Official Title of the study	**LUNAR: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure**
NCT number	**NCT02973789**
Document Date	**December 18, 2021**

LUNAR: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure

Study	**EF-24 (LUNAR)**
Sponsor	**Novocure GmbH** **Park 6** **CH-6039 Root D4** **Switzerland**
Doc number	[redacted]
[redacted]	[redacted]

Revision history:

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LIST OF ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Effect
ADL	Activities of Daily Living
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
APC	Antigen Presenting Cell
aPTT	Activated Partial Thromboplastin Time
ASADE	Anticipated Serious Adverse Device Effect
AST	Aspartate Aminotransferase
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
C57BL/5	Mouse strain
CA	Competent Authority
CFR	Code of Federal Regulations
CI	Confidence Interval
Cm	Centimeter
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte Antigen 4
CT	Computed Tomography
CVA	Cerebrovascular Accident
DD	Device Deficiency
DMC	Data and Monitoring Committee
DSS	Device Support Specialist
EC	Ethic Committee
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
ERP	Enterprise Resource Planning system
FDA	Food and Drug Administration
FFPE	Formalin-Fixed and Paraffin-Embedded tumor blocks
GBM	Glioblastoma
H1299	Human Adenocarcinoma NSCLC
HTB 182	human Squamous NSCLC cell line
IFU	Instruction for Use
ILE	Insulated Lung Electrodes
INR	International Normalized Ratio
IRB	Institutional Review Board
irRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
ITT	Intent to Treat

kHz	Kilo Herz
LLC1	Murine Lewis lung carcinoma cell line
mA	Mili Amper
MHC	Major Histocompatibility Complex
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic Resonance Imaging
NSCLC	Non-Small-Cell Lung Cancer
NYHA	New York Heart Association
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFS-6	Progression Free Survival at 6 months
PD-L1	Programmed Death Ligand 1
PT	Prothrombin time
PTT	Partial Thromboplastin Time
QLQ C-30	EORTC's Quality of life Questionnaire
RECIST	Response Evaluation Criteria In Solid Tumors
RMS	Root Mean Square
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SOC	Standard of Care
TKI	Tyrosine Kinase Inhibitor
TMZ	Temozolomide
TTFields	Tumor Treatment Fields
UADE	Unanticipated adverse device effect
ULN	Upper Limit Normal
USADE	Unanticipated Serious Adverse Device Effect
V/cm	Volt/centimeter

