
OPTUNE LUA® FOR NON-SMALL CELL LUNG CANCER (NSCLC)

# Physician Instructions for Use



Caution: Federal law restricts this device to sale by or on the order of a physician

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*This manual is intended for physicians prescribing the use of Optune Lua™ for NSCLC.*

# 1. 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.

# 2. Contraindications, Warnings, Precautions & Notices

The following content provided is copied from the Patient Information and Operation Manual (PIOM) and therefore the language in this section is written to address the patient.

## 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.

## Warnings

**Warning** – Use Optune Lua only after receiving training from Novocure or other qualified personnel, such as your doctor, a nurse, or other medical personnel who have completed a training course given by Novocure (the device manufacturer).

Your training will include a detailed review of the patient user manual and practice in the use of the device. In addition, you will be trained in what to do if there are problems with treatment. Use of Optune Lua without receiving this training can result in breaks in treatment and may rarely cause increased skin irritation, open sores on your chest or back, or allergic reactions or even an electric shock.

**Warning** - In case of skin irritation, which appears as redness under the transducer arrays (a mild rash), contact your doctor who will prescribe you high potency topical steroids (hydrocortisone cream) to use when replacing the transducer arrays. Using this cream will help relieve your skin irritation. If you do not use this cream, the skin irritation can become more serious and may even lead to skin breakdown, infections, pain and blisters. If this happens, stop using the topical steroid cream and contact your doctor. Your doctor will supply you with an antibiotic cream to use when replacing transducer arrays. If you do not use this cream, your symptoms may continue and your doctor may ask you to take a break from treatment until your skin heals.

**Warning** - All device servicing must be performed by qualified and trained personnel. No modification of this equipment is allowed. If you attempt to open and service the device yourself, you may cause damage to the device. You could also get an electric shock by touching the inner parts of the device.

## Precautions

**Caution** - Do not use Optune Lua with any parts that did not come with the device, that were not sent to you by the device manufacturer, or that were not given to you by your doctor. Use of other parts, manufactured by other companies or for use with other devices, can damage the device. This may lead to a break in treatment.

**Caution** - Do not use Optune Lua if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Use of damaged components can damage the device, and cause a break in treatment.

**Caution** - Do not get the device, transducer arrays or other parts wet. Getting the device wet may damage it, preventing you from receiving treatment. Getting the transducer arrays very wet is likely to cause them to come loose from your skin. If this happens, the device will turn off and you will need to change the transducer arrays.

**Caution** - Before connecting or disconnecting the transducer arrays, make sure that Optune Lua power switch is in the OFF position. Disconnecting transducer arrays with the power switch in the ON position may cause a device alarm to go off, and could damage the device.

**Caution** - If you have an underlying serious skin condition on the chest, discuss with your doctor whether this may prevent or temporarily interfere with Optune Lua treatment.

**Caution** - Do not use Optune Lua if you are pregnant, you think you might be pregnant, or are trying to get pregnant. If you are a woman who is able to get pregnant, you must use birth control when using the device. Optune Lua was not tested in pregnant women. It is unknown what side effects the device may cause if you are pregnant, or if it will be effective.

**Caution** – There is a hazard of falling due to entanglement in the connection cable. You may consider clipping the cable to your belt.

## Notices

**Notice** - Optune Lua and transducer arrays will activate metal detectors.

**Notice** - If you plan to be away from home for more than 1 hour, carry an extra battery and/or the power supply with you in case the battery you are using runs out. If you do not take a spare battery and/or the power supply, you may have a break in your treatment.

**Notice** - Make sure you have at least 12 extra transducer arrays at all times. This will last you until the next transducer array shipment arrives. Remember to order more transducer arrays when there are at least 12 extra transducer arrays left. If you do not order transducer arrays in time, you may have a break in your treatment.

**Notice** - Batteries may weaken over time and need to be replaced. You will know this has happened when the amount of time the device can run on a fully charged battery begins to shorten. For example, if the low battery indicator light flashes within only 1 hour from the start of treatment, replace the battery. If you do not have replacement batteries when your batteries run out, you may have a break in your treatment.

**Notice** - You should carry the Troubleshooting Guide at all times. This guide is necessary to ensure Optune Lua works properly. If you do not work device correctly, you may have a break in your treatment.

**Notice** - Do not block the device vents located on the front and back of the device. Blocking the vents may cause the device to overheat and turn off, leading to a break in treatment. If this happens, unblock the vents, wait 5 minutes and restart the device. In case the vents are blocked with pet hair/dust, return the device to the manufacturer for service.

