years (range of 22 to 86 years). The study included both males (66%) and females (34%); was multi-ethnic and multi-racial, although the majority of subjects were Caucasian (78%). Ninety-six percent (96%) had an ECOG performance score of zero or one; 57% had tumors with non-squamous histology; and 31% had liver metastasis at time of enrollment. The majority of subjects had received one line of treatment in the front-line setting (87%), with 32% of all study subjects having received an immune checkpoint inhibitor (ICI) as part of their front-line treatment, in addition to platinum-based chemotherapy. Median time from initial diagnosis of NSCLC was 10 months (range of 2.5 and 164.6 months). Half of study subjects (54%) had a Tumor Proportion Score (TPS) available from their initial biopsy. Of those with a TPS available, 16.2% (47 patients) had a TPS < 1%; 27.5% (80 patients) had a TPS between 1-50%; and (10%) (29 patients) had a TPS ≥ 50%.

Table 8. Demographics and Baseline Characteristics – ITT Population

Characteristic	Optune Lua+SOC (N=145)	SOC (N=146)	Total (N=291)
Age (Years)			
Median (min, max)	64.0 (36, 85)	65.0 (22, 86)	65.0 (22, 86)
Gender, No. (%)			
Male	99 (68.3)	92 (63.0)	191 (65.6)
Female	46 (31.7)	54 (37.0)	100 (34.4)
Race, No. (%)			
American Indian/Alaska Native	0	2 (1.4)	2 (0.7)
Asian	19 (13.1)	17 (11.6)	36 (12.4)
Black or African American	4 (2.8)	3 (2.1)	7 (2.4)
Pacific Islander	1 (0.7)	0	1 (0.3)
White	115 (79.3)	113 (77.4)	228 (78.4)
Other/Missing	6 (4.1)	11 (7.5)	17 (5.8)
Ethnicity, No. (%)			
Hispanic or Latino	6 (4.1)	7 (4.8)	13 (4.5)
Not Reported/Unknown	6 (4.2)	11 (7.5)	17 (5.9)
Region, No. (%)			
North America	44 (30.3)	43 (29.5)	87 (29.9)
Western Europe	42 (29.0)	41 (28.1)	83 (28.5)
Eastern Europe	43 (29.7)	45 (30.8)	88 (30.2)
East Asia	16 (11.0)	17 (11.6)	33 (11.3)
ECOG Performance Status, No. (%)			
0	41 (28.3)	41 (28.1)	82 (28.2)
1	97 (66.9)	101 (69.2)	198 (68.0)
2	7 (4.8)	4 (2.7)	11 (3.8)
Smoking History, No. (%)			
Never smoked	20 (13.8)	24 (16.4)	44 (15.1)
Current smoker	36 (24.8)	30 (20.5)	66 (22.7)
Former smoker	88 (60.7)	92 (63.0)	180 (61.9)
Unknown	1 (0.7)	0	1 (0.3)
Tumor Histology, No. (%)			
Non-Squamous	83 (57.2)	82 (56.2)	165 (56.7)
Squamous	62 (42.8)	64 (43.8)	126 (43.3)
Liver metastases at baseline, No. (%)	22 (15.2%)	23 (15.8%)*	45 (15.5)
Brain metastases at baseline, No (%)	0	2 (1.4)*	4 (1.4)
Receive Any Prior Therapy for NSCLC, n (%)			
Yes	145 (100)	146 (100)	291 (100)
Prior lines at baseline, No. (%)			
1	126 (86.9)	127 (87.0)	253 (86.9)
2	10 (6.9)	11 (7.5)	21 (7.2)
	6 (4.2)	2 (1.4)	8 (2.7)
Missing	3 (2.1)	6 (4.1)	9 (3.1)

Characteristic	Optune Lua+SOC (N=145)	SOC (N=146)	Total (N=291)
Prior ICI, No. (%)			
Yes	48 (33.1)	46 (31.5)	94 (32.3)
Median time since initial NSCLC Dx, (min,max)	10.3 (2.7, 127.2)	10.0 (2.5, 164.6)	10.1 (2.5, 164.6)
Tumor Proportion Score, No. (%)			
< 1%	24 (16.6)	23 (15.8)	47 (16.2)
1% and <50%	40 (27.6)	40 (27.4)	80 (27.5)
50%	10 (6.9)	19 (13.0)	29 (10.0)
Unknown	71 (49.0)	64 (43.8)	135 (46.4)

Duration of treatment exposure was also comparable, as presented in **Table 9** below. Specifically, the number of cycles and duration of exposure to SOC therapies was comparable between the TTFields+SOC arm and the SOC arm (13.9 weeks vs. 12.1 weeks, respectively). With respect to TTFields duration of exposure in the TTFields+SOC arm, median duration of exposure to TTFields was 11.6 weeks and 13.9 weeks in the TTFields+docetaxel and TTFields+ PD-1/PD-L1 inhibitors subgroups, respectively. The average usage by patients who received TTFields therapy together with docetaxel was 54.25%, which was comparable to the PD-1/PD-L1 inhibitor group, at 52.33%. In sum, irrespective of which SOC treatment received, patients in the TTFields+SOC arm used TTFields therapy about half the time on average, translating into about 12 hours per day.