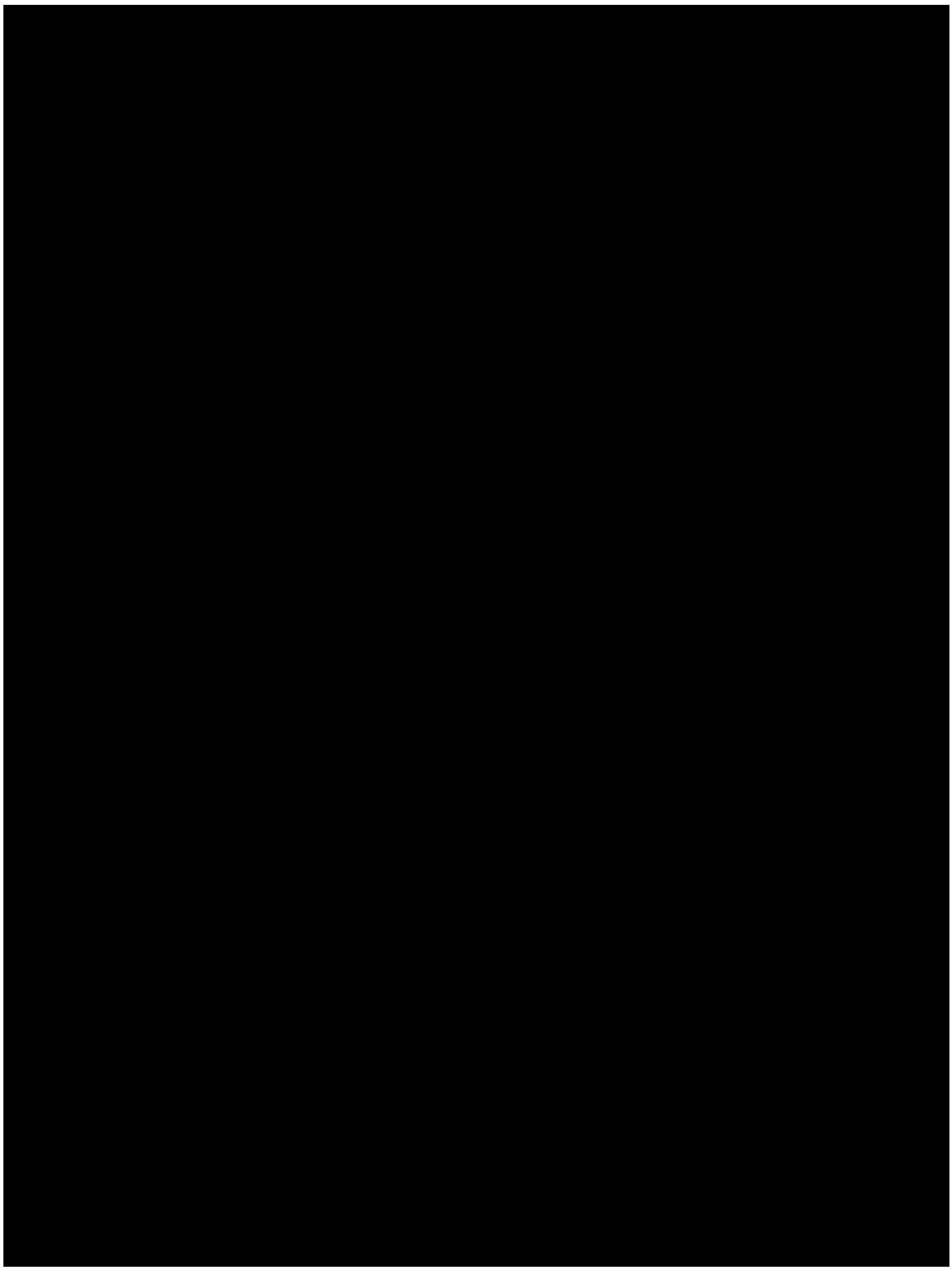
SYNOPSIS OF THE CLINICAL STUDY

Title	LUNAR: Pivotal, randomized, open-label study of Tumor Treating Fields (TTFields) concurrent with standard of care therapies for treatment of stage 4 non-small cell lung cancer (NSCLC) following platinum failure
Device	NovoTTF-200T System (150kHz output frequency)
Study Objectives	To test the efficacy and safety of TTFields, using the NovoTTF-200T System, concurrent with standard therapies for stage 4 NSCLC patients, following progression while on or after platinum based treatment.
Study Design	Prospective, randomized control, open-label study
[redacted]	[redacted]
Study Hypothesis	The hypothesis of this study is that the use of TTFields concurrent to standard of care therapies in stage 4 NSCLC after platinum failure will increase overall survival compared to patients receiving standard therapies alone.
Sample Size	276 patients (randomized 1:1 to TTFields with standard of care therapies Vs. standard therapies alone)
Study Population	Patients with histology or cytology based diagnosis of metastatic NSCLC, 22 years of age and older, following disease progression on or after receiving platinum based chemotherapy.
Primary Endpoint	• Overall Survival (OS) of patients treated with TTFields + docetaxel or immune checkpoint inhibitors Vs. docetaxel or immune checkpoint inhibitors alone (Superiority analysis)
Secondary Endpoints	Key secondary endpoints: • Overall Survival of patients treated with TTFields + Docetaxel Vs. Docetaxel alone (Superiority analysis) • Overall Survival of patients treated with TTFields + Immune checkpoint inhibitors Vs. immune checkpoint inhibitors alone (Superiority analysis) Additional secondary endpoints: • Overall Survival of patients treated with TTFields + Docetaxel Vs. immune checkpoint inhibitors alone (non-inferiority analysis)