**Notice** - Do not block the battery charger vents located on the sides of the battery chargers. Blocking the vents may cause the charger to overheat. This could prevent your batteries from charging. In case the vents are blocked with pet hair/dust, return the battery charger to the manufacturer for service.

**Notice** - Before using a transducer array, make sure its package is sealed by gently rubbing the package between thumb and pointer finger on all four sides. The package should be closed on all sides. There should be no openings in the package seal. If the package is not sealed, the transducer array may be damaged. A damaged transducer array will not work properly and may cause the device to turn off.

**Notice** - The transducer arrays are for single use and should not be taken off your body and then put back on again. If you put a used transducer array back on your chest again, it may not stick well to your skin and the device could turn off.

**Notice** - Keep the device out of the reach of children and pets.

**Notice** – The device has a cord that may cause tripping when connected to an electric socket

# 3. Summary of Effectiveness of Optune Lua for NSCLC from the LUNAR Study

The effectiveness of Optune Lua for NSCLC, as demonstrated in the LUNAR study, was as follows:

- The LUNAR study met its primary endpoint, demonstrating that TTFields therapy when used together with standard of care (SOC) therapies (PD-1/PD-L1 inhibitors or docetaxel) in previously treated metastatic NSCLC patients extended median OS by over 3 months as compared to SOC alone. This extension in median OS is statistically significant and clinically meaningful for this patient population.
- The LUNAR study pre-specified two powered secondary endpoints to assessed median OS by type of SOC (PD-1/PD-L1 inhibitors or docetaxel), which were to be tested only if the primary endpoint was met.
    - o PD-1/PD-L1 inhibitors: LUNAR demonstrated a statistically significant extension in median OS of 8 months when TTFields therapy was used together with PD-1/PD-L1 inhibitors versus PD-1/PD-L1 inhibitors alone.
    - o Docetaxel: In the docetaxel cohort of the LUNAR study, an extension of 2 months in median OS was observed when TTFields therapy was used together with docetaxel compared with docetaxel alone, although this difference did not provide a statistically demonstrated benefit.

Please refer to Section 7 of this IFU for a detailed description of the LUNAR study and results.

# 4. Device Description

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 surface transducer arrays that are placed on the patient's chest and connected to the electric field generator. TTFields physically disrupt the rapid cell division exhibited by cancer cells.

Optune Lua is comprised of two main components: (1) an Electric Field Generator (the Optune Lua device) and (2) Insulated Transducer Arrays (the transducer arrays). In addition, the following components are also included: power supply, battery, battery charger, connection cable and carrying bag.

Optune Lua for NSCLC 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 for NSCLC 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 treatment without changing their daily routine.

Optune Lua should be used for at least 12 hours per day, on average.

# 5. Principles of Operation

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.[1] 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 NSCLC).

In contrast, 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 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. In addition, various in vitro experiments have demonstrated abnormal mitotic process outcomes following TTFields application, which can lead to different forms of cellular death. Specifically, the abnormal chromosome segregation induced by TTFields can lead to mitotic cell death, or to the formation of abnormal daughter cells experiencing endoplasmic reticulum (ER) stress and autophagy, leading them to downstream immunogenic cell death. 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 of temperature.

# 6. Preclinical Data

TTFields have been shown in vitro to inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase.[2]

Specifically, TTFields have been shown to inhibit NSCLC cells in vitro at a frequency of 150 kHz and an intensity of 1 V/cm. Based on realistic finite element mesh simulations, Novocure has concluded that intended TTFields intensities can be generated in the lungs of large animals and humans.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for TTFields has been determined to be approximately 4 weeks to reach tumor stabilization. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

# 7. Clinical Data

## METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC)

### Pilot Clinical Study in Stage 3B/4 NSCLC

The use of TTFields together with chemotherapy was tested in a single arm, pilot study involving 42 subjects with inoperable stage 3B and stage 4 NSCLC who had tumor progression after at least one line of prior chemotherapy. Study 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 the historical control of 8.3 months reported in the phase III study of pemetrexed alone). The 1-year survival rate was 57% (compared to the historical control of 30% reported for pemetrexed alone). 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 adhering to the recommended 12 hours per day.

