Study Title:	Prophylactic Tumor Treating Fields in management of patients with Small Cell Lung Cancer
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SUMMARY OF CHANGES

#	Section	Page(s)	Change	Justification
1.	7	44, 45	1. Changing screening to up to 12 weeks from 4 weeks (which in the schedule of events changed from 28 to 60 days) kept H&P and such to 60 days but used the footnote to expand the scans to 3 months. 2. Phone Follow up for screening was unchecked for both LS-SCLC and ES-SCLC. 3. For CR imaging body and Gd-MRI for EOT were deleted	1. kept H&P and such to 60 days but used the footnote to expand the scans to 3 months. 2. Not necessary as patients will be seen in clinic. 3. as to not put excessive cost on patient /insurance
2.	4.3 and 4.3.1	30,31	Addition of 4th participating study center (Ohio State University) and updated calculations for subject accrual.	To assist with target recruitment numbers
3.	12.3	62	Change of EDC to Forte EDC	Improved EDC through KCI
4.				
5.				

SYNOPSIS

Study Title	Prophylactic Tumor Treating Fields in management of patients with Small Cell Lung Cancer
Protocol #	18029
Study Center	multicenter [U.S. only]
	Oregon Health & Science University University of Washington (UW Seattle) Mayo Clinic (Arizona) Ohio State University
Clinical Phase	Phase II
Investigational Component(s)	Medical Device (FDA approved - used for an unapproved indication)
Interventional Study Type	*Single-arm*
Précis	Small Cell Lung Cancer (SCLC) is a common disease, with a high propensity for brain metastases. Prophylactic cranial irradiation (PCI) is a standard therapy for reducing the risk of SCLC brain metastases. While PCI is associated with added survival benefit to patients with SCLC, the approach is associated with both acute and long-term toxicity. As an alternative treatment option, directed electrical fields to the brain using the Optune® device is associated with decreasing the risk of tumor progression and improvement in overall survival in patients with glioblastoma multiforme (GBM). Applying a similar methodology, this pilot study will evaluate the safety and preliminary efficacy of Optune®-Tumor Treating Fields (TTFields) therapy as a prophylactic approach to reducing SCLC brain metastases.
Primary Objective	Primary: Observed rate of brain metastases following TTField therapy at 6 months.
Secondary Objectives	1. Rate of brain metastases following TTField therapy at 12 months. 2. Overall survival of participants with SCLC after using TTField therapy. 3. TTField therapy related side-effects. 4. Quality of life among participants using TTField therapy. 5. Observed rate of brain metastases 6-month from the beginning of the 4th cycle of chemotherapy to development of brain metastases
Primary Endpoints	Incidence of SCLC brain metastases at 6 months from the start of TTField therapy
Secondary Endpoints	1. Incidence of SCLC brain metastases at 12 months 2. Overall survival 3. Incidence of TTfield related adverse events 4. Quality of life 5. Incidence of SCLC brain metastases at 6 month from the beginning of the 4th cycle of chemotherapy to development of brain

	metastases
Number of Participants	A total of 106 participants will be enrolled in this study. Among these, target enrollment will include 45 participants with extensive stage disease, and 61 participants will have limited stage disease.
Duration of Therapy	Participants will receive TTField therapy for 12 months, or until development of brain metastases, whichever comes first.
Duration of Follow Up	Participant followed up will continue until death.
Inclusion Criteria	• ≥ 22 years of age • Biopsy-proven SCLC • Clinical Response to standard of care chemo- and/or radiotherapy, as defined by no thoracoabdominal tumor progression on CT imaging within 12 weeks prior to enrollment. • No contraindications to treatment with Optune®. • No other active malignancies, with exception of non-metastatic prostate cancer, treated Stage I breast cancer, skin malignancies • No brain metastases [gadolinium MRI < 12 weeks before enrollment]. • No mental conditions that would prevent compliance. • Life expectancy of at least 3 months. • ECOG ≤ 2.
Exclusion Criteria	• Progressive disease. • Pregnant • Implanted pacemaker, programmable shunts, defibrillator, deep brain stimulator, other implanted electronic devices in the brain, or documented clinically significant arrhythmias. • Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)
Investigational Product(s)	Optune® is a portable battery powered device that produces alternating electrical fields, termed tumor treatment fields (“TTFields”) within the human body. These TTFields are applied to the patient by electrically insulated surface transducer arrays, which function to disrupt the rapid cell division of cancer cells.
Statistical Considerations	**Primary Evaluations:** Incidence of brain metastases 6 months after start of Optune® **Sample Size (statistical assumptions)** For extensive stage, we need 45 subjects for 80% power to detect a 50% reduction at a 5% significance level using a test for one proportion, assuming the incidence rate is 40% for subjects not receiving Optune®. For limited stage, we need 61 subjects for 80% power to detect a 50% reduction at a 5% significance level, using a test for one proportion, assuming the incidence rate is 30% for subjects not receiving Optune®.

	Efficacy Endpoints • Presence of brain metastasis at 6 and 12 months • Overall Survival • Incidence of SCLC brain metastases at 6 month from the beginning of the 4th cycle of chemotherapy to development of brain metastases **Safety Endpoints:** • Quality of life questionnaire • Side effects, particularly cognitive side effects (mental status exam and questionnaire)

SCHEMATIC OF STUDY DESIGN

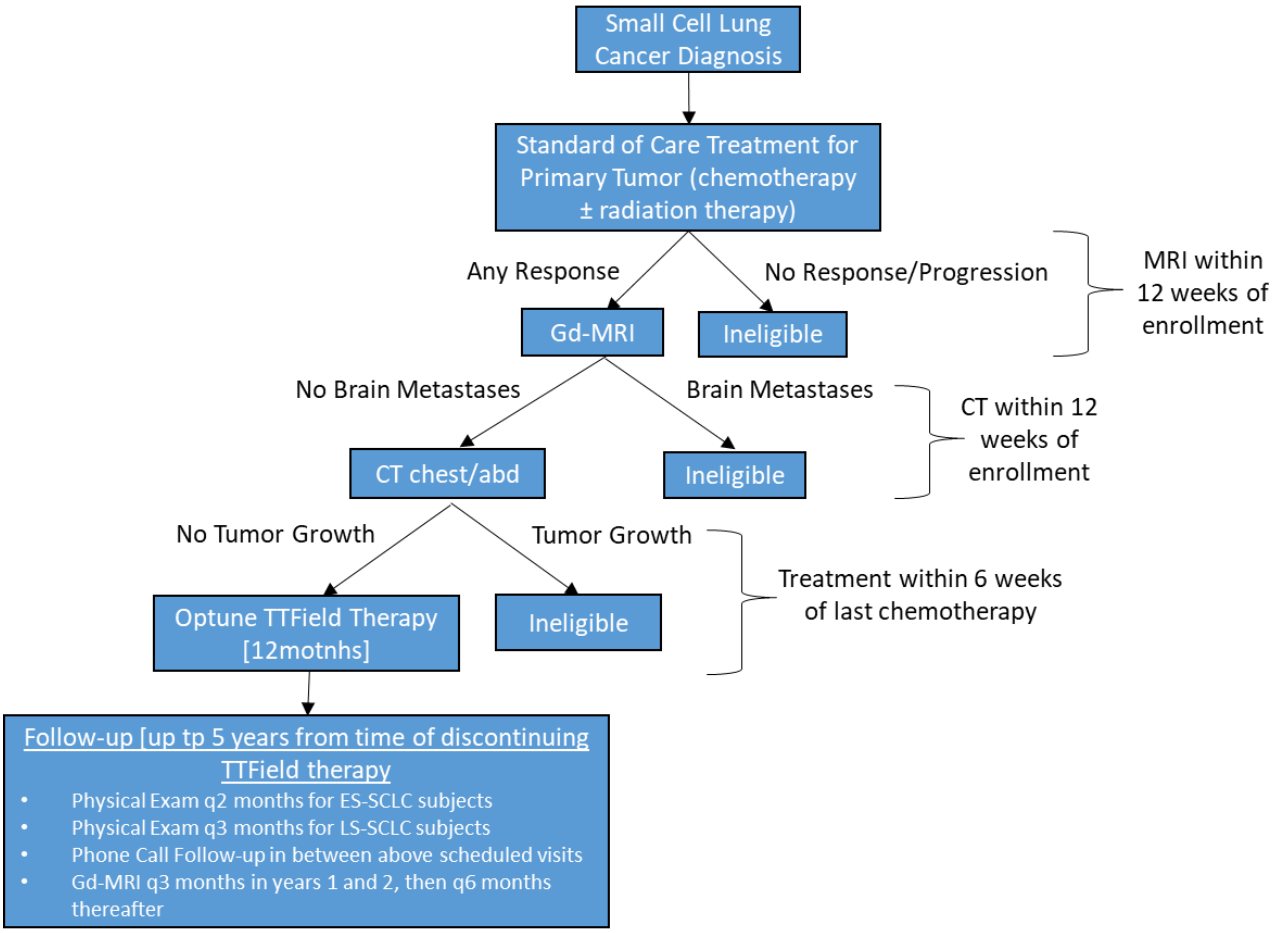

Figure 1. Study Overview.
Participants with small cell lung cancer (SCLC) will be considered for enrollment if no more than 6 weeks have passed since last standard-of-care chemotherapy or thoracic radiation treatment of their primary tumor. Participants must have demonstrated partial response to treatment and show no tumor recurrence within 12 weeks prior to enrollment. Similarly, participants cannot have metastatic brain lesions in the 12 weeks leading up to enrollment. Participants eligible to receive Optune®-generated electrical tumor-treatment field (TTField) therapy will undergo continuous treatment for 12 months, or until disease progression, whichever comes first. This study will assess whether Optune® therapy to the brain can be used as a prophylactic approach to reducing the formation of brain lesions. The primary endpoint is the incidence of metastatic SCLC brain lesions. Participants will be clinically evaluated throughout the study for evidence of tumor recurrence or metastases, and will also be periodically assessed during the on-treatment and off-treatment portions of the study to evaluate treatment effects on quality of life and cognitive function. This study anticipates the accrual of 106 participants over 24-months.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AC	Alternating current
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area under the curve
BUN	Blood urea nitrogen
CBC	Complete blood cell (count)
CFR	United States Code of Federal Regulations
CoC	National Institutes of Health (NIH) Certificate of Confidentiality
COWA	Controlled Oral Word Association
CR	Complete response
CRC	Clinical Research Coordinator
CRMS	Clinical research management system
CRQA	Clinical Research Quality & Administration
CRRC	Clinical Research Review Committee (OHSU)
CRF	Case report form
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CTMS	Clinical Trial Management System
DFS	Disease-free survival
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECG, EKG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCRIS	Electronic Clinical Research Information System
EDC	Electronic data capture
FCBP	Female of childbearing potential
FDA	United States Food and Drug Administration
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
HCT	Hematocrit
HGB	Hemoglobin
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HVLT	Hopkins Verbal Learning Test-Revised
IB	Investigator's brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational device exemption
IND	Investigational new drug application
IRB	Institutional Review Board
IV	Intravenous
kHz	Kilo Hertz
LDH	Lactate dehydrogenase

LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
OHRP	Office for Human Research Protections
OHSU	Oregon Health & Science University
ORR	Overall response rate
PCI	Prophylactic cranial irradiation
PD	Progressive Disease
PET	Positron emission tomography
PI	Principle Investigator
PK	Pharmacokinetics
PO	*Per os* (by mouth, orally)
PR	Partial response
QOL	Quality of Life
RBC	Red blood cell (count)
RNI	Reportable new information
ROS	Reactive oxygen species
RT	Radiation therapy
SAE	Serious adverse event
SCLC	Small Cell Lung Cancer
SD	Stable disease
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SRS	Stereotactic radio surgery
TMT	Trail Making Test
TMZ	Temozlomide
TSMP	Trial Specific Monitoring Plan
TTField	Tumor-treatment field
UA	Urinalysis
ULN	Upper limit of normal
UP	Unanticipated problem
WBC	White blood cell (count)

1. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 OVERVIEW OF SMALL CELL LUNG CANCER (SCLC)

Comprising approximately 14% of all lung cancers, SCLC has an annual incidence of 31,000 new cases, which are most often attributable to cigarette smoking. SCLC is characterized as having a rapid doubling time and early development of widespread metastases, and without treatment, the disease is associated with survival rates of 2 to 4 months.[2] SCLC is frequently classified as being either a limited-stage or extensive-stage.[3] Limited disease (LS-SCLC) is defined as the patient having the SCLC involvement restricted to one hemithorax that can be encompassed within a tolerable radiation field. Alternatively, extensive disease (ES-SCLC) is defined as disease beyond one hemithorax and may include malignant pleural or pericardial effusion or hematogenous metastases.