Table 9. Treatment Exposure Duration – ITT Population

	TTFIELDS+SOC		SOC	
	Docetaxel n (%)	**PD-1/PD-L1 inhibitors n (%)**	**Docetaxel n (%)**	**PD-1/PD-L1 inhibitors ICI n (%)**
TTFields - Duration of Exposure (weeks)				
n	69*	71		
Mean (SD)	16.70 (21.94)	34.54 (49.03)		
Median	11.57	13.86		
Min, Max	0.14, 162.57	0.29, 245.14		
TTFields - Average Usage (%)				
n	69*	71		
Mean (SD)	54.26% (24.11)	52.31% (22.91)		
Median	56.82%	55.92%		
Min, Max	4.00%, 92.70%	0.40%, 94.70%		
SOC - Number of Cycles Received				
n	70	71	71**	69
Mean (SD)	4.8 (3.47)	15.7 (18.87)	6.0 (5.73)	12.1 (13.88)

	TTFIELDS+SOC		SOC	
	Docetaxel n (%)	PD-1/PD-L1 inhibitors n (%)	Docetaxel n (%)	PD-1/PD-L1 inhibitors ICI n (%)
Median	4.5	9.0	4.0	6.0
Min, Max	1, 20	1, 99	1, 28	1, 70
SOC - Duration of Exposure (weeks)				
n	70	71	71**	69
Mean (SD)	14.46 (17.36)	35.64 (47.70)	15.78 (17.69)	29.36 (34.97)
Median	11.14	16.00	10.14	15.14
Min, Max	0.14, 162.57	0.14, 245.14	0.14, 81.57	0.14, 171.71

** 1 patient assigned to TTFields+SOC decided they did not want TTFields therapy and thus, did not receive any amount of TTFields therapy. **One patient's dose was unknown and therefore, duration was not calculated*

D. Safety and Effectiveness Results

1. Safety Results

Adverse events were compiled from the Safety population. The safety findings from LUNAR are consistent with the known low toxicity profile of TTFields therapy seen in both the clinical use of TTFields in numerous completed and ongoing clinical studies, as well as from commercial use of Optune Lua for MPM (H180002) and Optune Gio for GBM (P100034).

The percentage of patients in both study arms who experienced an AE during the study was similar. The most frequently reported AEs were those associated with SOC therapies or with the underlying disease. With respect to AEs relating to bleeding in the lung, similar rates were reported in the TTFields+SOC arm and the SOC arms. All such events in both arms were determined to be related to the underlying NSCLC disease.

More than half of TTFields-treated patients experienced the expected skin-related disorders under the transducer arrays (89; 63.1%); the majority of these events were low grade (Grade 1-2), with only six patients (4%) experiencing a Grade 3 skin toxicity that required a break from treatment. There were no Grade 4 or Grade 5 toxicities related to Optune Lua, and no device-related AEs that caused death.

As shown in **Table 10** below, while the total incidence of SAEs was numerically higher in the TTFields+SOC arm, when the AE occurrence is normalized with safety follow-up time, the occurrence of SAEs is approximately the same (7% for the TTFields+SOC arm versus 6% for the SOC arm) in both arms.