### Pivotal Clinical Study in Stage 4 NSCLC – The LUNAR Study

**Study Design:** The LUNAR study was a prospective, randomized, open-label, multicenter study comparing the use of Optune Lua concurrent with standard of care therapies (PD-1/PD-L1 inhibitors, which are a specific type of immune checkpoint inhibitor (ICI) 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 docetaxel, 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 through the United States, Europe, China and Canada. The LUNAR study objectives were:

- To assess the safety and effectiveness of Optune Lua concurrent with SOC therapies for metastatic NSCLC patients following progression while on or after platinum based treatment;
- To collect evidence of the safety of Optune Lua when used together with SOC therapies.

**Eligibility Criteria:** The inclusion and exclusion criteria 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. 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 ULN; AST and/or ALT > 2.5 x ULN or > 5 x ULN if patient has documented liver metastases; and serum creatinine > 1.5 x ULN.
    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

**Study Procedures:**

**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 judgment and the patient's wishes). The SOC therapy was administered as described below.

**SOC Arm:** Patients received either docetaxel or physician-choice PD-1/PD-L1 Inhibitor 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 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 irRECIST or unacceptable toxicity.

**Follow-up:** 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).

**Analyses:** Primary and powered secondary effectiveness endpoints were analyzed in the ITT population, which included all 291 randomized patients regardless of whether or not they received any treatment (145 in the TTFields+SOC arm and 146 in the SOC arm). Safety endpoints were analyzed in the Safety population, which included all 282 randomized subjects who received any amount of TTFields or SOC treatment (141 subjects in the TTFields+SOC arm, and 141 subjects in the SOC arm).

**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.

**Subject Characteristics and Treatment Details:** A total of 291 metastatic NSCLC patients who had progressed on or after a platinum-based regimen were enrolled in the study. Seven patients (2%) were lost to follow up before completing the required minimum 12 months follow-up. Demographics and baseline characteristics were well-balanced between the TTFields+SOC arm and the SOC arm in the ITT population.

| Characteristic | TTFields+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) |

| Characteristic | TTFields+SOC (N=145) | SOC (N=146) | Total (N=291) |
|---|---|---|---|
| **Brain metastases at baseline, No (%)** | 0 | 2 (1.4)* | 2 (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) |
| **≥3** | 6 (4.2) | 2 (1.4) | 8 (2.7) |
| **Missing** | 3 (2.1) | 6 (4.1) | 9 (3.1) |
| **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) |

**One patient had both liver and brain metastases at baseline*

As seen below, 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 Inhibitor groups, respectively. The average usage by patients who received TTFields therapy together with docetaxel was 54.26%, which was comparable to the PD-1/PD-L1 Inhibitor group, at 52.31%. 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.

The number of cycles and duration of exposure to SOC therapies was comparable between the TTFields+SOC arm and the SOC arm. The slight difference in median duration of SOC between the TTFields+SOC arm and the SOC (13.9 weeks vs. 12.1 weeks, respectively) is reflective of the similarly prolonged time until disease progression in the TTFields+SOC arm, during which subjects continued to receive treatments.