- Progression-free survival of patients treated with Docetaxel or Immune checkpoint inhibitors + TTFields vs. Docetaxel or Immune checkpoint inhibitors alone, based on RECIST criteria
- Overall radiological response rate (based on RECIST criteria) of patients treated with Docetaxel or Immune checkpoint inhibitors + TTFields vs. Docetaxel or Immune checkpoint inhibitors alone.
- Quality of life using the EORTC QLQ C30 questionnaire with LC13 addendum
- Analyses of the effects of NovoTTF-200T with each type of immune checkpoint inhibitor on OS and PFS
- Analysis of the effects of NovoTTF-200T on OS and PFS within each histological subgroup (squamous and non-squamous)
- The effect of treatment usage time with NovoTTF-200T (as calculated from the device log file) to check whether average monthly usage time of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields
- Adverse events, severity and frequency based on Common Terminology Criteria for Adverse Events (CTCAE) V4.03

Sponsor Novocure GmbH, Park 6, CH-6039 Root D4, Switzerland

STUDY SCHEMA



1 CLINICAL STUDY BACKGROUND AND RATIONALE

1.1 DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND ITS INTENDED PURPOSE

The NovoTTF-200T System is intended for the treatment of adult patients with stage 4 non-small cell lung cancer concurrent with standard of care therapies following platinum failure. It is intended to be used exclusively by patients in a clinical study.

The device is a portable, battery-operated system, which delivers TTFields at 150 kHz to the patient by means of insulated Transducer Arrays (ILE transducer arrays). NovoTTF-200T produces electric forces intended to disrupt cancer cell division.

The NovoTTF-200T device, additional parts and ILE Transducer arrays (sterile) are a portable device intended for use in this study as a home treatment for at least 18 hours a day for patients with stage 4 NSCLC together with standard chemotherapy or immune checkpoint inhibitors.

[redacted]

In the current study, NovoTTF-200T is an investigational device.

1.2 THE MANUFACTURER OF THE INVESTIGATIONAL DEVICE

The NovoTTF-200T System is manufactured by Novocure GmbH, Park 6, CH-6039 Root D4 Switzerland.

1.3 SYSTEM PARTS AND THEIR IDENTIFICATION

[redacted]

[redacted]

1.4 TRACEABILITY

[redacted]

[redacted]

1.5 MATERIALS THAT WILL BE IN CONTACT WITH TISSUES

[redacted]

[redacted]

[redacted]

	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

1.6 TRAINING PATIENTS ON USING THE NOVOTTF-200T SYSTEM

[redacted]

2 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATIONAL PLAN

2.1 ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Lung cancer is the most common primary malignancy and the leading cause for cancer mortality. Worldwide, lung cancer caused 1.6 million deaths in 2012[1]. It was estimated that 225,000 new cases of lung cancer and over 160,000 deaths due to lung cancer would occur in 2016. Lung cancer deaths are declining in men and have plateaued in women, secondary to decrease in smoking rates. The SEER study[2] has demonstrated the decline in prognosis of patients based on the stage of their disease, from 60 months for stage IA to 6 months for stage IV patients. Poor performance status and weight loss have also been associated with shorter survival[3,4].