Table 10. Serious Adverse Events – Safety Population

System Organ Class Preferred Term	TTFields +SOC (N=141) n (%)	SOC (N=141) n (%)	TOTAL (N=282) n (%)
Any serious adverse event	77 (54.6)	55 (39.0)	132 (46.8)
Adverse events			
Blood and lymphatic system disorders	10 (7.1)	9 (6.4)	19 (6.7)
Cardiac disorders	6 (4.3)	4 (2.8)	10 (3.5)
Endocrine disorders	1 (0.7)	0	1 (0.4)
Gastrointestinal disorders	9 (6.4)	6 (4.3)	15 (5.3)
General disorders and administration site conditions	6 (4.3)	7 (5.0)	13 (4.6)
Hepatobiliary disorders	0	2 (1.4)	2 (0.7)
Infections and infestations	32 (22.7)	23 (16.3)	55 (19.5)
Injury, poisoning and procedural complications	3 (2.1)	0	3 (1.1)
System Organ Class Preferred Term	**TTFields +SOC (N=141) n (%)**	**SOC (N=141) n (%)**	**TOTAL (N=282) n (%)**
Investigations	1 (0.7)	1 (0.7)	2 (0.7)
Metabolism and nutrition disorders	5 (3.5)	2 (1.4)	7 (2.5)
Musculoskeletal and connective tissue disorders	0	2 (1.4)	2 (0.7)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	7 (5.0)	3 (2.1)	10 (3.5)
Nervous system disorders	8 (5.7)	5 (3.5)	13 (4.6)
Renal and urinary disorders	1 (0.7)	1 (0.7)	2 (0.7)
Respiratory, thoracic, and mediastinal disorders	26 (18.4)	23 (16.3)	49 (17.4)
Skin and subcutaneous tissue disorders	2 (1.4)	0	2 (0.7)
Vascular disorders	1 (0.7)	0	1 (0.4)

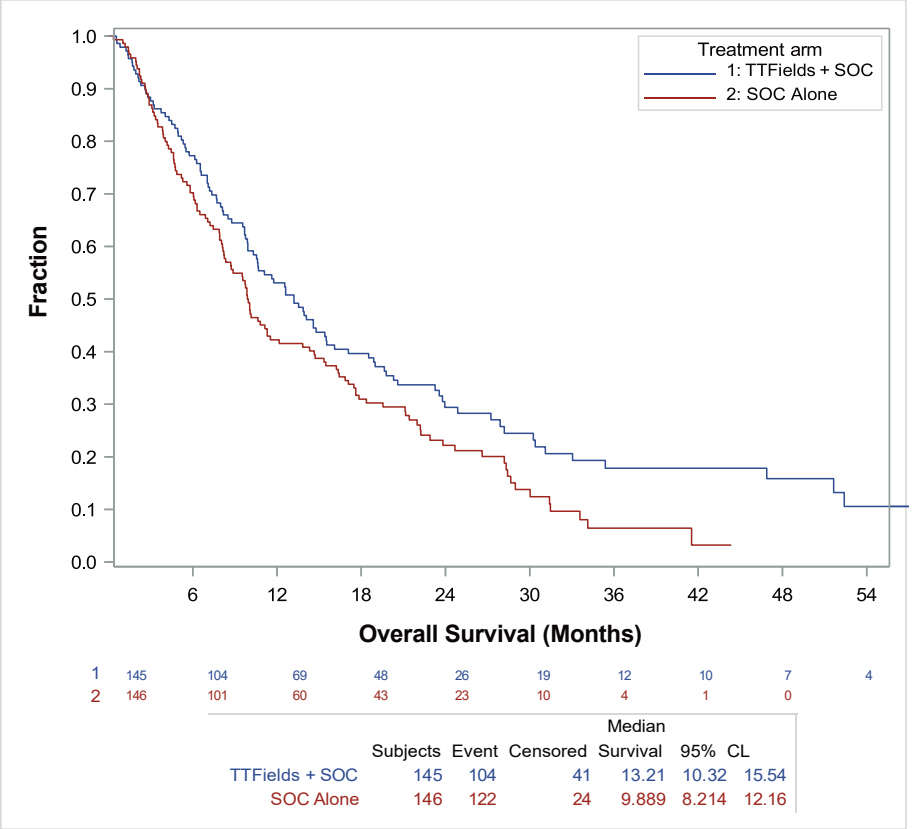
2. Effectiveness Results

Primary Effectiveness Endpoint – Overall Survival (ITT):

Overall survival (OS) was measured as time from randomization to date-of-death of any cause, or censored at the last follow up date. The updated threshold for statistical significance of the OS primary endpoint based on the Lan-DeMets O'Brien-Fleming method at the final analysis was 0.04994 in the ITT population. The OS at the final analysis in the ITT population met this threshold. Median OS in the TTFields+SOC arm was 13.2 months (95% CI, 10.3 to 15.5) and 9.9 months

(95% CI, 8.2 to 12.2) in the SOC arm. The hazard ratio of death was 0.76 (95% CI, 0.58 to 0.99; P=0.042). The 1-year OS rate was 53% (95% CI, 44 to 61) with TTFields+SOC, and 42% (95% CI, 34 to 50) with SOC. An extension in median OS of over 3 months is statistically significant (P=0.041) and highly clinically significant for this patient population.