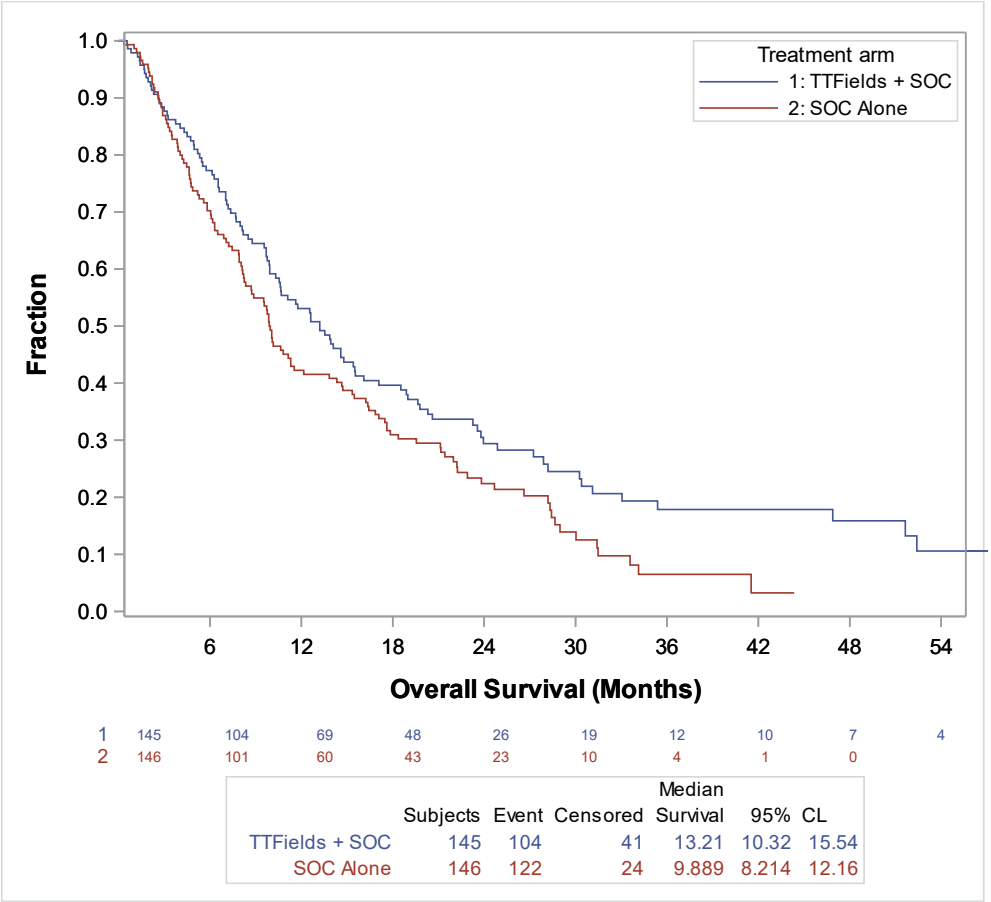
| | TTFields+SOC | | SOC | |
|---|---|---|---|---|
| | Docetaxel n (%) | PD-1/PD-L1 Inhibitors n (%) | Docetaxel n (%) | PD-1/PD-L1 Inhibitors n (%) |
| **TTFields - Duration of Exposure (weeks)** | | | | |
| n | 69* | 71 | | |
| Mean (SD) | 16.70 (21.94) | 34.54 (49.03) | | |
| Median | 11.57 | 13.86 | | |
| Min, Max | 0.14, 162.57 | 0.29, 245.14 | | |
| **TTFields - Average Monthly 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) |
| 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.*

## 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 group 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 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 difference of more than 3 months in median OS is statistically significant (P=0.041) and highly clinically significant in this patient population.