The majority of patients (70%) present with ES-SCLC. Treatment with combination therapies is associated with a median survival time of approximately 9 to 10 months from diagnosis, and though 20% of these patients have a complete response, 5-year survival is only 2%.[4] In contrast, LS-SCLC is associated with an 80% complete response rate and an approximate 18 months survival time. Multimodal treatment of LS-SCLC, which includes concurrent chemotherapy and radiotherapy, can achieve long-term disease-free of 20 to 25%.[5,6]

PROPHYLACTIC CRANIAL IRRADIATION

Approximately 20% of patients with SCLC have a detectable brain lesion, and the actuarial risk of developing brain metastases within 2 years of diagnosis is nearly 80%.[5,7,8] Randomized studies have shown that prophylactic cranial irradiation (PCI) decreases the risk of developing central nervous system metastases by more than 50%.[7] The 3-year overall survival of complete responders (predominately those with LS-SCLC) that received PCI was 21%, whereas survival was only 15% in the control group.[7,8]

Figure 2. Optune system components and usage.
A. (1) electric field generator, (2) portable batteries, (3) charger for portable batteries, (4) plug-in power supply, (5) connection cable and box, (6) transducer arrays, (7) power cord, (8) shoulder bag and strap, (9) portable battery case. **B**. Model demonstrating wearing of Optune device.

1.2 OVERVIEW OF OPTUNE

Optune® is a portable battery or power supply operated device that produces alternating electrical fields, called tumor treatment fields (TTFields) within the human body. These TTFields are applied to the patient by electrically insulated surface transducer arrays, which function to disrupt the rapid cell division exhibited by cancer cells.[1,9]

The Optune system is comprised of two main components: (1) an Electric Field Generator (i.e., the Optune device); (2) INE Insulated Transducer Arrays (i.e., the transducer arrays), and 3) additional Optune Treatment Kit components that include a power supply, portable battery, battery rack, battery charger, connection cable and carrying case.(**Figure 2**)

Refer to Section 0 for specific details regarding the components of the Optune device.

MECHANISM OF ACTION

TTFields therapy involves the production of alternating electrical fields within the human body that disrupt the rapid cell division exhibited by cancer cells with the alternating electrical fields applied through the surface of the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them.[1] The TTField technology takes advantage of the unique characteristics, geometrical shape, and rate of dividing cancer cells, which make them susceptible to the effects of the alternating electric 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., 200 kHz for glioblastoma multiforme [GBM]). TTFields have been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis. These processes lead to physical disruption of the cell membrane and to programmed cell death.[9]

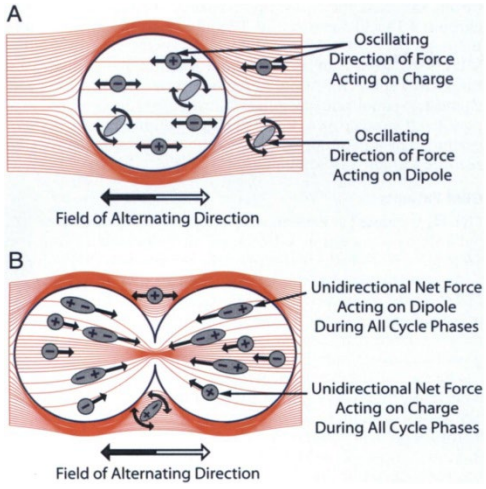

Figure 3. Alternating current field around quiescent and dividing cells.

(A) Inside quiescent cells, the field is uniform, and the oscillating electric forces result only in "vibration" of ions and dipoles (the forces associated with each half cycle are denoted white and gray arrows).

(B) In dividing cells, the non-uniform field induces forces pushing all dipoles toward the furrow. Note that at frequencies of 0.1-1.0 MHz, the cell membrane impedance is relatively high, so only a small fraction of the currents penetrate the cells as seen from the density of lines.
Adapted from Kirson et al[1]

PRE-CLINICAL EXPERIENCE

The application of TTFields has very limited effect on non-dividing cells. In the case of the adult brain, most normal adult brain cells have a very slow rate of cellular proliferation and are minimally affected by the TTFields. Preclinical testing in animal models, which compared

TTFields-treated groups to controls showed that there are no histological differences in the major internal organs (including the brain), nor differences in blood characteristics, cardiac rhythm, body temperature, or in animal behavior. Additionally, because the electrical fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles.[1,9]

TTFields have been shown both in vitro and in vivo to effectively inhibit cancer cell replication during mitosis without any systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively 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.[9]

TTFields have been shown to inhibit glioblastoma cells in vitro and in vivo at a frequency of 200 kHz and an intensity of 0.7 V/cm.[1] Extensive safety studies in healthy animals (mice, rats and rabbits) and humans have shown that TTFields are not associated with significant systemic toxicities. Neither acute, nor chronic systemic toxicities were seen when TTFields were applied to the torso or head, at different frequencies (100-200 kHz), different intensities and for different periods of time.[1,10,11]

CLINICAL STUDIES OF OPTUNE

The first-in-human studies of TTFields therapy in a clinical setting evaluated short duration therapy to cutaneous metastases in melanoma and advanced breast cancer.[12] In this pilot trial, TTFields therapy was shown to decrease the growth rate of skin metastases from breast cancer and melanoma. Subsequent studies evaluated TTFields therapy in the setting of the most common primary malignant brain tumor, GBM, both as a single-treatment agent and in combination with chemotherapy.

1.2.1.1 *Effect of TTFields therapy on Recurrent GBM Subjects - A Pilot Study*

In a European pilot study of patients with recurrent GBM, 10 participants were treated with the Optune device. All patients underwent surgery and radiotherapy for the primary tumor, and were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. Patients completed between 1 and 18 treatment courses leading to maximal treatment duration of 18 months. Overall, more than seventy four-week treatment courses were completed (> 7 courses per patient on average). The treatment was well tolerated with no treatment- related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time, indicating that compliance with treatment was very high. Mild to moderate contact dermatitis appeared beneath the transducer arrays in 8 of the 10 patients during treatment following the first treatment course. The skin irritation improved with use of topical corticosteroids. Regular relocation of the transducer array was necessary in order to allow for continuous treatment. The median progression free survival (PFS) of the patients in this study exceeded historical controls1 (26.1 weeks versus 9 weeks, respectively).

The PFS at 6 months was 50% compared to 15% in historical controls.[13] At the end of the study, 8 of the 10 patients had died (at 4 years from study initiation); the remaining 2 patients we reported are alive at 5 years follow up and are progression free. Median OS from diagnosis was 14.7 months (compared to 6 months in the historical control).

1.2.1.2 *Effect of TTFields therapy on Newly Diagnosed GBM Subjects - A Pilot Study*

In a European pilot study of patients with newly diagnosed GBM, 10 participants were treated

with the Optune® device. All participants underwent surgery and radiotherapy for the primary tumor, and after radiotherapy, the patients then received maintenance temozlomide (TMZ) in conjunction with TTField therapy. TTField therapy was administered in the same manner as in the pilot recurrent GBM study described by Wong et al[13]. Participants completed between 1 and 17 treatment courses leading to maximal treatment duration of 16.5 months. Overall, patients completed more than 96, four-week treatment courses (> 9.6 courses per patient on average). The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Participants received scheduled treatment ~80% of the time, again indicating that compliance with treatment was very high. Mild to moderate contact dermatitis was experienced by all patients during treatment following the first treatment course, but was improved with use of topical corticosteroids. Regular relocation of the transducer arrays was necessary in order to allow for continuous treatment.

Median PFS of the patients in this study exceeded historical controls (14.4 months versus 7.1 months, respectively). At the end of the study (4 years from initiation), 5 of the 10 patients died, and of the remaining 5 patients: 2 were lost to follow up and 3 were reported alive; these patients were progression free. Median OS from diagnosis was greater than 40 months (compared to 14.6 months in historical controls).[14]

1.2.1.3 *Pivotal Study for Recurrent GBM*

In a prospective, randomized, open label, active parallel control trial to compare the effectiveness and safety outcomes of recurrent GBM subjects treated with TTField therapy (n=120) to those treated with an effective best standard of care chemotherapy (including bevacizumab; n=117).[10] Participants receiving TTField therapy had comparable overall survival to subjects receiving the best available chemotherapy in the United States today (OS = 6.3 vs. 6.4 months; HR 1.0; p=0.98). Similar results showing comparability of TTField therapy to BSC chemotherapy were seen in all secondary endpoints (e.g., PFS at 6 months = 21.4% for Optune vs. 15.2% for chemotherapy).

In this pilot trial, 20 patients in total were treated (10 newly diagnosed glioblastoma; 10 recurrent glioblastoma). All patients were treated with multiple 4-week treatment courses using continuous TTFields therapy at 200 kHz (optimal frequency for glioblastoma). Patients with recurrent glioblastoma received TTFields therapy alone, while patients with newly diagnosed glioblastoma received TTFields therapy in combination with TMZ. The treatment was well tolerated with no serious TTFields therapy-related adverse events reported. Mild-to-moderate contact dermatitis was the most common adverse event attributed to device use, which improved with the use of topical corticosteriods and periodic repositioning of the arrays. Patients received TTFields therapy about three quarters of the scheduled time on average. Considering the continuous nature of TTFields therapy (i.e., 24 h/day for many months), this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment, and stopping treatment only for short periods of time for personal needs. Although the number of patients in this pilot trial was small, the favorable safety profile and promising efficacy data (20% survival at 7-years follow-up) resulted in Novocure embarking on a pivotal trial in recurrent glioblastoma.

1.2.1.4 *TTFields therapy for newly diagnosed GBM*

A large randomized controlled study was designed to assess safety and effectiveness of TTFields therapy in 700 patients with newly diagnosed GBM. Patients were randomized to receive TTFields therapy and TMZ (TTFields/TMZ), or TMZ alone. The primary endpoint of PFS at final analysis was 7.1 months for those receiving TTFields/TMZ compared to 4.2 months among those treated with TMZ alone. This difference of 2.9 months was highly clinically

significant (log-rank p = 0.001). Overall, those in the combined therapy group had a nearly 31% decreased risk of progression compared to patients receiving TMZ alone. Likewise, the OS was almost 30% longer in the TTFields/TMZ arm compared to TMZ alone (19.6 months [95% CI 16.6-24.1] vs. 15.2 months [95% CI 13.5-18.2], respectively).

1.2.1.5 *Effect of TTFields therapy for non-small cell lung cancer (NSCLC)*

TTFields therapy for NSCLC has also been evaluated by developing transducer arrays and field-generating devices for the torso. In a single-arm pilot study (phase I/II) of 42 patients with advanced NSCLC who had tumor progression after at least one prior chemotherapy.[11,15] Participants in this study received pemetrexed together with continuous daily TTFields therapy (for a minimum of 12 hrs/day) applied to the chest and upper abdomen until disease progression. The primary endpoint was time to "in-field" progression in the lungs and liver (i.e., areas where the TTFields therapy was applied). The median age of patients was 63 years; 76% had stage IV disease; 78% had adenocarcinoma and 17% had a performance status of two. TTFields was used for an average of 11.2 hrs/day. The median time to in-field progression was 28 weeks and the median time to systemic progression was 22 weeks. The authors reported that using this treatment approach, 6 patients (14.6%) had a partial response (PR) and 20 (48.8%) had stable disease (SD). Compared to the historical control of 8.3 months reported for pemetrexed alone compared to docetaxel[16], the median overall survival among participants receiving TTFields therapy was 13.8 months. Likewise, the 1-year survival rate was 57% for participants receiving TTFields therapy, compared to the historical control of 30% administered pemetrexed alone.[16] The authors reported that the combination of chemotherapy and TTFields therapy was we well tolerated and, compared to pemetrexed historical control, there was no increase in the adverse event rate, or in gastrointestinal or hepatic toxicity. Except for device-related mild-to-moderate contact dermatitis in 14 participants, there were no device-related cardiac arrhythmias reported and no serious TTFields therapy–related adverse events.