In addition, poolability analyses found no interaction for geographic region, country, site, protocol version or device version, signifying the appropriateness of pooling the data for purposes of assessing the effectiveness endpoints.



	TTFields + SOC (N=145)	SOC (N=146)
Median OS, mo	13.2	9.9
95% CI, mo	10.3; 15.5	8.2; 12.2
Log Rank	P = 0.044	
HR (95% CI)	0.76 (0.58; 0.99)	

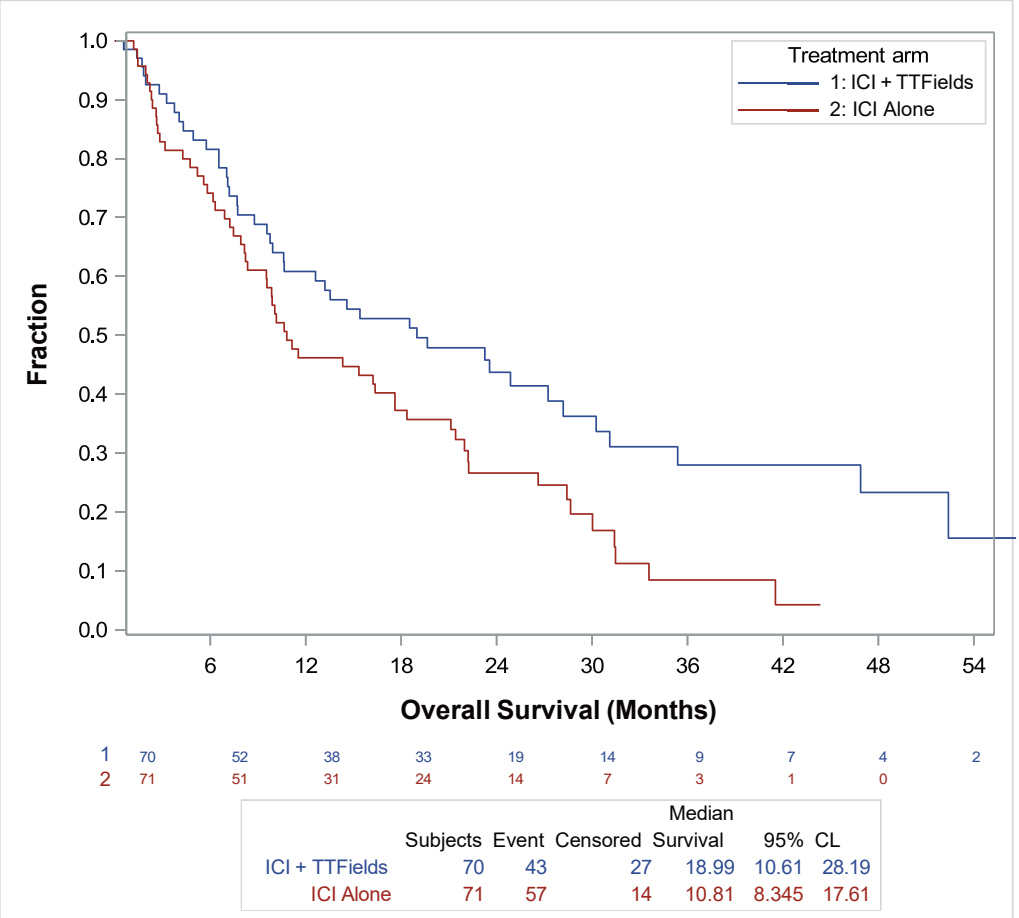
Figure 4. OS of TTFields+SOC vs. SOC – ITT Population

Key Secondary Effectiveness Endpoints:

The LUNAR study included two key secondary endpoints to assess OS in the ITT population per type of SOC (PD-1/PD-L1 inhibitors and docetaxel). The key secondary study endpoints were powered under the original sample size. They were to be tested only if the primary endpoint of OS met its pre-defined threshold, and were to be tested simultaneously (each at the 0.025 one-sided level), as pre-

specified in the protocol.

TTFields+PD-1/PD-L1 Inhibitors vs. PD-1/PD-L1 Inhibitor – Overall Survival: Median OS in the TTFields+ PD-1/PD-L1 Inhibitors group (n=70) was 19.0 months (95% CI, 10.6 to 28.2) compared to 10.8 months (95% CI, 8.3 to 17.6) in the PD-1/PD-L1 Inhibitors group (n=71). The HR was 0.63 (95% CI, 0.42 to 0.95; P=0.026), and thus this key secondary endpoint was met. The 1-year survival rate was 61% (95% CI, 47.7% to 71.6%) with TTFields+PD-1/PD-L1 Inhibitors, and 46% (95% CI, 34.1% to 57.4%) with PD-1/PD-L1 Inhibitors alone. The difference of more than 8 months in median OS when Optune Lua is used together with PD-1/PD-L1 Inhibitors is highly statistically significant (P=0.024) and clinically meaningful.