## Primary Effectiveness Endpoint – Overall Survival (ITT)

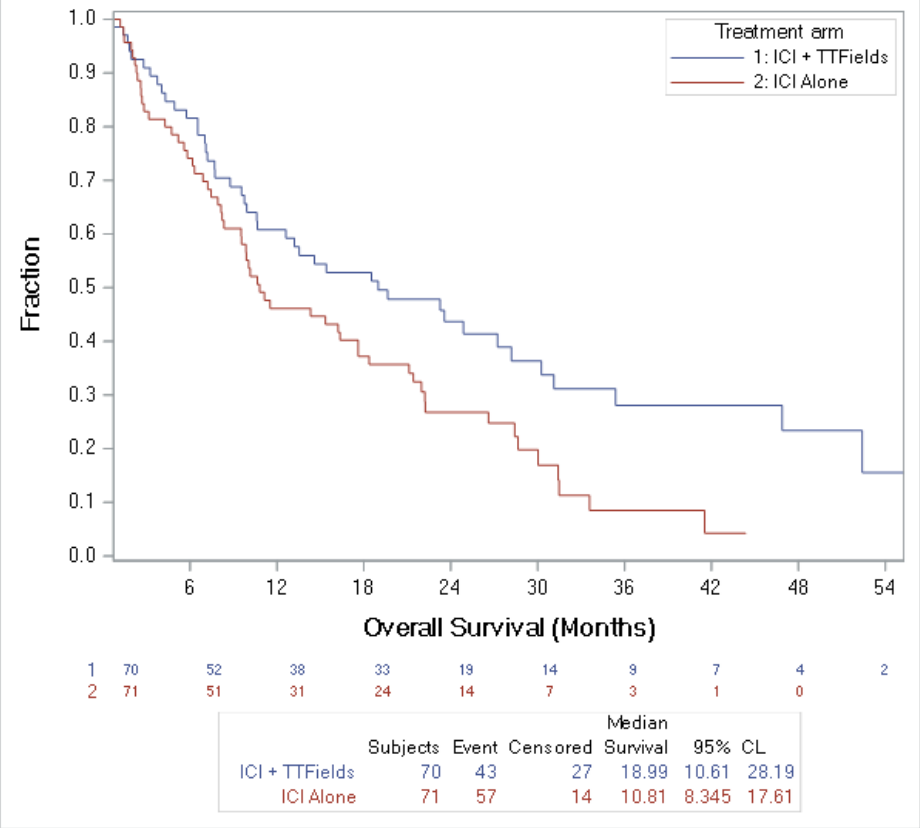



| | TTFields+SOC (N=145) | SOC (N=146) |
|---|---|---|
| Median OS, mo | 13.2 | 9.9 |
| 95% CI, mo | (10.3; 15.5) | (8.2; 12.2) |
| Log Rank | P=0.041 | |
| HR (95% CI) | 0.76 (0.58; 0.99) | |

**Key Secondary Effectiveness Endpoints:** The LUNAR study included secondary endpoints, powered under the original sample size to assess OS in the ITT population per type of SOC - PD-1/PD-L1 Inhibitors and docetaxel. To avoid multiplicity, testing of OS for the key secondary study endpoints was performed only after the primary endpoint of OS met its pre-defined threshold. As pre-specified in the SAP, these powered secondary endpoints were tested simultaneously (each at the 0.025 one-sided level).

- **TTFields+PD-1/PD-L1 Inhibitors vs. PD-1/PD-L1 Inhibitors – 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. In the subgroup of patients using PD-1/PD-L1 inhibitors, 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.

## Overall Survival of TTFields+PD-1/PD-L1 Inhibitors vs. PD-1/PD-L1 Inhibitors

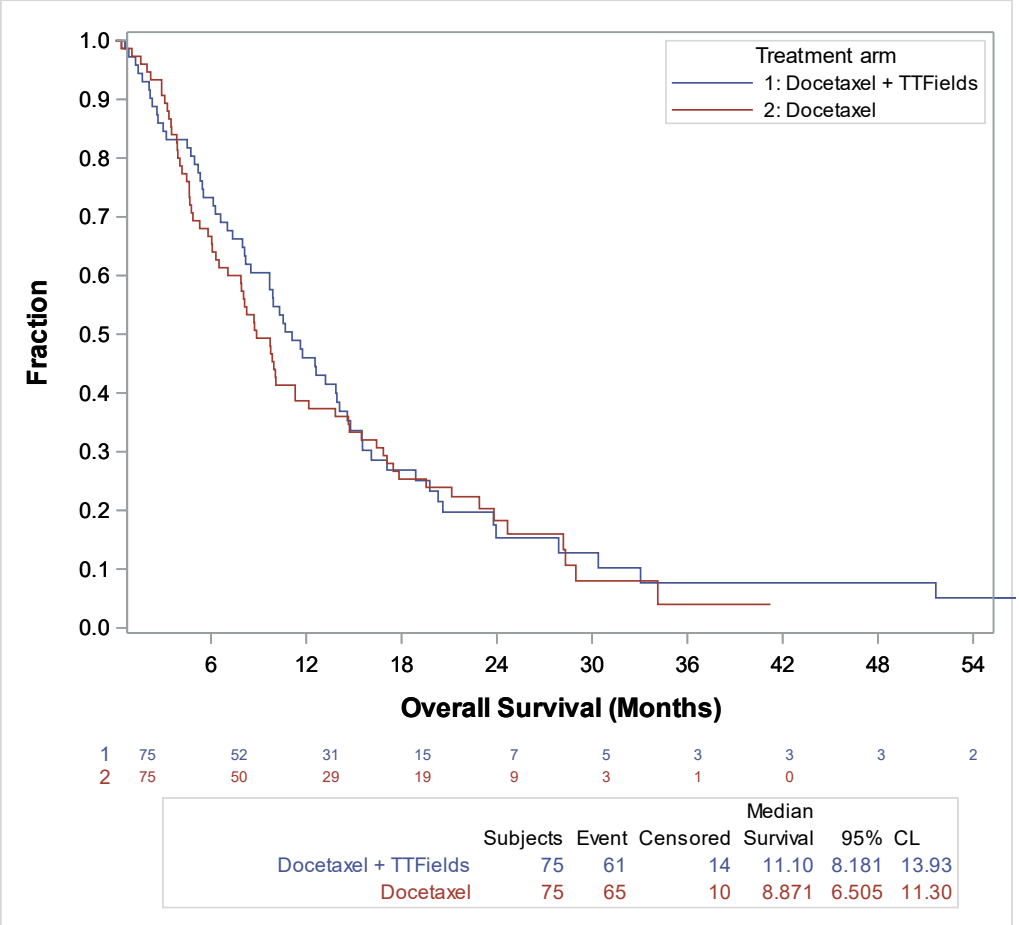



*ICI refers to PD-1/PD-L1 inhibitors*

| | TTFields+ICI (N=70) | ICI (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) | |

- **TTFields+Docetaxel vs. Docetaxel – Overall Survival:** 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=0.471). 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.