The clinical benefit of TTField therapy for brain metastases from NSCLC is currently being investigated in a phase 3, pivotal, open-label study (METIS, NCT02831959).[17] In this ongoing trial, 270 patients with NSCLC with 1-10 brain metastases are randomized (1:1) to receive stereotactic radio surgery (SRS) followed by either TTFields or supportive care alone. The primary objectives of this trial is to test the efficacy, safety and neurocognitive outcomes of TTFields in this patient population by assessing the time to first cerebral progression. Additional study endpoints include assessing the time to neurocognitive failure based on functional tests (e.g., HVLT, COWA and TMT). The planned treatment for this study includes continuous TTFields therapy at 150 kHz to be applied to the brain within 7 days of SRS. The METIS trial has received investigation device exemption from the FDA.

1.3 **RATIONALE**

SCLC is a common disease, with a high propensity for brain metastases. Although the use of PCI has for a long time been considered a standard therapy for patients with both LS-SCLC and ES-SCLC, recent results from a randomized trial examining PCI vs observation with frequent use of brain MRI imaging, revealed no difference in outcomes.[18] The findings of this study have changed the practice in large academic institutions overnight (*personal communication*), and patients with ES-SCLC are no longer offered PCI as a standard of care in many academic centers in the United States. Large cooperative groups are planning to start a similar randomized trial for patients with LS-SCLC. Overall, this leaves patients with very limited treatment options, and given the high risk of brain metastases, the need for novel therapies is greatly needed.

TTFields therapy has entered the oncology treatment landscape as an FDA-approved cancer treatment for recurrent GBM and is part of the National Comprehensive Cancer Network (NCCN) Treatment Guidelines for this disease. The success of this approach in reducing the risk of recurrent GBM has been adopted in the randomized phase 3 METIS trial for patients with known brain metastases from NSCLC, which is currently on-going at many US centers. We hypothesize that TTFields can be similarly adapted to prevent the formation of SCLC metastatic brain lesions. TTFields therapy is shown to be safe and lacks the conventional cytotoxic systemic side effects. Thus this alternative interventional could significantly decrease the brain metastatic rate as well as lower the need for toxic whole brain irradiation

This study will evaluate the potential for TTFields therapy as a novel approach to reducing the rate of in-brain failures in patients with SCLC that have completed standard-of-care chemo-radiotherapy. It is hypothesized that TTFields therapy can be used prophylactically to reduce the incidence of brain metastases as compared to historical observational reports, and have no effect on the cognitive function of those receiving this treatment modality.

1.4 **POTENTIAL RISKS AND BENEFITS**

KNOWN POTENTIAL RISKS

Refer to Section 9.4.1 for a detailed description of any adverse events that have been recorded in patients with GBM on clinical trials investigating TTFields therapy, after brain-directed therapies (such as surgery, radiation therapy), systemic therapies, and most often with evidence of GBM progression.

Results from a randomized study examining TTFields therapy in patients with newly diagnosed GBM showed that the only TTFields-related AEs are skin irritation, falls that were observed at a slightly higher incidence among patients carrying the Optune® device, headaches related to wearing the transducer arrays 24 hours a day, and mild psychiatric symptoms (e.g., anxiety, insomnia, confusion) that could be caused by the need to incorporate the device and arrays into daily life.

Since TTFields are only applied to the brain, they are unlikely to have an effect on rapidly proliferating cells in the rest of the body.

KNOWN POTENTIAL BENEFITS

Given the high rate of brain metastases among patients with SCLC, prophylactic TTFields therapy may reduce the risk of brain metastatic lesions and improve overall patient outcomes. It cannot, however, be guaranteed that participants in this study will directly benefit from treatment during participation, as the clinical trial is designed to provide information about the safety and effectiveness of this investigational approach.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

Observed rate of brain metastases following TTFields therapy at 6 months

2.2 SECONDARY OBJECTIVES

1. Observed rate of brain metastases following TTFields therapy at 12 months.
2. Survival of participants with SCLC after using TTFields therapy.
3. Usage and overall safety characteristics of TTFields therapy.
4. Quality of life among participants using TTFields therapy.
5. Observed rate of SCLC brain metastases at 6 month from the beginning of the 4th cycle of chemotherapy to development of brain metastases

3. STUDY DESIGN AND ENDPOINTS

3.1 DESCRIPTION OF THE STUDY DESIGN

Refer to Section 10*,* STATISTICAL CONSIDERATIONS *for additional information regarding statistical methods used in this study.*

This is a Phase II pilot study to assess the safety and efficacy of prophylactic TTFields therapy in patient with SCLC. Participants must meet the inclusion criteria, have none of the exclusion criteria, and have provided written informed consent before the conduct of any screening tests not performed routinely in their treatment.

Participants with either LS-SCLC or ES-SCLC must be no more than 6 weeks from having received last dose of chemotherapy for primary tumor (per institutional guidelines), and must have at least demonstrated a partial response to treatment, to be considered eligible for TTField therapy with the Optune® device. Participants are encouraged to undergo TTField therapy (200 kHz) for a minimum of 18 hours per day for a period of 12 months, or until the confirmed appearance of metastatic brain lesions, whichever comes first. Participants that develop numerous (>10) supratentorial metastatic lesions before 12 months will discontinue further use of TTFields and will receive palliative/supportive care per institutional guidelines (e.g., whole brain radiotherapy). Participants that develop either limited (≤10) supratentorial or any number of infratentorial metastases will remain eligible to continue with TTFields therapy for the duration of the 12 months after the brain metastatic lesions are addressed according to institutional guidelines (e.g. partial brain irradiation stereotactic radiosurgery, stereotactic body radiation therapy). Systemic progression will be managed per institutional guidelines (e.g. systemic chemotherapy, immunotherapy, radiation therapy, etc.) and patients will remain eligible to continue with TTFields therapy for the duration of the 12 months. While on-study, participants will be clinically evaluated every 2-3 months per NCCN guidelines and will all be monitored remotely by phone calls monthly and will undergo gadolinium (gd)-MRI of the head at 6 months to assess occurrence of disease progression (per RECIST v1.1). Participants will be subject to periodically answering quality of life (QoL) questionnaires (i.e., baseline, 6 and 12 months after initiating treatment). At the end of study, participants will undergo clinical follow-up 1 and 3 months after completion of TTField therapy. Subsequent follow-up until death (up to 5 years) will be in accordance with standard of care (i.e., every 3 months during years 1 and 2 following last chemo-radiotherapy, then every 6 months thereafter).

3.2 STUDY ENDPOINTS

PRIMARY ENDPOINT

Objective	**Endpoint**	**Start**	**End**
Observed rate of brain metastases following TTFields therapy at 6 months	Incidence of SCLC brain metastases at 6 mo	Start of TTFields [baseline]	6 mo

SECONDARY ENDPOINTS

Objective	**Endpoint**	**Start**	**End**

Observed rate of brain metastases following TTFields therapy at 12 months	Incidence of any SCLC brain metastases at 12 mo	Start of TTFields [baseline]	12 mo
Overall survival of participants with SCLC after using TTFields therapy.	Overall survival	Start of TTFields [baseline]	Death or last follow-up at 60 months.
TTFields therapy related side effects.	1. Incidence of TTFields related AEs 2. Incidence of cognitive AEs using Mini Mental State Exam (MMSE)	Start of TTFields [baseline]	12 mo 6, 12 mo 12 mo
Quality of life among participants using TTFields therapy.	EORTC QLQ-C30 questionnaire at 6 and 12 mo	Start of TTFields [baseline]	6, 12 mo
Observed rate of SCLC brain metastases at 6 month from the beginning of the 4th cycle of chemotherapy to development of brain metastases	Incidence of SCLC brain metastases at 6 month from the beginning of the 4th cycle of chemotherapy to development of brain metastases	Start of the 4th cycle of chemotherapy [baseline]	6 mo

4. STUDY ENROLLMENT AND WITHDRAWAL

4.1 PARTICIPANT INCLUSION CRITERIA

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Ability to understand and the willingness to sign a written informed consent document.
2. Age ≥ 22 years at time of informed consent. Both men and women and members of all races and ethnic groups will be included.
3. Pathologically confirmed LS-SCLC or ES-SCLC.
   a. LSCLC – Stage I-III (T_{any}, N_{any}, M0) that can be safely treated with radiation doses. Excludes T3-4 due to multiple nodules that are too extensive of have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.[19]
   b. ESCLC – Stage IV (T_{any}, N_{any}, M1), or T3-4 due to multiple nodules that are too extensive of have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.[19]
4. Must be no more than 6 weeks from having received last dose of chemo- and/or radiotherapy for primary tumor to anticipated start of TTField therapy.
5. Partial response to standard of care (chemo- and/or radiotherapy) as judged by treating physicians with no evidence of recurrence as observed by thoracoabdominal CT within 12 weeks of enrollment.
6. No brain metastases as observed by gd-MRI within 12 weeks of enrollment.
7. No previous or currently active second malignancy, with exception of non-metastatic prostate cancer, treated Stage I breast cancer, skin malignancies.
8. Life expectancy of at ≥3 months.
9. ECOG performance status ≤ 2 (Karnofsky ≥ 60; Refer to **Appendix A**).
10. Participants must be willing and able to fully comply with the minimum required 18 hours/day of TTField therapy.
11. Women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation.

4.2 PARTICIPANT EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Malignant disease, other than that being treated in this study, with exception of non-metastatic prostate cancer, treated Stage I breast cancer, skin malignancies.
2. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias.
3. Active implanted medical device (e.g. deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts).
   a. External medical devices (e.g., insulin pumps) are permitted.
4. Skull defect (e.g. missing bone with no replacement).
5. Shunt.
6. Bullet fragments
7. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness).
8. Sensitivity to conductive hydrogels.

9. Pregnant or lactating women.
10. Underlying serious skin condition on the scalp, which in the opinion of the investigator, would prevent or interfere with TTField therapy.
11. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of participant safety or study results.

4.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants for this study will primarily be recruited from Hematology/Oncology or Radiation Oncology practices within either OHSU, UW Seattle, Mayo Clinic Arizona or Ohio State Univeristy. Participants may be identified and referred to this study by their primary treating physician from within OHSU, UW Seattle, Mayo Clinic Arizona, Ohio State University or from the outside community. Participants may also initiate contact with the investigator through information of this study posted on the clinicaltrials.gov website. This pilot study aims to enroll 106 participants, approximately half from each investigational study site. Total time to accrual will be approximately 24 months.

ACCRUAL ESTIMATES

A total of 106 participants anticipated to be equally enrolled from the four participating study sites, OHSU, UW Seattle, Mayo Clinic Arizona, and Ohio State University. Among these 106 participants, we expect to enroll 45 patients with extensive stage disease and 61 patients with limited stage disease. We will continue enrolling patients from the four sites until the targeted sample size has been reached within each disease category (i.e. we will stop enroll patients with extensive stage disease if the number has reached 45, but will continue to enroll subjects with limited stage disease until we have 61 patients in the sub-category, and vice versa.) .

No OHSU Knight Cancer Institute study will focus on any particular gender, racial or ethnic subset. No participant will be excluded from the study on the basis of gender, racial or ethnic origin. Male, female and minority volunteers will be recruited for this study from the general population and approximately 50% men and 50% women will be studied. Gender-nonconforming and gender-fluid individuals as members of the general population will also be recruited.

The projected gender, racial, and ethnic composition of the study will represent that of the states of Oregon (**Table 1**), Washington (**Table 2**), Arizona (**Table 3**), and Ohio (**Table 4**).

4.3.2 Medicare Coverage Related to Investigational Device Exemption (IDE) Studies

In this study Medicare beneficiaries will be given access to potentially useful therapies available in the clinical trial context. Enrollment of Medicare beneficiaries in clinical trials will allow collection of sufficient evidence to demonstrate or not demonstrate a new therapy's effectiveness for use in the Medicare population based on age, disability, or other eligibility status. The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) allowed Medicare payment of the routine costs of care furnished to Medicare beneficiaries in certain categories of Investigational Device Exemption (IDE) studies. Covering the costs in these IDE studies removes a financial barrier that could otherwise discourage medicare beneficiaries from participating. CMS finalized changes to the IDE regulations (42 CFR § 405 Subpart B), effective January 1, 2015. CMS added criteria for coverage of IDE studies and changed from local Medicare Administrative Contractor (MAC) review and approval of IDE studies to a centralized review and approval of IDE studies.

An approval for a Category A (Experimental) IDE study will allow coverage of routine care items and services furnished in the study, but not of the Category A device, which is statutorily excluded from coverage.