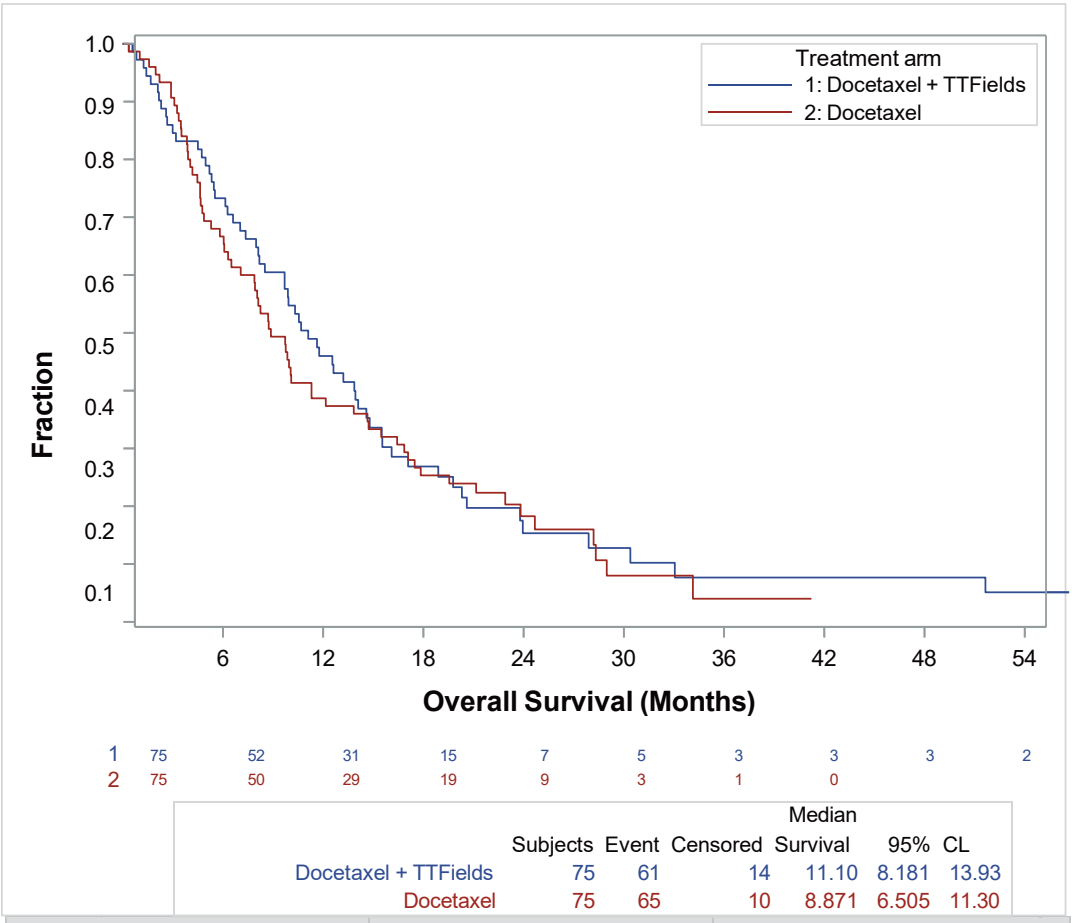


ICI refers to PD-1/PD-L1 inhibitors

	TTFields+ PD-1/PD-L1 Inhibitors (N=70)	PD-1/PD-L1 Inhibitors (N=71)
Median OS, mo	19.0	10.8
95% CI, mo	10.6, 28.2	8.3, 17.6
Log Rank	P = 0.024	
HR (95% CI)	0.63 (0.42; 0.95)	

Figure 5. OS of TTFields+PD-1/PD-L1 Inhibitors vs. PD-1/PD-L1 Inhibitors

TTFields+Docetaxel vs. Docetaxel – Overall Survival (ITT):
Median OS in the TTFields+Docetaxel group (n=75) was 11.1 months (95% CI, 8.2 to 13.9), compared to 8.9 months (95% CI, 6.5 to 11.3) in the docetaxel group (n=75), with a hazard ratio of death of 0.88 (95% CI, 0.61 to 1.26; p=0.469). The 1-year survival rates were 46% (95% CI, 34.1 to 57.1) and 39% (95% CI, 27.7 to 49.5), respectively. The difference of over 2 months in median OS did not reach statistical significance, but demonstrated a clear positive trend that is supportive of the primary endpoint results. These results are also clinically meaningful and compelling in the context of the established smaller effect size seen with docetaxel at this stage of the disease as compared to PD-1/PD-L1 inhibitors, and a revised sample size that was considerably smaller than the original sample size, on which the endpoint was powered.