The treatment of NSCLC is multi-modal and includes surgery, chemotherapy, radiation therapy or a combination of the above. These modalities are associated with substantial toxicity. Surgical resection is the best option offering long-term survival and a cure in selected patients whose pulmonary function and comorbidities allow such resection. Since the vast majority of patients do not have resectable tumors, the intention of therapy is to prolong survival while minimizing treatment-related side effects and maintaining quality of life. Most patients with TNM stage IV disease are treated with systemic chemotherapy and palliative treatments to reduce symptoms. Whenever possible, the selection of systemic therapy should be based on molecular and histologic characteristics of the tumor. Treatments that target specific genetic alterations in NSCLC are widely used. Specifically, mutations in the epidermal growth factor receptor (EGFR) are more commonly found in adenocarcinoma patients, never smokers, women and/or of Asian ethnicity. Tumors bearing such mutations are highly sensitive to EGFR tyrosine kinase inhibitors (TKIs), such as erlotinib, gefitinib and afatinib[5]. First-line treatment with EGFR TKIs improved progression free survival (PFS) compared with standard platinum-based chemotherapy[1]. The impact on OS is unclear and may have been masked in studies due to the fact that these agents are used as second-line therapy after standard chemotherapy. The use of these TKIs significantly improved the prognosis of EGFR-mutated patients. In the TORCH trial, OS was significantly longer in unselected patients assigned to initial chemotherapy followed by second-line erlotinib, compared with patients who received an inverse regimen that started with the administration of erlotinib (median 11.6 Vs. 8.7 months, HR 1.24, 95% CI 1.04-1.47)[6]. For patients known to be EGFR mutation negative, OS was significantly longer with initial chemotherapy compared with initial erlotinib (median OS 9.6 Vs. 6.5 months). EML4-anaplastic lymphoma kinase (ALK) fusion oncogene is more frequently found in nonsmokers and younger patients, whose tumors respond well to the ALK inhibitor crizotinib. Other mutations found in NSCLC tumors are under investigation as potential targets for therapy.

Platinum-based therapy is normally limited to 4-6 cycles[7] as long as there is no evidence of disease progression and the chemotherapy is tolerated. Platinum-based doublets have demonstrated survival benefit across multiple studies compared to supportive care alone (one-year survival rate 29% Vs. 20%, HR 0.77, 95% CI 0.71-0.83)[3,8], and also compared to a single agent treatment (objective response rate 26% Vs. 13% with single agent therapy, and one-year survival rate 35% Vs. 30%)[9]. No single regimen has demonstrated consistent superiority, and cisplatin/carboplatin are therefore commonly combined with either pemetrexed, taxanes, gemcitabine, vinorelbine and irinotecan/topotecan. Once the chemotherapy

has been completed, either maintenance chemotherapy until progression followed by targeted therapy, or targeted therapy as maintenance have been employed. Pemetrexed-based treatments are sometimes used as therapy in non-squamous tumors[10]. Survival in 847 NSCLC patients with adenocarcinoma was significantly prolonged with cisplatin plus pemetrexed compared with cisplatin plus gemcitabine (median OS 12.6 Vs. 10.9 months)[11], with an opposite outcome in squamous cell histology patients[12]. Bevacizumab may also be added in this case, and even continued as a maintenance therapy if the tumor is responding or stable[13], as it has been shown to prolong PFS and OS. Patients treated with bevacizumab had an increased response rate (35% Vs. 15% with carboplatin and paclitaxel alone) and OS (median 12.3 Vs. 10.3 months) compared to patients on maintenance therapy alone[14]. In a meta-analysis, the addition of bevacizumab significantly increased both OS and PFS compared to chemotherapy alone[15]. Other maintenance therapies include gemcitabine and pemetrexed[8].

As almost all patients with advanced NSCLC develop progressive disease, patients with metastatic NSCLC are usually treated with several lines of therapies throughout their illness. The selection of second line therapies is based on prior treatments and response to them, histology (squamous / non-squamous), PD-L1 expression and genetic analysis of the tumor, extent of disease and patient characteristics such as performance status. If no known driver mutation is present, and not administered already as part of first line, immunotherapy using checkpoint inhibitors that target PD-1 is the preferred option at time of progression.

Immunotherapy in NSCLC

Immunotherapy aims at enhancing the immune system responsiveness to tumor cells by increasing the recognition of cancer as foreign by immune system cells on one hand, and removing inhibition mechanisms that decrease the cytotoxic activity of the immune system against cancer cells by allowing tumor tolerance.

Immune recognition is mediated by antigen presenting cells (APCs) such as dendritic cells and macrophages that process tumor antigens and display them on major histocompatibility complexes (MHCs) on their surface. Such cells then migrate to lymph nodes, where they present the antigens to resting T cells through interaction with the T cell receptor. Interaction between B7.1 / B7.2 on the APC and CD28 on the T cell activates the T cell, which leaves the lymph node. At the tumor site, as the T cell recognizes antigens expressed on the tumor that have been previously presented to it by the APCs, it releases cytolytic enzymes and cytokines, thereby recruiting additional immune cells, and proliferates. This process destroys tumor cells and creates memory T cells.