## Overall Survival of TTFields+Docetaxel vs. Docetaxel




| | 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=0.471 | |
| HR (95% CI) | 0.88 (0.61; 1.26) | |

**Additional Secondary Endpoints:**

- **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. While non-inferiority was not met statistically, the addition of Optune Lua to docetaxel suggests a comparable median OS to PD-1/PD-L1 Inhibitors alone.

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

| Additional Endpoints - TTfields + SOC vs. SOC | TTFields+SOC (Median) | SOC (Median) | p-value |
|---|---|---|---|
| PFS | 4.4 months | 4.2 months | p=0.458 |
| ORR | 19.3% | 18.5% | p=0.859 |

LUNAR's PFS results are generally consistent with trends in PFS reported for other immunotherapy studies in this same patient population. Regarding ORR, it was notable that four of the five cases of Complete Response occurred in patients treated with Optune Lua.

QoL was measured throughout the study using the 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.

- **Analyses of Sub-Populations:** 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 PD-1/PD-L1 inhibitors used together with Optune Lua, or tumor histology (squamous/non-squamous).

| Additional Endpoints - Sub-Populations | TTFields+SOC (median) | SOC (median) | p-value |
|---|---|---|---|
| **OS – Tumor Histology** | | | |
| Non-squamous TTFields+SOC (n=83) vs. SOC (n=82) | 13.2 months | 9.9 months | p=0.193 |
| Squamous TTFields+SOC (n=62) vs. SOC (n=64) | 13.9 months | 10.1 months | p=0.108 |
| **PFS – Tumor Histology** | | | |
| Non-squamous TTFields+SOC (n=83) vs. SOC (n=82) | 5.3 months | 4.0 months | p=0.237 |
| Squamous TTFields+SOC (n=62) vs. SOC (n=64) | 4.2 months | 4.9 months | p=0.851 |

- **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 GBM. Moreover, the median 12 hour daily usage of Optune Lua reached in the ITT population (140 patients) is consistent with the pilot study in NSCLC, where 85% of patients achieved the recommended 12 hours of TTFields usage per day.

**Safety Results:**

In the LUNAR study Safety population, 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 6 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.

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

| 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) | 232 (16.3) | 55 (19.5) |
| Injury, poisoning and procedural complications | 3 (2.1) | 0 | 3 (1.1) |
| 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) |

The safety findings from LUNAR are consistent with the known low toxicity profile of TTFields therapy seen in both the clinical and commercial use of Optune Lua for MPM, and company's other TTFields device, Optune Gio for GBM.

**Conclusions:** 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 QoL.

# 8. Additional Information

Detailed information for patients on the use of Optune Lua for NSCLC can be found in the following documents:

- Optune Lua® for NSCLC Patient Information and Operation Manual (ILE Transducer Arrays) – QSD-QR-808
- Optune Lua® for NSCLC Patient Information and Operation Manual (ITE Transducer Arrays) - QSD-QR-809

Information for physicians on determining the optimal array layout for patients

- Clinical Practice Guidelines: layout optimization in thoracic malignancies

# 9. Glossary

**AE** – Adverse event

**GBM** – Glioblastoma

**MPM** – Malignant Pleural Mesothelioma

**NSCLC** – Non-small cell lung cancer

**ITT** – Intent-to-Treat. This analysis population includes all randomized subjects.

**kHz** – kilo hertz; number of cycles per second

**Optune Lua** – A portable, battery, or power supply, operated device for delivering 150 kHz TTFields to the lungs of patients with advanced NSCLC

**OS** – Overall survival

**PFS** – Progression free survival

**Radiological Response Rate** - sum of complete and partial radiological response rates

**SOC** – Standard of care

**Disease Control Rate** – sum of stable disease, complete and partial radiological response rates

**TTFields** – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated transducer arrays to the region of the body inflicted with a solid tumor. The fields have been shown in vitro to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase

**V/cm** – Volts per centimeter; the unit of intensity measurement of electric fields

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