	Subjects	Event	Censored	Median Survival	95% CL	
Docetaxel + TTFields	75	61	14	11.10	8.181	13.93
Docetaxel	75	65	10	8.871	6.505	11.30

	TTFields+ Docetaxel (N=75)	Docetaxel (N=75)
Median OS, mo	11.1	8.9
95% CI, mo	8.2; 13.9	6.5;11.3
Log Rank	P = 0.47	
HR (95% CI)	0.88 (0.61; 1.26)	

Figure 6. OS of TTFields+Docetaxel vs. Docetaxel

Additional Secondary Endpoints:

Quality of Life: QoL was measured throughout the study using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 and LC-13 Addendum. Mean baseline QoL scores between the two arms found no differences on any of the general scales or symptom scales. Furthermore, the addition of Optune Lua to SOC therapies did not impact patients' time-to- deterioration on the relevant QoL variables. In sum, the addition of Optune Lua to SOC treatments for metastatic NSCLC patients did not adversely affect patients' quality of life.

TTFields Therapy Usage: Usage data was available for 141 subjects in the TTFields+SOC arm. Over the entire course of the study, close to one quarter (23%) of patients who used Optune Lua achieved a monthly average device usage of at least 18 hours per day (75% of each day). A statistical association could not be established between an average monthly usage of 75% and effectiveness outcomes, given the small numbers. However, the correlation between higher durations of usage and improved survival outcomes has been established in Novocure's other clinical data of TTFields for the treatment of MPM and glioblastoma multiforme (GBM). Moreover, the median 12-hour daily usage of Optune Lua reached in the ITT population is consistent with the pilot study in NSCLC, where 85% of patients achieved the recommended 12 hours of TTFields usage per day.

TTFields+Docetaxel vs. PD-1/PD-L1 Inhibitors – Overall Survival: PD-1/PD-L1 inhibitors have been shown to extend survival with a HR ratio of 0.86 compared to docetaxel (a non-inferiority margin of 50% is equal to an upper bound of HR Confidence interval of 1.25). Thus, if the upper limit of the 95% confidence interval excludes 1.25 it can be concluded that TTFields+Docetaxel is non-inferior to PD-1/PD-L1 Inhibitors alone. A non-inferiority analyses of OS was performed using a stratified Cox Proportional Hazard model on the ITT population comparing the TTFields+Docetaxel group (n=75) with the PD-1/PD-L1 Inhibitors group (n=71). Median OS was 11.1 months and 10.8 months for the TTFields+Docetaxel group and PD-1/PD-L1 Inhibitors group, respectively. (p=0.431), with a HR of 1.2 (95% CI, lower limit was 0.80 and the upper limit was 1.7). The 1-year survival rates were 46% (95% CI, 34.1 to 57.1) and 46.2% (95% CI, 34.1 to 57.4), respectively.

PFS and ORR: LUNAR assessed progression-free survival (PFS), Overall Radiological Response Rate (ORR) between the two main study arms, demonstrating a slight advantage in favor of adding Optune Lua to SOC on PFS and ORR.

Sub-Population Analyses: LUNAR included analyses of outcomes in specific sub-populations. While these cohorts had small sample sizes, limiting definitive conclusions that can be drawn from the analyses, no statistically significant differences in OS or PFS were seen when looking at the specific ICI used together with Optune Lua, or tumor histology (squamous/non-squamous).

3. Subgroup Analyses

No analyses were performed for sex-, gender-, age-, race-, or ethnicity- specific subgroups.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 68 participating investigators, of which none were full-time or part-time employees of the sponsor. Two of the investigators reported disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f). However, neither held a proprietary interest in the device, an equity interest in the Sponsor, or had entered into any arrangements with the Sponsor whereby the value of compensation could have been influenced by the outcome of the study. Details of the disclosable financial interests for each investigator, along with the steps taken to minimize the potential bias were submitted in the PMA.