Immune checkpoints, normally preventing autoimmune responses and helping in regulating the inflammatory process, are used by cancer cells to create immune tolerance to tumor cells; cytotoxic T-lymphocyte antigen 4 (CTLA-4) regulates early T cell activity and is upregulated on T cells after exposure to antigen. It competes with CD28 and gives negative signal to T cells through B7.1 and B7.2. This prevents T cell activation. PD-1 on the other hand does not act in lymphatic tissues but rather at the site of the tumor, where it is upregulated on activated T cells, and following interaction between the T cell receptor and the tumor may interact with programmed death ligand 1 (PD-L1), which leads to T cell inactivation.

Several studies have been conducted to date, exploring the potential benefit of targeting the development of tolerance through PD-1/PD-L1 interactions. Nivolumab, a monoclonal antibody against PD-1, has been approved by the Food and Drug Administration (FDA) based on an increase in OS compared to docetaxel

in advanced squamous NSCLC patients after disease progression following platinum doublet therapy (median 9.2 Vs. 6.0 months, in the CheckMate 017 study)[16]. One-year survival was 42% Vs. 24%, HR=0.59, 95% CI 0.44-0.79, and there were less treatment-related severe adverse events reported. In non-squamous patients at the same phase in the course of their disease, Nivolumab was approved by FDA based on the CheckMate 057 study which demonstrated that nivolumab significantly prolonged OS compared with docetaxel (median 12.2 Vs. 9.4 months)[17], again with a decrease in severe treatment-related adverse events.

Pembrolizumab is another monoclonal antibody against PD-1, and was approved by FDA based on the KEYNOTE-010 trial which demonstrated that pembrolizumab improved OS in patients previously treated for advanced NSCLC who expressed PD-L1 on at least 1% of tumor cells (which correlates with response to pembrolizumab[18]). In this study, the median OS was 12.7 Vs. 8.5 months in patients treated with docetaxel (HR=0.71, 95% CI 0.49-0.75)[19]. There were also fewer severe treatment related adverse events associated with pembrolizumab compared with docetaxel.

Atezolizumab is the first monoclonal antibody against PD-L1, and was approved by FDA based on the OAK trial which demonstrated that atezolizumab improved OS in stage 3B or 4 NSCLC patients who previously received platinum based therapy. In this study, the median OS was 13.8 vs. 9.6 months in patients treated with atezolizumab vs. docetaxel, respectively (HR=0·73 [95% CI 0·62–0·87], p=0·0003). Fewer patients had treatment-related grade 3 or 4 adverse events with atezolizumab (90 [15%] of 609 patients) versus docetaxel (247 [43%] of 578 patients).

Based on the above studies in immune checkpoint inhibitors, these approved agents for second line treatment of advanced NSCLC are gradually becoming the standard of care worldwide. However, due to differences in health authority approvals and coverage in different countries, docetaxel is still being widely used for the second line treatment of advanced NSCLC in many patients and platinum based therapies are still considered standard treatment either prior to or in combination with immune checkpoint inhibitors. Please see Section 2.9 for a rationale of the study design within the current treatment options globally.

Following progression on PD-1/PD-L1 inhibitors, a single agent chemotherapy with no cross-resistance to previous chemotherapies is normally selected for treatment. An EGFR-inhibitor is also sometimes selected for such patients. Targeted treatment against a diagnosed mutation continues to be the preferred option at progression, if not previously used. The two most common single chemotherapy agents following progression on prior treatments are pemetrexed and docetaxel. Both have demonstrated OS prolongation as single agents in previously treated patients. While pemetrexed has been observed to be beneficial only in non-squamous histology patients, docetaxel is not histology-dependent. Docetaxel led to longer OS, better pain control and better quality of life compared to supportive care[20,21]. Weekly 33.3 mg/m^2 docetaxel (instead of 75 mg/m^2 every three weeks) for six of every eight weeks could decrease toxicity without compromising median OS and one-year survival rates[22,23]. It is mostly used for patients with squamous cell histology or those with non-squamous who initially received pemetrexed. Survival of patients treated with pemetrexed is identical to that of docetaxel in NSCLC, but with less toxicity[24,25]. In a secondary analysis, pemetrexed led to a better median OS compared to docetaxel in non-squamous patients (9.3 Vs. 8.0 months, HR=0.78, 95% CI 0.61-1.00)[26]. Ramucirumab, a monoclonal anti-VEGF-R2 antibody, increases OS when combined with docetaxel in second line treatment, compared to docetaxel