Table 1. Projected accrual for present study based on Oregon population demographics

	Females		Males		Totals	
	N	***% OR pop.***	**N**	***% OR pop.***	**N**	***% OR pop.***
Ethnic category						
Hispanic or Latino	2	*6.6*	3	*6.5*	5	*13.1*
Not Hispanic or Latino	12	*43.8*	10	*37.9*	22	*86.9*
Ethnic category participant totals*	**14**		**13**		**27**	*100**
Racial category						
American Indian or Alaskan Native	0-1	*0.9*	0-1	*0.9*	1	*1.8*
Asian	1	*2.4*	1	*2.3*	2	*4.7*
Black or African American	0-1	*1.1*	0-1	*1.0*	1	*2.2*
Native Hawaiian or other Pacific Islander	0	*0.2*	0	*0.2*	0	*0.4*
White	10	*43.9*	9	*43.2*	21	*87.1*
Two or more races	1	*1.9*	1	*1.9*	2	*3.8*
Racial category participant totals*	**14**	*50.4*	**13**	*49.6*	**27**	*100*

Source: Adapted from U.S. Census Bureau, 2017.
N, projected participant accrual based on percentage of OR population demographic (*% OR pop.).*
*Totals may not equal 100 due to rounding.

Table 2. Projected accrual for present study based on Washington population demographics

	Females		Males		Totals	
	N	***% WA pop.***	**N**	***% WA pop.***	**N**	***% WA pop.***
Ethnic category						
Hispanic or Latino	3-4	*6.4*	3-4	*6.4*	7	*12.7*
Not Hispanic or Latino	10	*43.7*	9	*43.7*	20	*87.6*
Ethnic category participant totals*	**14**		**13**		**27**	*100**
Racial category						
American Indian or Alaskan Native	1	*1.0*	1	*1*	1	*1.9*
Asian	2-3	*4.5*	2-3	*4.5*	5	*8.9*
Black or African American	1	*2.1*	1	*2.1*	2	*4.2*
Native Hawaiian or other Pacific Islander	0	*0.4*	0	*0.4*	0	*0.8*
White	9	*39.8*	9	*39.8*	18	*79.5*
Two or more races	1	*2.4*	1	*2.3*	2	*4.6*
Racial category participant totals*	**14**	*50.0*	**13**	*50.0*	**27**	*100*

Source: Adapted from U.S. Census Bureau, 2017.
N, projected participant accrual based on percentage of WA population demographic (*% WA pop.).*
*Totals may not equal 100 due to rounding.

Table 3. Projected accrual for present study based on Arizona population demographics

	Females		Males		Totals	
	N	***% AZ pop.***	**N**	***% AZ pop.***	**N**	***% AZ pop.***
Ethnic category						
Hispanic or Latino	3	*15.5*	3	*15.5*	6	*31.1*

Not Hispanic or Latino	10	*43.7*	10	*43.7*	20	*54.1*
Ethnic category participant totals*	**13**		**13**		**26**	*100**
Racial category						
American Indian or Alaskan Native	1	*2.5*	1	*2.5*	1	*5.3*
Asian	2-3	*1.6*	2-3	*1.6*	5	*3.2*
Black or African American	1	*2.1*	1	*2.1*	2	*5.2*
Native Hawaiian or other Pacific Islander	0	*0.*	0	*0.4*	0	*0.3*
White	8	*41.3*	8	*41.3*	16	*82.6*
Two or more races	1	*1.4*	1	*1.4*	2	*2.9*
Racial category participant totals*	**13**	*50.0*	**13**	*50.0*	**26**	*100*

Source: Adapted from U.S. Census Bureau, 2017.
N, projected participant accrual based on percentage of AZ population demographic (*% AZ pop.).*
*Totals may not equal 100 due to rounding.

Table 4. Projected accrual for present study based on Ohio population demographics

	Females		**Males**		**Totals**	
	N	***% OH pop.***	**N**	***% OH pop.***	**N**	***% OH pop.***
Ethnic category						
Hispanic or Latino	3	*6.0*	3	*6.0*	6	*14.0*
Not Hispanic or Latino	10	*44.7*	10	*44.7*	20	*78.4*
Ethnic category participant totals*	**13**		**13**		**26**	*100**
Racial category						
American Indian or Alaskan Native	1	*1.0*	1	*1*	1	*0.3*
Asian	1-2	*1.2*	1-2	*1*	1	*2.5*
Black or African American	2-3	*6.5*	2-3	*6.5*	4	*13.1*
Native Hawaiian or other Pacific Islander	0	*0.05*	0	*0.05*	0	*0.1*
White	8	*40.5*	8	*40.5*	20	*81.1*
Two or more races	1	*1.2*	1	*1.2*	2	*2.4*
Racial category participant totals*	**13**	*51.0*	**13**	*49.0*	**26**	*100*

Source: Adapted from U.S. Census Bureau, 2017.
N, projected participant accrual based on percentage of OH population demographic (*% OH pop.).*
*Totals may not equal 100 due to rounding.

4.3.3 INCLUSION OF CHILDREN

This protocol does not include children (<18-years-old) as the number of children with SCLC is limited.

4.4 **REGISTRATION PROCEDURES**

In order to participate in this study signed informed consent will be obtained from the participant. The Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

PARTICIPANT REGISTRATION

4.4.1.1 *Local Registration*

This is a single-arm phase II trial, and there is no randomization for treatment.

Participants will be required to give written informed consent to participate in the study before any screening tests or evaluations are conducted that are not part of standard care.

Registration from all consented participants must be entered into the OHSU electronic Clinical Research Management System (CRMS, e.g., eCRIS). At a minimum, registration of OHSU participants will include: Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization

4.4.1.2 *Multicenter Registration*

The OHSU coordinating center study team manages the participant registration process. Investigators at participating sites identify eligible participants and send source documents that support eligibility to OHSU for review and verification before the participating site may enroll and treat the participant. The OHSU coordinating center team verifies completeness of documents, enters registration information into the Knight CRMS, and assigns a study number/identifier. The coordinating center sends an email to the participating site indicating whether or not the participant is eligible and assigns a participant number/identifier.

Registration will include a minimum of the following:
- De-identified source documentation of eligibility
- Signed copies of the most recently IRB-approved, informed consent form and HIPAA authorization.

Each site is expected to maintain a screening log of all participants who are approached for the study. The log documents an explanation for exclusion due to screen failure. This log should be submitted to the coordinating center on a regular basis. Participating sites are required to retain, in a confidential manner, sufficient information on each participant so that the participant may be contacted should the need arise.

4.5 PARTICIPANT SCREENING AND ENROLLMENT

In order to participate in this study, signed informed consent must be obtained from the participant or the participant's legally acceptable representative. The current Institutional Review Board (IRB) approved informed consent must be signed and dated by each participant prior to undergoing any study procedures or before any prohibited medications are withheld from the participant in order to participate in this study.

Screening will begin once the participant has provided written informed consent to participate in the study and ends on Day 1 of the study. All screening and baseline evaluations will be performed during the screening phase (i.e., up to 10 days before initiating TTField therapy). Day 1 of the clinical trial will be when participants start TTField therapy. Total accrual of all participants is anticipated to take a total of 24 months.

4.6 PARTICIPANT WITHDRAWAL OR DISCONTINUATION

Participants are free to withdraw consent and discontinue participation in the study at any time and without prejudice to further treatment. If a participant no longer wants to receive investigational product, but is willing to come for follow-up appointments, the participant’s

request should be honored, if possible. The following are examples demonstrating why a participant's treatment might be discontinued:

- Toxicity precludes further study treatment.
- There is a need for any treatment not allowed by the protocol.
- The participant fails to meet the criteria for study treatment.
- Disease recurrence or progression.
    - TTFields therapy has been established to control supratentorial primary glioblastoma. TTfields may control supratentorial disease better than infratentorial disease. Participants that develop supratentorial metastatic lesions will be removed from the study. Participants that develop infratentorial metastases, or systemic metastases, will be able to continue with treatment for the duration of the 12 months treatment period.
- Investigator's discretion.

No further participant contact should be made if the participant withdraws consent for participation in the study. Information about the reason(s) for discontinuation and collection of any new or ongoing adverse events (AEs) should be collected at the time the participant withdraws consent.

For all other reasons for discontinuation from the study treatment phase, the participant should return to the clinic for the end of treatment (EOT) visit according to Section 7.

HANDLING PARTICIPANT WITHDRAWAL AND DISCONTINUATION

Participants that withdraw or discontinue from this study will not be replaced.

4.7 OFF-STUDY CRITERIA

Criteria that can take a participant off-study include:

- Participant requests to be withdrawn from study without further follow-up,
- Completed study follow-up period,
- Death,
- Screen failure

4.8 STUDY DISCONTINUATION

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to Novocure, IRB, and other regulatory authorities as needed. If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension. Reasons for terminating the study may include the following:

- Incidence or severity of adverse events, in this or other studies, indicates a potential health hazard to participants.
- Demonstration of efficacy that would warrant stopping.
- Data that are not sufficiently complete and/or evaluable.
- Investigator(s) do not adhere to the study protocol, or applicable regulatory guidelines in conducting the study.
- Participant enrollment is unsatisfactory.
- Submission of knowingly false information from the study site to Novocure, or local or other regulatory authorities.
- Upon instruction by local or other regulatory, or oversight authority.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the Sponsor, IRB and/or FDA.

5. INVESTIGATIONAL PRODUCT

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 9.4.

5.1 **OPTUNE®**

The second generation Optune® device weighs 2.7 lbs and the treatment kit is comprised of the following components: an Electric Field Generator, INE Insulated Transducer Arrays (i.e., the transducer arrays), and additional device components that include a power supply, portable battery, battery rack, battery charger, connection cable and carrying case (**Figure 2**).

The investigator, or other qualified designee, will provide participants, as well caregiver or family member (if needed), with training and instruction on how to operate the Optune® device for continuous at-home treatment. Along with providing training and instruction, participants issued an Optune® device will be provided a patient information and operation manual.

Please refer to patient information and operation manual for instructions on using device.

ACQUISITION

The Optune® device and components of the treatment kit will be supplied by manufacture (Novocure, Inc) to the individual participant. Transducer arrays will be shipped as per company's policy.

For investigator and study team: The manufacturer will contact each participant after eligibility is confirmed and the individual is enrolled on the study. A nurse coordinator, or other designated healthcare provider, from Novocure Inc. will meet with each participant to discuss the application of device, skin care, in the same way patients with GBM are started on the device.

For participants: Participants are required to make arrangements with Novocure Inc. representative for this study to arrange for replacement of device parts and transducer arrays.

DEVICE COMPONENTS

5.1.1.1 *Optune Electric Field Generator*

The Optune Electric Field Generator is a portable, battery or power supply operated device. The outputs are connected to two pairs of insulated transducer array sets operated sequentially. The intensity of the field, the frequency of the waves, and the temperature of the transducer arrays are pre-set, and are controlled by two microcontrollers that run Novocure's software. The output parameters of the Electric Field Generator are either pre-programmed or set by the service technician through a "service only" USB-type connector. The device status and monitored parameters are continuously stored in an internal log memory and can be transferred by an isolated serial connection to a PC. In addition, the front panel includes visual indicators for power ON, Treatment ON, alarms and low battery.

5.1.1.2 *INE Insulated Transducer Arrays*

Two sets of INE Insulated Transducer Arrays are connected to the Electric Field Generator. Each set includes a pair of arrays, with 9 serially interconnected single transducers in each

array. Each transducer array includes 8 thermistors. A single, sterile, 'ready to use' INE Insulated Transducer Array unit incorporates the following: one INE transducer array; conductive gel layer; mid-pads; medical tape; and overlapping liner. The transducer arrays are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature of the thermistors. At the set parameters, the electrodes do not cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue. As an additional safety feature, the temperature of the transducer arrays is monitored by a temperature sensor. If temperature rises beyond 41°C, the device automatically shuts off.

5.1.1.3 *Additional Components*

In addition, the following components are also included in the Optune Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case Optune can be powered by a mains-connected power supply of 24V± 2 V. The power supply connects to the power connector on the front panel of the device. Alternatively, Optune can also be powered by battery using a portable, external 33 V ± 2 V (when fully charged) rechargeable battery. Several batteries placed in a battery rack can be recharged at the same time using a dedicated battery charger, when not connected to the device. The connection between the battery and the device is through a dedicated connector on the device's front panel. The transducer arrays are connected to the device by a spiral extension cable. Patients carry the device and the battery in a specialized over-the-shoulder bag, which allows them to receive continuous treatment without changing their daily routine.