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XII. PANEL MEETING RECOMMENDATION AND POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to an FDA Advisory Panel for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

This PMA was not reviewed by an FDA Advisory Panel. A panel has previously reviewed the safety and effectiveness of the Applicant's technically similar TTFields device under P100034 that is indicated for the treatment of recurrent and newly diagnosed glioblastoma multiforme. In addition, the safety and probable benefit of the subject TTFields device has been approved by FDA under H180002 for the treatment of malignant pleural mesothelioma. This PMA does not raise any unanticipated safety or effectiveness issues that warrant submission to an Advisory Panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The LUNAR study demonstrated that TTFields therapy, when used together with SOC therapies extends median OS by over 3 months as compared to SOC in previously treated metastatic NSCLC patients. At the final analysis in the ITT population, median OS in the TTFields+SOC group was 13.2 months (95% CI, 10.3 to 15.5) compared to 9.9 months (95% CI, 8.2 to 12.2) in the SOC group. The hazard ratio of death was 0.76 (95% CI, 0.58 to 0.99; P=0.042). The 1-year OS rate was 53% (95% CI, 44 to 61) with TTFields+SOC, and 42% (95% CI, 34 to 50) with SOC. The study met its pre-specified threshold for statistical significance (P=0.041) at the final analysis. Furthermore, poolability analyses found no interaction for geographic region, country, site, protocol version or device version. An extension in median OS of over 3 months is statistically significant and clinically meaningful for this patient population.

The LUNAR study's key secondary endpoints, designed to assess OS in the ITT population per type of SOC (PD-1/PD-L1 Inhibitors and docetaxel), were assessed after the primary endpoint of OS had met its pre-defined threshold, and were tested simultaneously (each at the 0.025 one-sided level), as pre-specified in the statistical analysis plan (SAP).

With respect to the PD-1/PD-L1 Inhibitors analysis, the study demonstrated that TTFields therapy, when used together with PD-1/PD-L1 Inhibitors extends median OS by over 8 months as compared to PD-1/PD-L1 Inhibitors in previously treated metastatic NSCLC patients. Median OS in the TTFields+ PD-1/PD-L1 Inhibitors group (n=70) was 19.0 months (95% CI, 10.6 to 28.2) compared to 10.8 months (95% CI, 8.3 to 17.6) in PD-1/PD-L1 Inhibitors group (n=71), with a hazard ratio of 0.63 (95% CI, 0.42 to 0.95; P=0.026). The 1-year survival rate was 61% (95% CI, 47.7% to 71.6%) with TTFields+ PD-1/PD-L1 Inhibitors, and 46% (95% CI, 34.1% to 57.4%) with PD-1/PD-L1 Inhibitors alone. The study met its pre-specified threshold for statistical significance at the final analysis. An extension in median OS of over 8 months when Optune Lua is used together with ICIs is statistically significant and highly clinically meaningful for this patient population.

Median OS in the TTFields+docetaxel group (n=75) was 11.1 months (95% CI, 8.2 to 13.9), compared to 8.9 months (95% CI, 6.5 to 11.3) in the docetaxel group (n=75). The hazard ratio of death of 0.88 (95% CI, 0.61 to 1.266; p=0.471). The 1-year survival rates were 46% (95% CI, 34.1 to 57.1) and 39% (95% CI, 27.7 to 49.5), respectively. In the subgroup of patients using docetaxel, the difference of over 2 months in median OS did not reach statistical significance. There is a clear positive trend in favor of TTFields+Docetaxel as compared to docetaxel alone out to 12 months, which is supportive of the primary endpoint results. While statistical significance was not reached for this secondary endpoint, a difference of over 2 months in median OS when Optune Lua is used together with docetaxel is clinically meaningful. This positive trend is also compelling when considered in the context

of docetaxel's smaller effect size at this stage of the disease as compared to PD-1/PD-L1 Inhibitors.

LUNAR demonstrated that the extension in median OS did not come at the expense of lower quality of life, or faster time to QoL deterioration. QoL metrics measured throughout the study using the EORTC QLQ C30 and LC-13 Addendum, found that mean baseline QoL scores of patients who received TTFields therapy together with SOC were not different on any of the general scales or symptom scales compared to the group who received SOC alone. Furthermore, the addition of Optune Lua to SOC did not impact patients' time-to-deterioration on the relevant QoL variables.

B. Safety Conclusions

The LUNAR study demonstrated that TTFields therapy was well-tolerated, and did not result in adverse interactions with SOC therapies. There was no difference in the incidence of severe AEs between the different study arms and strata. Most TTFields-treated patients had the expected device-related skin toxicity (89, 63.1%). The majority of these events were low (Grade 1-2) severity, with six patients (4%) reported to experience a Grade 3 skin toxicity, which required a treatment break. There were no Grade 4 or Grade 5 toxicities related to the device, no adverse events related to the device that caused death, and no unanticipated adverse device effects.