alone (median OS 10.5 Vs. 9.1 months, HR=0.86, 95% CI 0.75-0.98)[27]. However, an increase in bleeding was reported in ramucirumab-treated patients.

2.2 TUMOR TREATING FIELDS (TTFIELDS) OVERVIEW

TTFields are a non-invasive, regional antimitotic treatment modality with minimal toxicity which have been approved for the treatment of recurrent and newly diagnosed glioblastoma (GBM) by the FDA in the United States and have obtained a CE mark in Europe for the same indications. TTFields treatment with the previous version of NovoTTF-200T (NovoTTF-100L) was also approved for the treatment of unresectable malignant pleural mesothelioma (MPM) by the FDA.

[redacted]

Figure 1: Effect of TTFields treatment, administered in different frequencies, on cell viability of various lung cancer cell lines (arrow indicates optimal frequency) (Giladi et al., *Semin Oncol, 2014*).

Figure 2: Clonogenic potential of various lung cancer cell lines after TTFields treatment at optimal frequency (150kHz). *P<.05,P<.01, and ***P<.001 versus control group (*Giladi et al., Semin Oncol, 2014*).**

[redacted]

Figure 3: Dose–response plots of (A) pemetrexed alone and in combination with TTFields on H1299 (adenocarcinoma) and LLC1 (Lewis lung carcinoma 1) cells; (B) cisplatin alone and in combination with TTFields on H1299, LLC1, KLN205 (squamous cell carcinoma), and HTB-182 (squamous cell carcinoma) cells; (C) paclitaxel alone and in combination with TTFields on H1299, LLC1, and HTB-182 cells; and (D) erlotinib alone and in combination with TTFields on HCC827 cells (adenocarcinoma, mutated in epidermal growth factor receptor tyrosine kinase domain) *(Giladi et al., Semin Oncol, 2014)*.

[redacted]

Figure 4: In vivo effects of treatment combination of TTFields therapy and chemotherapy. Volume of LLC1 (Lewis lung carcinoma 1) or KLN205-T1 (murine squamous cell carcinoma cells derived from DBA/2 mice lung tumors) tumors in mice treated with (A) pemetrexed, (B,D) cisplatin,and (C) paclitaxel.*P<.05 and **P<.01 versus control group.

2.6 CLINICAL RESULTS WITH OPTUNE™ IN GLIOBLASTOMA

[redacted]

200 kHz TTFields

[redacted]

200 kHz TTFields

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.7 CLINICAL RESULTS WITH TTFIELDS APPLIED TO THE THORAX

2.7.1 TTFIELDS IN NSCLC

[redacted]

2.7.2 TTFIELDS IN MESOTHELIOMA

[redacted]

[redacted]

2.8 RATIONALE FOR CONDUCTING THE CLINICAL INVESTIGATION

TTFields are a novel, non-invasive regional anti-mitotic treatment modality. Pre-clinical studies and clinical data in glioblastoma have demonstrated a favorable safety profile and clear clinical superiority when treating the brain with TTFields. Furthermore, the safety and efficacy with 150 kHz TTFields has been demonstrated in NSCLC in pre-clinical models and in a phase I/II pilot study concomitant with chemotherapy. [redacted] Taken together with the poor prognosis of stage 4 NSCLC patients, TTFields should be clinically researched as a potential treatment in stage 4 NSCLC after failure of standard platinum therapy, concurrent with the standard of care docetaxel or immune checkpoint inhibitors.