DEVICE SETTINGS AND PROGRAMMING

TTField therapy will be administered at a set frequency of 200 kHz. These treatment parameters are preset by the manufacturer such that there are no electrical output adjustments available to the participant.

DEVICE USAGE AND MAINTENANCE

The investigator, or other qualified healthcare provider from either participating site or Novocure Inc., will provide participants with training and instruction on how to operate the Optune® device for continuous at-home treatment.

Please refer to patient information and operation manual for instructions on using device.

5.1.1.4 *Battery replacement*

Participants will be trained to change and recharge depleted device batteries and to connect to the external power supply. Use of the external power supply does not have a time limit and can be used with either U.S. (120V AC) or European (230V AC) outlets.

For battery use: the Optune® device uses a single battery at a time. All other supplied batteries should remain in the battery charger. Each battery lasts 2 to 3 hours, and a yellow low Battery indicator light will turn on; indicating that the battery requires replacement. The treatment will continue to run while the yellow low battery indicator is illuminated until the audible alarm sounds and the red error light illuminates. Once this happens the treatment will stop and the device must be turned off and the battery replaced.

5.1.1.5 *Transducer array placement and replacement*

The investigator other designated healthcare provider will provide detail instructions regarding the placement/replacement and positioning of the transducer arrays on the participants head.

Placement of the transducers arrays to the head requires that the entire scalp be shaved using an electric razor (ensuring that there is no remaining stubble). The shaved scalp should be wiped with 70% isopropyl alcohol prior to placement of transducer arrays. The two black transducer arrays are to be placed in the front and back of the head and the two white arrays are placed on the sides. Removing liner covering gel on the transducer arrays, place each transducer array on head and press the entire edge of transducer array tape to the scalp.

Transducer arrays need to be replaced 1 to 2 times per week (every 4 days at most). The Optune® device's alarm will beep with increased frequency if not properly functioning, and this is a likely indicator that hair growth is preventing the transducer arrays from making good contact with the scalp. The old transducer arrays should be removed and the scalp needs to be re-shaved in order to maintain optimal contact. To ensure consistency, the new transducer arrays should be replace in the same general location as before, but a shift the transducer arrays less than an inch is permitted.

5.1.1.6 *Connecting transducer arrays to device*

Each of the 4 transducer array connectors with black and white connection ends must be connected to the matching sockets on the connection cable. That is, the 2 connectors with the black connection ends are to be plugged into the two black sockets and the 2 white connection ends are to be plugged into the white sockets. Press firmly to be sure the connectors are pushed in all the way.

DURATION OF EXPOSURE

Participants are required to have a minimum 18 hours per day of TTField therapy. Participant will be able to carry the device in an over-the-shoulder bag or backpack so that they can receive continuous treatment.

DEVICE STORAGE AND STABILITY

Storage conditions for the device and additional parts has an allowable temperature range of -5°C to 40°C (23°F to 104°F), and a relative humidity range of 15-75%. Storage conditions for the transducer arrays has an allowable temperature range of 5°C to 27°C (41°F to 81°F), and relative humidity range of 35-50%.

SPECIAL CONSIDERATION FOR ADMINISTRATION

5.1.1.7 *Topical creams or ointments*
Allow for 15 minutes after the application of a cream or ointment to the scalp before replacing transducer arrays. After 15 minutes, the scalp should be wiped again with 70% isopropyl alcohol and the transducer arrays applied to the scalp once dry.

5.1.1.8 *Traveling with device*

Optune's portable batteries contain lithium ion material and are restricted from being checked as luggage for passenger aircraft travel. They can be carried in the passenger cabin. The Optune device and transducer arrays will activate metal detectors.

5.1.1.9 *Troubleshooting Guide*

Participants should carry a copy of the Troubleshooting guide (Section 26 of the Patient information and operation manual). This guide is necessary to ensure the Optune® device is properly functioning and prevent any unwanted break in treatment. Participants that continue to experience problems with the device should contact the Principle Investigator or designated member of the study team to resolve these issues.

ACCOUNTABILITY

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of each study device.

Responsibility for device accountability at the study site rests with the Investigator; however, the Investigator may assign some of these accountability duties to an appropriate designee. Inventory and accountability records must be maintained and readily available for inspection by the study monitor and are open to inspection at any time by any applicable regulatory authorities or other oversight bodies.

The Investigator or designee will collect and retain all used and unused components of the Optune® device treatment kit until full accounting has been completed. The Investigator or designee must maintain records that document:

- Device delivery to the study site.
- The inventory at the site.
- Device use by each participant.
- Return of device and components of treatment kit to the Investigator or designee.
- Destruction or return of device and components of treatment kit for final disposal.

These records should include dates, quantities, serial numbers (if available), and the unique code numbers (if available) assigned to the device and components of the treatment kit and study participants.

The investigational product must be used only in accordance with this protocol. The Investigator will also maintain records adequately documenting that the participants were provided with the correct investigational device specified.

Completed accountability records will be archived by the site. At the completion of the study, the Investigator or designee will oversee shipment of any remaining study drug back to Novocure, Inc. for destruction according to institutional standard operating procedures.

DEVICE RETURN

Participants are required to return used transducer arrays to the investigational site for subsequent return to manufacturer. Upon participant withdrawal from the study or upon completion of treatment, participants are required to return the Optune® device and any used or unused components of the treatment kit to the investigational site for return to manufacturer.

6. TREATMENT PLAN

6.1 DOSAGE AND ADMINISTRATION

In this study, a treatment cycle is defined as 4 weeks (or 1 month). Using the Optune® device, participants will receive multiple 1-month treatment courses, in which TTField therapy will be administered to the participants' head continuously (18-24 hours per day) for the entire duration of the 12 month study, or until disease progression, whichever comes first.

Treatment will be administered on an out-patient basis. Reported adverse events and potential risks are described in Section 9. No investigational or commercial agents or therapies other than those described in this protocol may be administered with the intent to treat the participant's malignancy.

ELECTRIC FIELD

Participants receiving TTField therapy will have 4 transducer arrays placed on their scalp and connected to the portable Optune® device which will be set to generate 200 kHz electric field in 2 perpendicular directions that are operated sequentially. The field intensity will be set at >0.7 V/cm at the center of the brain. These device settings are preset by the manufacturer. Participants will receive detailed written instructions and practical training by the Principle Investigator or designated member of the study team on how to operate the device for continuous at-home treatment.

TRANSDUCER ARRAY PLACEMENT

TTFields are applied to the shaved scalp via two pairs of orthogonally positioned transducer arrays. Since no brain metastatic lesions are present (or clinically observable) at time of enrollment, there is no need to precisely position arrays around a tumor as is the case in treating GBM.[20,21] Instead to create the 2 perpendicular field directions, each pair of transducer arrays will be centered on the participants head such that one pair is placed on the left and right side of the head, and the second pair placed anteriorly and posteriorly. Transducer arrays should be replaced every 2 to 3 days, with a slight relocation of the new arrays ~2 cm from prior location (**Figure 4**).

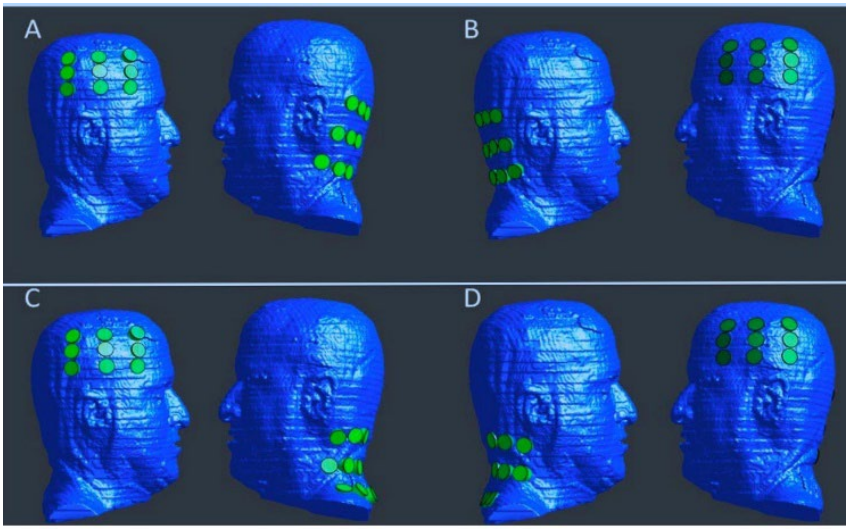

Figure 4: Transducer array layouts found to deliver a uniform field distribution to the entire brain. Each layout comprises two pairs of arrays. One layout comprises the pairs of arrays shown in schematics A and B. The second layout comprises the pairs of arrays shown in schematics C and D.

6.2 TREATMENT INTERRUPTIONS AND DELAYS

Although uninterrupted treatments are preferred, participants are allowed 2 daily breaks in treatment not to exceed 1 ± 2 hours each for personal needs (e.g. bathing). Additionally, participants are allowed to suspend TTField treatment for 2 ± 1 days at the end of each 4 week treatment cycle.

TTField therapy may be delayed for up to 8 weeks (i.e., two treatment cycles) for any reason, but should be clearly documented in the case report form (CRF). If TTField therapy is not restarted after a delay of two treatment cycles, then the participant will be removed from the study.

6.3 TREATMENT PERIOD AND MAINTENANCE

Participants will receive TTField therapy on continuous basis (i.e., 18-24 hours a day, 7 days a week) for a period of 12 months. Participants that develop supratentorial metastatic lesions (>10) before 12 months will discontinue further use of TTFields and will be provided supportive/palliative treatments and supportive care (e.g., management of radionecrosis) consistent with institutional standard of care (e.g., whole brain radiation therapy). Participants that develop either limited (≤10) supratentorial or any number of infratentorial mestastases will remain eligible to continue with TTFields therapy for the duration of the 12 months after the brain metastatic lesioins are addressed according to the institutional guidelines (e.g. partial brain irradiation, stereotactic radiosurgery, stereotactic body radiation therapy). These participants will be clinically monitored per institutional guidelines. Participants that develop systemic progression, which can be treated per institutional standard of care (e.g. systemic chemotherapy, immunotherapy, radiation therapy, etc.), may remain eligible to continue with TTField therapy for the duration of the 12 months treatment period. Information regarding systemic therapy must be recorded in CRF.

After 12 months study period, participants will not be able to stay on the TTField therapy, and will be clinically monitored per institutional guidelines.

6.4 CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES

In keeping with the community standards of medical care, all treatments considered necessary for a participant's welfare may be administered at the discretion of the investigator. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days before starting TTField therapy and 30 days after completing TTField therapy should be recorded. Concomitant medications administered after 30 days after the last TTField treatment should be recorded for SAEs as defined in Section 9.

Supportive measures for optimal medical care are to be given throughout the study as indicated by the treating physician's assessment of the participant's medical need and institutional and

general medical guidelines for the care of participants undergoing treatment of SCLC. In general, medications required to treat AEs, manage cancer symptoms, concurrent diseases and supportive care agents, such as pain medications, anti-emetics and anti-diarrheals are allowed.

Participants may use a wig or hat to cover the transducer arrays for cosmetic reasons.

If patient develops radionecrosis after stereotactic radiosurgery (SRS) for disease progression in the brain with a single brain metastatic lesion, patient will be managed by the treating team per standard of care for SRS-related radionecrosis. Radionecrosis will be managed clinically by oral corticosteroids (dexamethasone). If the symptoms do not respond to steroids after appropriate duration and corticosteroid dose administration, subjects will be treated with administration of bevacizumab (10 mg/kg every two weeks for 4 doses), followed by a period of observation with surveillance MRI every six to eight weeks. If radionecrosis is not controlled medically, patient will be considered for surgical resection, delayed by 4 weeks after the last administration of bevacizumab.

DERMATITIS

Dermatitis is often observed at sites on the scalp where the transducer arrays are located, should be managed with topical corticosteroids (e.g., clobetasol 0.5% [twice daily for ≤2 weeks])[22] and/or per institutional guidelines. The transducer arrays can also be slightly moved, but no more than 2 cm (0.75 inch) from original location.

INFECTION PROPHYLAXIS

Use of topical antibiotics (e.g., bacitracin, triple antibiotic ointment [polymixin B, neomycin, and bacitracin)]) may be administered per institutional guidelines to the scalp prior to replacing transducer arrays.