With respect to AEs related to bleeding in the lungs, which is a safety issue FDA has previously inquired about, as previously communicated during the pre-PMA meeting, the only AEs relating to bleeding in the lung that were reported in the LUNAR study were Pulmonary Hemorrhage and Hemoptysis. None of these events that occurred in the TTFields arm were determined to be related to the investigational device. Rather, all such events were determined to be the result of the underlying NSCLC disease by the treating investigator.

The SAE occurrence rate over the safety follow-up time did not differ clinically nor significantly, observing 7% of SAEs for the TTFields+SOC arm versus 6% of SAEs for the SOC arm.

The safety findings from LUNAR are consistent with the known low toxicity profile of TTFields therapy, and are fully supported by the Quality of Life data, which found no significant differences in the quality of life or time to deterioration of patients in the two arms.

C. Benefit-Risk Determination

Non-small cell lung cancer is the most common type of lung cancer, comprising between 80% and 90% of lung cancer cases. Unfortunately, because lung cancer symptoms are non-specific, more than half of patients have metastatic disease at the time of initial diagnosis. The median overall survival (OS) of patients with metastatic NSCLC is typically between 7 and 12 months, depending on factors such as tumor histology and treatment.

Treatment of NSCLC is multi-modal and includes surgery, chemotherapy, radiation therapy or a combination of the above. These modalities are associated with substantial toxicity. While surgical resection is the best option offering long-term survival and a cure in selected patients, sadly, the vast majority of patients do not have resectable tumors, and thus, the intention of therapy is to prolong survival while minimizing treatment-related side effects and maintaining quality of life. There is a lack of effective and tolerable treatment options for this patient population who are heavily burdened by disease. Therefore, there is an urgent need for efficacious treatment, which may offer improved outcomes, without added systemic toxicity or negative impact on quality of life.

In this context, the LUNAR study demonstrated that TTFields therapy when used together with current SOC therapies in previously-treated metastatic NSCLC patients led to a statistically significant and clinically meaningful extension in median OS of over 3 months, compared to SOC in the ITT population. The improvement of more than 3 months in median OS is also clinically meaningful and justifies the addition of TTFields therapy to SOC therapies already in use for this patient population.

The study also demonstrated that TTFields therapy is well-tolerated, and does not lead to adverse interactions with PD-1/PD-L1 Inhibitors or docetaxel. There was no difference in the incidence of severe AEs between the different study arms and strata. Most TTFields-treated patients had the expected device-related skin toxicity (89, 63.1%). However, the majority of these events were low severity (Grade 1-2), with only a handful of patients experiencing Grade 3 skin toxicity that required a short treatment break. Notably, there were no Grade 4 or Grade 5 toxicities related to the device, no adverse events related to the device that led to death, and no unanticipated adverse device effects. The safety findings from LUNAR are consistent with the known low toxicity profile of TTFields therapy based on the Company's extensive clinical and commercial experience in both GBM and MPM. Furthermore, these findings are fully supported by the Quality of Life data, which found no significant differences in the quality of life or time to deterioration of patients in the two arms.

When assessing the benefit/risk profile, the risk of adding Optune Lua to second-line SOC therapies in the treatment of metastatic NSCLC is negligible when considering the statistically significant extension in median OS compared to SOC, the device's safety profile, the devastating nature of this disease, and the ongoing need for more treatment options for this population. Given the available information presented in the PMA, the totality of the data support that the benefits of adding Optune Lua to second-line SOC therapies for the treatment of patients with metastatic NSCLC outweigh its risks.

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

Optune Lua is a portable, battery-powered or mains-powered device that delivers TTFields to patients with metastatic NSCLC who have progressed on a platinum-based chemotherapy. The results of the LUNAR pivotal study showed that when Optune Lua is used together with SOC therapies (PD-1/PD-L1 Inhibitors or docetaxel), it extends overall survival significantly compared to SOC alone. This statistically significant extension in OS was achieved in the ITT population, and one that was mixed (as half of patients received docetaxel, which is known to be significantly inferior to PD-1/PD-L1 Inhibitors in its clinical activity). These data are also highly significant from a clinical perspective, given that this patient population has a median OS of around one year (and lower for those treated with docetaxel alone). These effectiveness outcomes were achieved without adding any systemic toxicity or negatively impacting patients' QoL.

XIV. CDRH DECISION

CDRH issued an approval order on October 15, 2024.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for Use:

See device labeling.

Hazards to Health from Use of the Device:

See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions:

See Approval Order.

XVI. REFERENCES