2.9 RATIONALE FOR DESIGN OF CLINICAL INVESTIGATION

Based on the extensive pre-clinical results and pilot study findings, the company is proposing to move to pivotal testing of the NovoTTF-200T device in patients with stage 4 NSCLC who have failed a platinum based regimen, concurrent with standard of care treatment for these patients.

[redacted]

[redacted]

3 RISKS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

[redacted]

[redacted]

4 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

4.1 PURPOSE AND OBJECTIVES

4.1.1 PURPOSE

To test the efficacy and safety of docetaxel or immune checkpoint inhibitors with or without TTFields, using the NovoTTF-200T System for stage 4 NSCLC patients, following progression while on or after platinum based therapy.

4.1.2 PRIMARY OBJECTIVE

To determine if stage 4 NSCLC patients treated with TTFields concomitant with docetaxel or immune checkpoint inhibitors following progression while on or after platinum treatment have a superior overall survival compared to patients who are treated with docetaxel or immune checkpoint inhibitors without TTFields.

4.1.3 KEY SECONDARY OBJECTIVES

1. To determine if the overall survival of patients treated with docetaxel + TTFields following progression while on or after platinum treatment is *superior* to the overall survival of patients treated with docetaxel alone.
2. To determine if the overall survival of patients treated with immune checkpoint inhibitors + TTFields following progression while on or after platinum treatment is *superior* to the overall survival of patients treated with immune checkpoint inhibitors alone.

4.1.4 ADDITIONAL SECONDARY OBJECTIVES

1. To determine if the overall survival of patients treated with docetaxel + TTFields following progression while on or after platinum treatment is *non-inferior* to the overall survival of patients treated with immune checkpoint inhibitors alone.
2. To determine if the progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors + TTFields following progression while on or after platinum treatment is *superior* to the progression-free survival of patients treated with docetaxel or immune checkpoint inhibitors alone, based on the RECIST criteria.
3. To compare the radiological response rate (based on RECIST criteria) of patients treated with docetaxel or immune checkpoint inhibitors + TTFields following progression while on or after platinum treatment compared with that of patients treated with docetaxel or immune checkpoint inhibitors alone.
4. To compare the quality of life of patients treated with docetaxel or immune checkpoint inhibitors concomitant with TTFields following progression while on or after platinum treatment to that of patients who are treated with docetaxel or immune checkpoint inhibitors without TTFields, using the EORTC QLQ C30 questionnaire with LC13 addendum.

5. To analyze the effects of NovoTTF-200T with each type of immune checkpoint inhibitor on OS and PFS.
6. To analyze the effects of NovoTTF-200T on OS and PFS within each histological subgroup (squamous and non-squamous).
7. To analyze whether average monthly usage time of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.
8. To assess adverse events, severity and frequency, associated with treating patients with docetaxel or immune checkpoint inhibitors concomitant with TTFields using the NovoTTF-200T System.

5 DESIGN OF THE CLINICAL INVESTIGATION

5.1 GENERAL

This is a prospective, randomized, open-label multicenter study. Patients will be stratified by their selected standard therapy (immune checkpoint inhibitor or Docetaxel) and their histology (squamous or non-squamous).

Patients with NSCLC will be randomized to 1 of 2 treatment arms [redacted]

Arm 1: Patients who receive docetaxel or immune checkpoint inhibitor concomitant with TTFields using the NovoTTF-200T System set to an output frequency of 150kHz.

Arm 2: Patients who receive docetaxel or immune checkpoint inhibitors without TTFields.

Treatment termination:

- On both arms, patients receiving docetaxel whose lung cancer progresses based on RECIST criteria will switch to a next line of treatment according to local practice.
- On both arms, patients receiving immune checkpoint inhibitors whose lung cancer progresses based on irRECIST [redacted] will switch to a next line of treatment according to local practice. Since irRECIST considers the disease progressed only after the second determination of progressive disease, this will ensure patients treated with immune checkpoint inhibitors do not stop treatment too early in the case of delayed response to treatment.
- [redacted]Therefore, patients receiving NovoTTF-200T treatment who have stable disease (SD) or partial/complete response (PR/CR) in the thorax and liver with progressive disease (PD) in other anatomic regions will remain on TTFields while receiving a next line of treatment, until progression (PD) in the liver or thorax according to RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively).