ALLERGIC REACTION / HYPERSENSITIVITY

The transducer arrays utilize a conductive hydrogel, which may cause allergic reactions. In the event of severe allergic reactions such as shock and respiratory failure, TTField therapy should be immediately discontinued, the transducer arrays removed from the scalp, and the scalp washed to remove residual conductive hydrogel. Appropriate supportive therapy should be administered per institutional guidelines, which may include (but not limited to): epinephrine, IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, antihistamines, or acetaminophen.

Participants with Grade 2 skin symptoms may be premedicated with Diphenhydramine, 50 mg po (or equivalent dose of antihistamine), as well as acetaminophen, 500-1000 mg po (or equivalent dose of antipyretic).

CONTRACEPTION

Participants of child bearing potential should start using birth control from time of enrollment (Day -60 to -10) and throughout the study period up to 30 days after the completing TTField therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom, copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will

include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including subcutaneous, intrauterine, or intramuscular agents).

Participants should be informed that receiving TTField therapy may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in this study participants must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in Section 9.6. If there is any question that a participant will not reliably comply with the requirements for contraception, that individual should not be entered into the study.

USE IN PREGNANCY

If a participant inadvertently becomes pregnant while receiving TTField therapy, the participant will immediately be removed from the study. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The investigative site will report the outcome of the pregnancy to the manufacturer without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The site investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the manufacturer.

6.5 PRECAUTIONS ASSOCIATED WITH USE OF OPTUNE® DEVICE

PRESENCE OF PLATES OR SCREWS IN THE PARTICIPANT'S SKULL BONE

The ceramic discs of the transducer array must not be placed directly on any existing plates or screws in the participant's skull bone.

DAMAGE TO OPTUNE® DEVICE AND/OR COMPONENTS

Participants are not to use the Optune® device or any component if any parts look damaged (torn wires, loose connectors, loose sockets, cracks or breaks in the plastic case). Likewise, the Optune® device and transducer arrays are not be used if they are wet.

6.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Participants can receive anti-cancer systemic chemotherapy, biological therapy, immunotherapy, or radiation therapy while receiving TTField therapy per standard of care or the clinical discretion of the investigator. Participants that have disease progression requiring clinical intervention with one or more of the aforementioned treatments can remain on the study as long as there is no widespread supratentorial disease progression (>10 lesions). Participants may receive other medications that the investigator deems to be medically necessary.

Participant exclusion criteria (Section 4.2) describes other medications prohibited in this trial.

7. STUDY PROCEDURES/EVALUATIONS AND SCHEDULE

7.1 STUDY SPECIFIC PROCEDURES

MEDICAL HISTORY

A medical history will be obtained by the investigator or qualified designee. In addition to collecting information on demographics, the medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the participant's urothelial cancer will be recorded separately and not listed as medical history.

DISEASE ASSESSMENT

The investigator or qualified designee will obtain prior and current details regarding the participant's SCLC.

MEDICATION HISTORY

A complete medication history will be acquired concurrent with medical history. Any AEs occurring prior to TTField therapy will be captured in the CRF.

PHYSICAL EXAMINATION

Physical exams must be performed by a medically qualified individual such as a licensed physician, Physician's Assistant or advanced Registered Nurse Practitioner as local law permits. The physical exam at baseline should include a complete physical exam per institutional standards. All other physical exams after baseline will include an evaluation of any AEs, or any previously reported symptoms, or prior physical examination findings.

A physical examination may include evaluating: weight, general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, and nervous system. A complete head and neck exam may include mirror and fiber-optic endoscopic examination.

As part of screening/baseline visit, physical examination is to be conducted within 14 days prior to start of treatment. All physical examinations will also include:

7.1.1.1 *Vital signs*
Vitals to be collected (BP, HR, temperature). As part of screening/baseline visit, vitals should be obtained within 14 days prior to start of treatment. Vitals will also be obtained during treatment.

Significant findings that were present prior to the signature of the informed consent must be included in the Medical History CRF page. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event CRF page.

7.1.1.2 *Height and weight*

Height is only required as part of screening.

7.1.1.3 *Performance status*

Performance status will be determined for all participants at screening and at select times during treatment as per assessment schedule in Section 7.8. Refer to **Appendix A** for performance criteria.

ADVERSE EVENT EVALUATION

Toxicities and adverse experiences will be assessed at each visit using the NCI CTCAE 5.03. Safety will be monitored by assessing physical examination, vital signs, body height and weight, performance status, and pregnancy, as well as collecting of AEs at every visit.

Adverse events will be monitored from the time the participant signs the Consent Form. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study, including and up to 3 months following completion of TTFields therapy. All AEs (serious and non-serious) must be recorded on the source documents and CRFs regardless of the assumption of a causal relationship with the study drug.

For details on AE collection and reporting, refer to Section 9.

ASSESSMENT OF STUDY AGENT ADHERENCE

Participants will be responsible for self-administering TTField therapy using the Optune® device. Participants will receive instruction on how to operate Optune® device and place transducer arrays on the scalp from the investigator or other qualified, designated member of the research team.

MAGNETIC RESONANCE IMAGING (MRI) / COMPUTED TOMOGRAPHY (CT) / POSITRON EMISSION TOMOGRAPHY (PET)

Tumor imaging for patients with SCLC may be performed by computed tomography (CT), or fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT, or magnetic resonance imaging (MRI) per institutional guidelines. Real-time determination of measurable disease by a radiologist will be used to determine participant eligibility.

A thoracoabdominal CT scan is required within 12 weeks prior to enrollment in this trial. Subsequent thoracoabdominal CT imaging should be performed according to standard of care (Section 7.8); or upon the discretion of the investigators if clinically indicated.

A gd-MRI of the head is required within 12 weeks prior to enrollment to assess presence of metastatic brain lesions. On-study, Gd-MRI will occur per standard of care, with imaging taking place every 3 months for the first 24 months, after which participants will have Gd-MRI every 6 months.[18] The brain MRI protocol specifies 1.5 Tesla magnetic resonance imaging and includes axial images of 3 mm slice thickness with T1-post gadolinium, T2 and T2 flair sequences. All MRI images will be centrally reviewed by expert neuroradiologist at OHSU.

All subsequent imaging assessment should be performed according to Schedule of Events (Section 7.8).

PATIENT REPORTED OUTCOMES

QoL care metrics will be assessed according to Schedule of Events (Section 7.8). Study participants will be asked to complete 2 questionnaires, each of which will be conducted prior to

TTField therapy (i.e., baseline), and again at 6 and 12 from starting TTField therapy (Table 3). The purpose of completing the questionnaires is to obtain a rich description of patients' experiences of QoL and various symptoms. It will take <45 minutes to complete the questionnaires. The validated questionnaires were selected based on our clinical knowledge and experience with this patient population.

Table 3. Method and Timing of QoL Assessments

	Measurement	Baseline	6 months	12 months (i.e. EOT
QoL	EORTC QLQ-C30	X	X	X
MMSE	Mini Mental State Exam	X	X	X

7.2 LABORATORY PROCEDURES AND EVALUATIONS

Except for on-study pregnancy testing, all laboratory evaluations will be performed as part of standard of care. Any additional on-study hematological and biochemical assessments will only be performed per physician's discretion, if clinically indicated.

HEMATOLOGY

Hemoglobin, hematocrit, white blood cells (WBC) with differential count, platelet count will be collected as needed

BIOCHEMISTRY

Serum chemistry (performed as needed) to include complete metabolic profile (albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, potassium, total protein, SGOT [AST], SGPT [ALT], sodium), and phosphorus.

PREGNANCY TEST
A serum or urine pregnancy test is required during screening for all persons of childbearing potential. The pregnancy test is required within 72 hours prior to starting TTField therapy and results must be available prior to administration of TTField therapy. If the urine pregnancy test is positive, a serum pregnancy test must be performed per institutional standards.

7.3 SCREENING ASSESSMENTS

Toxicities which occur prior to the start of treatment will not be subject to analysis. Consent must be obtained before initiation of any clinical screening procedure that is performed solely for the purpose of determining eligibility for this research study. Evaluations performed as part of routine care before informed consent can be utilized as screening evaluations if done within the defined time period.

Participants will undergo screening evaluations to determine study eligibility. All qualifying screening and eligibility assessments must be performed within 60 days prior to study registration. Laboratory baseline evaluations are to be conducted within 14 days prior to study registration. Radiologic imaging must be done within 12 weeks of study registration. For participants for whom there are 14 days or fewer between registration and the start of treatment, the day 1 laboratory data may be omitted. Refer to schedule of events (Section 7.8) for additional details.

INFORMATION TO BE COLLECTED ON SCREENING FAILURES

A participant who signed an informed consent form but failed to be started on treatment for any reason will be considered a screen failure. Those found not to be eligible after signing the main study consent will be considered screening failures, and data will be handled in the same manner. The demographic information, informed consent, and inclusion/exclusion pages must also be completed for screen failures. No other data will be entered into the clinical database for individuals who are screen failures.

7.4 **ASSESSMENTS DURING TREATMENT**

Refer to the schedule of events (Section 7.8) for timing and details of specific procedures to be conducted. Except for head MRI scans that is scheduled every three months for the 1st year while participants are on-treatment, all other imaging will be in accordance with standard-of-care guidelines. Clinical evaluations are scheduled to occur every two months for ES-SCLC patients, and every three months for LS-SCLC patients while participants are on-treatment. Follow-up phone calls will occur every other month for months patients are not seen for clinical evaluation at the clinic. Follow-up and clinical evaluations will resume to standard-of-care after completion of the treatment period. Imaging can be done within ± 1 week. All other studies can be obtained ± 3 days of the stated time point.

7.5 **END OF TREATMENT VISIT**

The end of treatment (EOT) visit should be conducted 10 ± 10 days following completion of TTField therapy. All AEs that occur prior to the EOT visit should be recorded. Participants with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. Imaging (CT and/or MRI as appropriate) will be used to assess disease staging.

7.6 **FOLLOW-UP**

Aside from clinical follow-up at 1 and 3 months after completion of TTField therapy, all subsequent follow-up, including imaging studies, clinical evaluations, and any laboratory procedures will be consistent with institutional standard of care oncology follow-up visit. Starting from the last chemo-radiotherapy treatment for the primary tumor, these standard of care oncology follow-up visits should occur every 3 to 4 months during years 1 and 2, and then every 6 months thereafter. All participants will be followed (via medical record, or by other means such as a phone call) for survival status following TTField therapy discontinuation at 6, 12, 24, 36, and 60 months.

7.7 **UNSCHEDULED VISITS**

Unscheduled study visits may occur at any time if medically warranted. Any assessments performed (e.g., imaging, laboratory or clinical assessments) at those visits should be recorded in the eCRF.

7.8 SCHEDULE OF EVENTS

Visit Days (± 5 Days)	Screening Days -60 to -1	Treatment Period (weeks)‡ 4	8	12	16	20	24	28	32	36	40	44	EOT 48	Follow-Up† 1 mo	+3 mo
Informed consent	X														
Inclusion/exclusion criteria	X														
Medical history	X	X	X	X	X	X	X	X	X	X	X	X	X		
Medications[A]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Exam[B]															
LS-SCLC	X		X			X			X			X		X*	X
ES-SCLC	X	X		X		X		X		X		X		X	X
Phone Follow-up[C]															
LS-SCLC		X		X	X		X	X		X	X		X	X*	
ES-SCLC			X		X		X		X		X		X		
CT imaging body	X[D]														X
Gd-MRI	X[D]			X			X			X					X
Device training	X[E]														
Hematology[F]	X			X			X			X			X		X
Biochemistry[F]	X			X			X			X			X		X
Pregnancy test[G]	X														
AE[H]		X----------											X	X	X
QoL[I]	X						X						X		
Survival status		X	X	X	X	X	X	X	X	X	X	X	X		X[I]

‡TTField therapy will be applied at a fixed frequency of 200 kHz. Treatment should be continuous, with an allowable 2 hr per day maximum break from treatment. Eligible participants must be no more than 6 weeks from last dose of chemo-radiotherapy of primary tumor with at least partial response to treatment.

†Aside from clinical follow-up at 1 and 3 months after completion of TTField therapy, all subsequent follow-up, including imaging studies and

laboratory evaluations will be consistent with standard of care oncology follow-up visit. Starting from the last chemo-radiotherapy treatment for the primary tumor [i.e., off-study], these standard of care oncology follow-up visits will occur every 3 months during years 1 and 2, and then every 6 months thereafter [up to 5 years]).

* 1 month follow-up visit could be an in-person visit or a phone call visit.

[A] For prior medications – record all medications taken within 30 days of Cycle 1. For concomitant medications – enter new medications started during the trial through the EOT visit. Record all medications taken for SAEs as defined in Section 7.8

[B] All physical exams will include assessing weight, vital signs, and ECOG performance status. Height will be measured at screening visit only.

[C]Phone calls will be done to follow-up on patient status in between in clinic evaluations.

[D]Initial imaging at screening must be within 12weeks prior to the first dose of TTField therapy. Scans performed as part of routine clinical management are acceptable for use as the screening scan if they are of diagnostic quality and performed within 12 weeks prior to the first dose of trial treatment. Measureable disease based on RECIST 1.1 must be confirmed by investigator and/or radiologist before enrollment.

[E]The investigator, or other qualified designee, will provide participants, as well caregiver or family member (if needed), with training and instruction on how to operate the Optune® device for continuous at-home treatment.

[F] Any additional on-study hematological and biochemical assessments will only be performed per physician's discretion, if clinically indicated.

[G] For persons of reproductive potential, a urine pregnancy test should be performed within 72 hours prior start of trial treatment. Persons will asked pregnancy status thereafter at the beginning of every treatment cycle. If persons are unsure, then a urine pregnancy test will be performed within 72 hours prior to the next trial cycle. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated, if required, per institutional guidelines.

[H] AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.03. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness. Record all AEs occurring within 30 days after the last trial treatment. Report all SAEs (related and unrelated to trial treatment) occurring up until 90 days after the last dose of trial treatment, or the start of new anti-cancer treatment, whichever comes first. Afterwards, report only SAEs that are related to trial treatment.

[I] QoL assessments will be administered before start of treatment (baseline), at 28 weeks, and again at end of treatment (12 months).

[I] All participants will be followed for survival status following TTField therapy discontinuation at 6, 12, 24, 36, and 60 months.

8. EFFICACY MEASURES

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[23].

8.1 DEFINITION OF EFFICACY MEASURES

Evaluable for toxicity: All participants who initiated TTFields therapy (regardless of duration) will be considered evaluable for safety.

Evaluable for objective response: Only those participants who have received at least one cycle of TTField therapy (i.e., 4 weeks) will be considered evaluable for response.

8.2 DISEASE EVALUATION

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Use of MRI is also acceptable.

8.3 EFFICACY CRITERIA FOR TUMOR RESPONSE

EVALUATION OF NEW LESIONS

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor. However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate progressive disease (PD). If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

8.4 EVALUATION OF SURVIVAL

Overall Survival: Overall Survival (OS) is defined as the time from start of TTField therapy (Day 1) to death due to any cause, or last follow-up at 60 months.

8.5 RESPONSE REVIEW

Response assessment will be determined by the investigator.

9. SAFETY

9.1 SPECIFICATION OF SAFETY PARAMETERS

The Investigator is responsible for monitoring the safety of participants who have enrolled in the study. Safety assessments will be based on medical review of adverse events and the results of safety evaluations at specified time points as described in Section 7.8, Schedule of Events. Any clinically significant adverse events persisting at the end of treatment visit will be followed by the Investigator until resolution/stabilization or death, whichever comes first.

9.2 DEFINITIONS

ADVERSE EVENT (AE)

An adverse event is defined as any undesirable physical, psychological or behavioral effect experienced by a participant during their participation in an investigational study, in conjunction with the use of the investigational product, whether or not considered intervention-related (21 CFR 312.32 (a)). In general, this includes signs or symptoms experienced by the participant from the time of signing the informed consent to completion of the study.

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the participant and/or observed by the Investigator or medical staff.
- Clinically significant laboratory abnormalities.
- A significant worsening of the participant's condition from study entry.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment that resolve but then recur after treatment.
- Disease signs and symptoms and/or laboratory abnormalities existing prior to the use of the study treatment which increase in frequency, intensity, or a change in quality after treatment.

SERIOUS ADVERSE EVENT (SAE)

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator, it results in any of the following outcomes:

- Death,
- A life-threatening adverse event,
- In-patient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and/or participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in in-patient hospitalization, or

- The development of drug dependency or drug abuse.

UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers UPs involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.
4. This definition could include an unanticipated adverse device effect, any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

This study will use the OHRP definition of UP.

SEVERITY OF EVENT

The Investigator will grade the severity of each AE using, when applicable, the current version of the CTCAE v5.0. In the event of an AE for which no grading scale exists, the Investigator will classify the AE as defined below:

- **Mild** (grade 1) – An event that is usually transient in nature and generally not interfering with normal activities
- **Moderate** (grade 2) – An event that is sufficiently discomforting to interfere with normal activities
- **Severe** (grade 3) – An event that is incapacitating with inability to work or do usual activity, or inability to work or perform normal daily activity
- **Life-threatening/debilitating** (grade 4) – An event that puts the participant at immediate or potential risk of death, requires hospitalization, or which drastically impacts a participant's well-being
- **Fatal** (grade 5)

ASSESSMENT OF CAUSALITY RELATIONSHIP TO OPTUNE® DEVICE

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- *Definite* – The AE is clearly related to the study treatment.
- *Probable* – The AE is likely related to the study treatment.

- *Possible* – The AE may be related to the study treatment.
- *Unlikely* – The AE is doubtfully related to the study treatment.
- *Unrelated* –The AE is clearly NOT related to the study treatment.

Per 21 CFR 803.3, Medical Device Reporting: the definition of caused or contributed means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:

1. Failure
2. Malfunction,
3. Improper or inadequate design
4. Manufacture
5. Labeling, or
6. User error.

9.3 EXPECTEDNESS

The Principle Investigator will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.4 ADVERSE EVENT LIST(S)

ADVERSE EVENT LIST FOR TTFIELD THERAPY WITH OPTUNE® DEVICE

Detailed information about the risks and expected AEs associated with using the Optune® may be found in the current edition of the manufacturer's Patient Information and Operation Manual. The most frequent adverse reactions associated with use of Optune® device is dermatitis.

9.5 ADVERSE EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an UP, AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, seriousness, expectedness, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and date of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the Investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

The Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for AEs) or 30 days (for SAEs) after the last day of study participation or until the participant receives alternative therapy for his/her SCLC, whichever occurs first. Any SAE that occurs after treatment with alternative therapy will be reported only if the Investigator or current treating physician has assessed the SAE as related to the study treatment. Adverse events will be evaluated using the current version of the CTCAE v5.0.

9.6 REPORTING PROCEDURES

OHSU IRB REPORTING OF UNANTICIPATED PROBLEMS AND ADVERSE EVENTS

Unanticipated Problems and AEs will be reported to OHSU IRB according to the policies, procedures and guidelines posted on the OHSU IRB web site.

Events that must be reported by the Investigator to the IRB are detailed in the OHSU IRB **Investigator Guidance: Prompt Reporting Requirements (HRP-801)**. At a minimum, events requiring reporting to the IRB include:

- Any new or increased risk related to the research, including AEs or IDE safety reports that require a change to the protocol or consent,
- New FDA black box warning,
- Publications identifying new risks,
- Data Safety Monitoring Board/Committee letters recommending changes or discussing new risks
- Unanticipated adverse device effect
- Unauthorized disclosure of confidential participant information

CENTRAL REPORTING OF ADVERSE EVENTS FOR MULTICENTER STUDIES

A participating site must report an SAE to the institution's local IRB for action as required, as well as to the OHSU coordinating center study team by phone, fax, or email within 24 hours of learning of the event (or as instructed in the protocol, if different). The participating center will send the coordinating center materials regarding the SAE.

The OHSU coordinating center study team will review and submit SAEs to the FDA, OHSU IRB, and any other required contacts as required by the Knight Data Safety Monitoring Plan (DSMP). The PI at the Coordinating Center is responsible for distributing IND and/or IDE Action Letters or Safety Reports, as applicable, to participating institutions for review and submission to their institution's local IRB.

MEDWATCH REPORTING

The Investigator is required to report AEs to the FDA through the MedWatch reporting program, even if the trial involves a commercially available agent or device. AEs to be reported include any UPs (i.e., not listed in the package insert) and any SAEs with a suspected association to the investigational product.

AEs that occur during clinical studies are to be reported to FDA as specified in the Form FDA 3500, the MedWatch Voluntary Reporting form (available here), or completed online. A copy of Form FDA 3500 and supporting materials will be kept on file in the study regulatory binder.

MANUFACTURER REPORTING REQUIREMENTS

In the event that a participant experiences an episode of seizure while on study, the investigator or treating physician must report the event to Novocure Inc., and describe the causality relationship of the event to the Optune® Device (refer to Section 9.2.5).

REPORTING OF PREGNANCY

To ensure participant safety, each pregnancy in a participant on study treatment must be reported within 24 hours of learning of its occurrence. The pregnancy should be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or any pregnancy- or childbirth-related and/or newborn complications.

The pregnancy should be recorded on the CRF and reported by the Investigator to Novocure, Inc., as well as any regulatory authority, as needed. Pregnancy follow-up should be reported using the same form. Any SAE experienced during pregnancy must be reported.

9.7 STUDY STOPPING RULES

The overall study will be paused, and appropriate authorities (e.g., IRB, Knight Data and Safety Monitoring Committee) notified if the following events occur:

- Life-threatening grade 4 toxicity attributable to protocol therapy that is unmanageable, or unexpected.
- Death suspected to be related to Optune® device.

10. STATISTICAL CONSIDERATIONS

Refer to Section 3.1, Description of the Study Design for a detailed description of the study design and endpoints.

10.1 ANALYSIS POPULATIONS

This is a phase II multi-center single-arm pilot study to evaluate the incidence of metastatic brain lesions in participants with SCLC that receive TTField therapy. All participants that initiated TTField therapy will be considered evaluable for efficacy analysis. All participants who initiated TTFields therapy (regardless of duration) will be considered evaluable for safety. The anticipated enrollment is 106 participants, of which 45 participants will have ESCLC and 61 participants will have LSCLC.

10.2 DESCRIPTION OF STATISTICAL METHODS

ANALYSIS OF PRIMARY ENDPOINT

The primary endpoint is the incidence of SCLC brain metastases following 6 months of TTField therapy. Descriptive statistical analysis will be conducted for all participants, overall and by disease group (extensive stage and limited stage). The incidence rate of SCLC brain metastases at 6 month will be reported with 95% confidence interval, overall and by disease group (extensive stage vs. limited stage), by type (infratentorial vs. supratentorial). One sample test of proportion will be used to determine if the incidence rate is significantly reduced compared to historical controls for each disease group (assumed to be 40% and 30% for extensive stage and limited stage, respectively). Logistic regression model will be conducted to identify if there is any center difference (Oregon, Washington, Arizona, vs Ohio) after controlling for other covariates (for example, the compliance of patients in using the device) of that may influence the incidence of SCLC brain metastases. Expecting the models for extensive stage and limited stage could be quite different, we will start with fitting two separate logistic regression models for each disease group. In addition to the above listed variables, patient characteristics, tumor characteristics will also be included as covariates to start the model building. Specifically, for each disease group, we will fit univariable logistic regression model for all potential covariates. Variables with p-value < 0.25 in the univariable logistic regression model will be included to build multivariable logistic regression model. Purposeful selection method combined with Akaike Information Criteria (AIC) will be used for final model determination for each disease group. If it turned out that the two final models have similar covariates and effect size, we will also develop a pooled logistic regression model using all subjects. The pooled logistic regression model will force the disease group as a covariate to the model, and all other variables included in the model will be carefully evaluated for confounding effect and for potential interaction with disease group.

ANALYSIS OF THE SECONDARY ENDPOINTS

For incidence of SCLC brain metastases following 12 months of TTField therapy, we will use exactly the same approach as described in Section 10.2.1.

The distribution of overall survival will be graphically described using Kaplan-Meier plot, for all subjects together, and for each disease group (extensive stage and limited stage). If estimable, the median survival time will be reported with 95% confidence interval. The analysis is just for description. No hypothesis testing is planned for this endpoint. However, we will fit two cox

proportional hazard regression model to identify risk factors that may impact the OS. Covariates evaluated in the univariable analysis in Section 10.2.1 will also be evaluated in the cox proportional hazard regression model. OS at 6, 12, 24, 36 and 60 months after completion of TTField therapy will be reported.

We will estimate TTField therapy-related toxicity and along with an exact confidence interval using the safety set. A summary table of observed AEs will also be reported by disease group (extensive stage and limited stage).

The Quality of life scores will be recorded over time (See Section 7.8 for details) using the EORTC QLQ-C30 questionnaire. Summary of QoLs and its change over time will be presented graphically using box plot and spaghetti plot, in addition to a summary table of QoL over time. No hypothesis testing is planned for QoL.

Incidence of cognitive AEs will be assessed by measuring changes in MMSE scores over time. Descriptive statistical analysis will be conducted on the endpoint. (See Section 7.8 for details on time points for measurement)
To evaluate how the time of last cycle of chemotherapy or chemoradiation therapy impact our observed indidence of SCLC brain metastases, we will also conduct a parellel analysis using SCLC brain metastases rate at 6-month from the beginning of the 4th cycle of chemotherapy to development of brain metastases as a secondary endpoint. We will use exactly the same approach as described in Section 10.2.1.

10.3 SAMPLE SIZE, POWER, ACCRUAL RATE AND STUDY DURATION

SAMPLE SIZE AND POWER

A total of 106 participants with SCLC will be accrued into this study of which 45 and 61 participants will be characterized as having either ESCLC or LSCLC disease, respectively. For ESCLC, we need 45 subjects for 80% power to detect a 50% reduction at a 5% significance level using a two-sided exact test for one proportion, assuming the incidence rate is 40% for subjects not receiving Optune®. PASS 15 “Test for one proportion” procedure was used for sample size computation. We will use two-sided exact test for one proportion to test the incidence rate against the null hypothesis of 40%. $P < 0.05$ will be considered statistically significant.

For participants with LSCLC, we need 61 subjects for 80% power to detect a 50% reduction at a 5% significance level, using a two-sided exact test for one proportion, assuming the incidence rate is 30% for subjects not receiving Optune®.PASS 15 “Test for one proportion” procedure was used for sample size computation. We will use two-sided exact test for one proportion to test the incidence rate against the null hypothesis of 30%. $P < 0.05$ will be considered statistically significant.

10.4 HANDLING OF MISSING DATA

Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant’s data may be excluded entirely or

partially, depending on the specific endpoints in question and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

11. CLINICAL MONITORING

11.1 OHSU KNIGHT CANCER INSTITUTE DATA & SAFETY MONITORING PLAN

This study is under the oversight of the Knight Cancer Institute's DSMC as described in the Knight institutional DSMP. The Knight DSMP outlines the elements required to ensure the safety of clinical trial participants, the accuracy and integrity of the data and the appropriate modification of cancer-related clinical trials for which significant benefits or risks have been discovered or when the clinical trial cannot be successfully concluded. The Knight DSMP also describes the methods and procedures for ensuring adequate oversight of cancer-related research at OHSU.

As described in the Knight DSMP, regardless of a trial's risk level and any specific Knight oversight in place, the Investigator is singularly responsible for overseeing every aspect of the design, conduct, and final analysis of his/her investigation.

The Knight DSMC will review and monitor study progress, toxicity, safety and other data from this study. Information that raises any questions about participant safety or protocol performance will be addressed by the Investigator, statistician and study team. Should any major concerns arise, the Knight DSMC may recommend corrective action and determine whether or not to suspend the study.

The Knight DSMC will review each protocol every 6 months, but may occur more often, if required, to review toxicity and accrual data (please refer to Knight DSMP for additional details on audit frequency). The Knight DSMC will review accrual, toxicity, response and reporting information. Information to be provided to the DSMC may include: participant accrual; treatment regimen information; AEs and SAEs reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

11.2 CLINICAL DATA & SAFETY MONITORING

The OHSU Investigator is ultimately, singularly responsible for overseeing every aspect of the investigation, including design, governing conduct at all participating sites, and final analysis of study data.

In the absence of a formal monitoring plan, the Investigator may work with his/her study team to conduct and document internal monitoring of the study to verify protection of human participants, quality of data, and/or ongoing compliance with the protocol and applicable regulatory requirements.

If at any time Investigator noncompliance is discovered at OHSU, the Investigator shall promptly either secure compliance or end the study with participating site.

Independent audits will be conducted by the Knight DSMC to verify that the rights and well-being of human participants are protected, that the reported trial data are accurate, that the conduct of the trial is in compliance with the protocol and applicable regulatory requirements, and that evidence of ongoing investigator oversight is present.

11.3 **QUALITY ASSURANCE & QUALITY CONTROL**

The investigational site will provide direct access to all trial related source data/documents, and reports for the purpose of monitoring by the monitor and/or sponsor, and auditing by the Knight DSMC and/or regulatory authorities.

Quality assurance (QA) auditing activities will occur as detailed in the Knight DSMP. All discrepancies, queries, deviations, observations, and findings will be compiled into a final audit report along with a Corrective and Preventative Action Plan.

The Sponsor-investigator, or study monitor, will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

12. DATA HANDLING AND MANAGEMENT RESPONSIBILITIES

12.1 SOURCE DATA/DOCUMENTS

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The Investigator will maintain adequate case histories of study participants, including accurate CRFs and source documentation.

12.2 PARTICIPANT & DATA CONFIDENTIALITY

The information obtained during the conduct of this clinical study is confidential, and unless otherwise noted, disclosure to third parties is prohibited. Information contained within this study will be maintained in accordance with applicable laws protecting participant privacy, including the provisions of the Health Insurance Portability and Accountability Act (HIPAA).

Participant confidentiality is strictly held in trust by the participating Investigator(s) and study team. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or manufacturer supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Upon enrollment, participants will be assigned a code that will be used instead of their name, medical record number or other personally identifying information. Electronic files for data analysis will contain only the participant code. Codes will not contain any part of the 18 HIPAA identifiers (e.g., initials, DOB, MRN). The key associating the codes and the participants' personally identifying information will be restricted to the Investigator and study staff. The key will be kept secure on a restricted OHSU network drive a in a limited access folder.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and institutional regulations. Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored within the Knight Cancer Institute per OHSU's Information Security Directives. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Knight Cancer Institute research staff will be secured and password protected per OHSU's Information Security Directives. At the end of the study, all study databases will be de-identified and archived within the Knight Cancer Institute.

12.3 DATA COLLECTION & STORAGE: PRIVACY, CONFIDENTIALITY & SECURITY

Data collection is the responsibility of the clinical trial staff at the site under the supervision of

the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. Standard institutional practices will be followed as described in the OHSU's Information Security Directives to maintain the confidentiality and security of data collected in this study. Study staff will be trained with regard to these procedures.

Loss of participant confidentiality is a risk of participation. Efforts will be made to keep study participant identities confidential except as required by law. Participants' samples will be identified by code only. Specifically, each consenting participant will be assigned a unique coded identifier consisting of numbers. This identifier will be associated with the participant throughout the duration of their participation in the trial. The coded identifier will also be used to identify any participant specific samples.

Basic accrual tracking information (demographic, consent, visit information) will be captured in OHSU's electronic clinical information research system (eCRIS), hosted on OHSU secure servers and managed by OHSU's information technology group at their data center in downtown Portland, Oregon. Any additional printed documents containing participant identifiers, such as those from the medical record to confirm eligibility, will be filed in binders and kept in a locked, secure location.

Study outcome data will be captured in electronic case report forms (eCRFs) using the electronic data capture (EDC) system, Forte. The Forte EDC is a web-hosted application is an approved EDC system that has been reviewed by OHSU Security.To further preserve confidentiality, PHI in the EDC system will be limited to just birth date and visit dates. The web-accessible EDC system is password protected and encrypted with role-based security, and administered by designated informatics staff within OHSU or Knight Cancer Institute. All users of the database are assigned a unique ID, username, and password and must complete training appropriate to their role before they are authorized to enter, access, and store data in the database.

Data from correlative studies will be entered into the EDC system by study personnel at OHSU. All other electronic data extracts will be stored only on OHSU encrypted computers and restricted drives, limited only to study investigators and staff with authorization to access the data. Quality assurance will be conducted as outlined in Section 11.3, Quality Assurance & Quality Control.

12.4 **MAINTENANCE OF RECORDS**

Records and documents pertaining to the conduct of this study, source documents, consent forms, laboratory test results and medication inventory records, must be retained by the Investigator for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indicate, until 2 years after the investigation is discontinued and FDA is notified. It is the responsibility of the sponsor to inform the Investigator when these documents no longer need to be retained.

If the Investigator relocates or for any reason withdraws from the study, the study records must be transferred to an agreed upon designee, such as another institution or another investigator at OHSU. Records must be maintained according to institutional or FDA requirements.

12.5 MULTICENTER GUIDELINES

OHSU Coordinating Center will manage trial data in the following ways:

1. Confirm that all sites have received and are using the most recent version of the protocol. The protocol must not be rewritten or modified by anyone other than the OHSU Investigator. Documentation of the version that was sent to the site must be kept in the regulatory binders.
2. Confirm that the protocol and informed consent form have local IRB approval at each site prior to registration of the first participant. Documentation of IRB approval from other sites for continuing review must be submitted and kept in the binder.
3. Provide centralized participant registration in the clinical research management system.
4. Ensure collection and review of applicable source documents and case reports by the OHSU Investigator to ensure protocol compliance.
5. Maintain documentation for all SAE reports and submit regular summaries of all AEs, SAEs and UPs from all sites to the Knight DSMC per DSMC requirements.
6. Ensure that relevant IRB correspondence and study status changes are communicated to all participating sites within 5 business days. Any changes that affect participant safety of study enrollments will be communicated immediately.
7. Submit documentation to the FDA such as protocol amendments, annual reports, and safety reports for unexpected, fatal or life-threatening events that are associated with the use of the investigational product.
8. Participating sites must submit regulatory documents including, but not limited to the following:
9. Current CV (signed and dated) for each Investigator.
10. Current medical license number for physician investigators.
11. Current signed FDA Form 1572.
12. Certificate of completion of institution-required human participant training course, the NIH online training in the protection of human research participants or other appropriate training.
13. Documentation of institutional Conflict of Interest.
14. IRB approved site-specific ICF (must be reviewed and approved by OHSU Investigator and study team prior to submission to the local IRB).
15. All IRB approved documents and approval memorandums.
16. Delegation log.
17. DSMP.
18. Completed CRFs (data entry) within 10 business days of study visit.

12.6 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. The investigators will work to expedite the analysis of data for release of results on all pre-specified outcomes in a timely and reasonable fashion at the completion of the study. If the results show negative outcomes and/or the study is terminated, the expedient release of such information and reporting will be of priority.

This study will adhere to the requirements set forth by the ICMJE and FDAAA that requires all clinical trials to be registered in a public trials registry (e.g., ClinicalTrials.gov) prior to participant enrollment.

13. ETHICS/PROTECTION OF HUMAN PARTICIPANTS

13.1 ETHICAL STANDARD

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR 312 (for IND studies), 21 CFR 812 (for IDE studies), and/or the ICH E6.

13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT

Written informed consent will be obtained from all participants, or the legally authorized representative of the participant, participating in this trial, as stated in the Informed Consent section of 21 CFR Part 50.. Documentation of the consent process and a copy of the signed consent shall be maintained in the participant's medical record.

CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreement to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families as appropriate. Consent forms will be IRB-approved and the participant will be asked to read and review the document. The Investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks/benefits of the study, alternatives to participation, and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

13.4 PROTOCOL REVIEW

The protocol and informed consent form for this study must be reviewed and approved in writing by the OHSU Knight Cancer Institute's Clinical Research Review Committee (CRRC) and the appropriate IRB prior to any participant being consented on this study.

13.5 CHANGES TO PROTOCOL

Any modification of this protocol must be documented in the form of a protocol revision or amendment submitted by the Investigator and approved by the CRRC and IRB, before the revision or amendment may be implemented. The only circumstance in which the amendment may be initiated without regulatory approval is for a change necessary to eliminate an apparent and immediate hazard to the participant. In that event, the Investigator must notify the IRB (and sponsor/FDA if under an IND/IDE) within 5 business days after the implementation.

An Investigator who holds an IND or IDE application must also notify the FDA of changes to the protocol per 21 CFR 312 or 21 CFR 812, respectively.

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15. APPENDICES

APPENDIX A: PERFORMANCE STATUS

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.