[redacted]

[redacted]

The study is designed as a randomized investigation to ensure a non-biased inclusion of all patients in each of the study arms. Stratification to ensure a balanced rate of patients with specific characteristics affecting prognosis in each of the study arms will be used to further ensure a non-biased inclusion of patients.

5.2 ELIGIBILITY CRITERIA

5.2.1 INCLUSION CRITERIA:

1. 22 years of age and older
2. Life expectancy of $\geq$ 3 months
3. Histological or cytological diagnosis of squamous or non-squamous, inoperable, metastatic NSCLC
4. Diagnosis of radiological progression while on or after first platinum-based systemic therapy administered for advanced or metastatic disease.
    a. Patients who received adjuvant or neoadjuvant platinum-based chemotherapy (after surgery and/or radiation therapy) and developed metastatic disease within 6 months of completing therapy are eligible.
    b. Patients with metastatic disease more than 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum- based regimen given to treat the advanced or metastatic disease, are eligible.

c. Patients should not receive any systemic therapy after platinum failure before enrollment into the study. Maintenance therapy after platinum based therapy and prior to progression is allowed.

5. ECOG Score of 0-2 (see **Appendix A**)
6. Assigned by the physician to receive either docetaxel or immune checkpoint inhibitor per standard of care regimens
7. Able to operate the NovoTTF-200T device independently or with the help of a caregiver
8. Signed informed consent for the study protocol

5.2.2 EXCLUSION CRITERIA

1. Metastases to central nervous system (CNS) with clinical symptoms or evidence of new metastases to CNS during screening. Patients who previously received treatments for the metastases to CNS, are stable and meet the following requirements are allowed to be enrolled:
    a. The patients are neurologically returned to baseline (except for residual signs or symptoms related to CNS treatment).
    b. No treatment for the metastases to CNS during the screening period (e.g. surgery, radiotherapy, corticosteroid therapy- prednisone > 10 mg/day or equivalent).
    c. No progress in CNS lesions as indicated by MRI within 14 days prior to randomization.
    d. No meningeal metastasis or spinal cord compression.
2. Patients planned to receive immune checkpoint inhibitor with contra-indications to receive immunotherapy
3. Patients planned to receive docetaxel with contra-indications to receive docetaxel
4. Severe comorbidities:
    a. Clinically significant (as determined by the investigator) hematological, hepatic and renal dysfunction, defined as: Neutrophil count < 1.5 x 10^9/L and platelet count < 100 x 10^9/L; bilirubin > 1.5 x ULN; AST and/or ALT > 2.5 x ULN or > 5 x ULN if patient has documented liver metastases; and serum creatinine > 1.5 x ULN.
    b. History of significant cardiovascular disease unless the disease is well controlled. Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea).
    c. History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the study.
    d. History of pericarditis.
    e. History of interstitial lung disease
    f. History of cerebrovascular accident (CVA) within 6 months prior to randomization or that is not stable.
    g. Active infection or serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.

h. History of any psychiatric condition that might impair patient's ability to understand or comply with the requirements of the study or to provide consent.
i. Any other malignancy requiring anti-tumor treatment in the past three years, excluding treated stage I prostate cancer, in situ cervical cancer, in situ breast cancer and non-melanomatous skin cancer.

5. Concurrent treatment with other experimental treatments for NSCLC while in the study
6. Implantable electronic medical devices (e.g. pacemaker, defibrilator) in the upper torso
7. Known allergies to medical adhesives or hydrogel
8. Pregnancy or breast-feeding (patients with reproductive potential must use effective contraception methods throughout the entire study period, as determined by their investigator/gynecologist)
9. Admitted to an institution by administrative or court order

5.3 CRITERIA FOR REMOVAL FROM STUDY TREATMENT

[redacted]

Follow-up per protocol will continue following [redacted].

5.4 ENROLLMENT PLAN

[redacted]

[redacted]

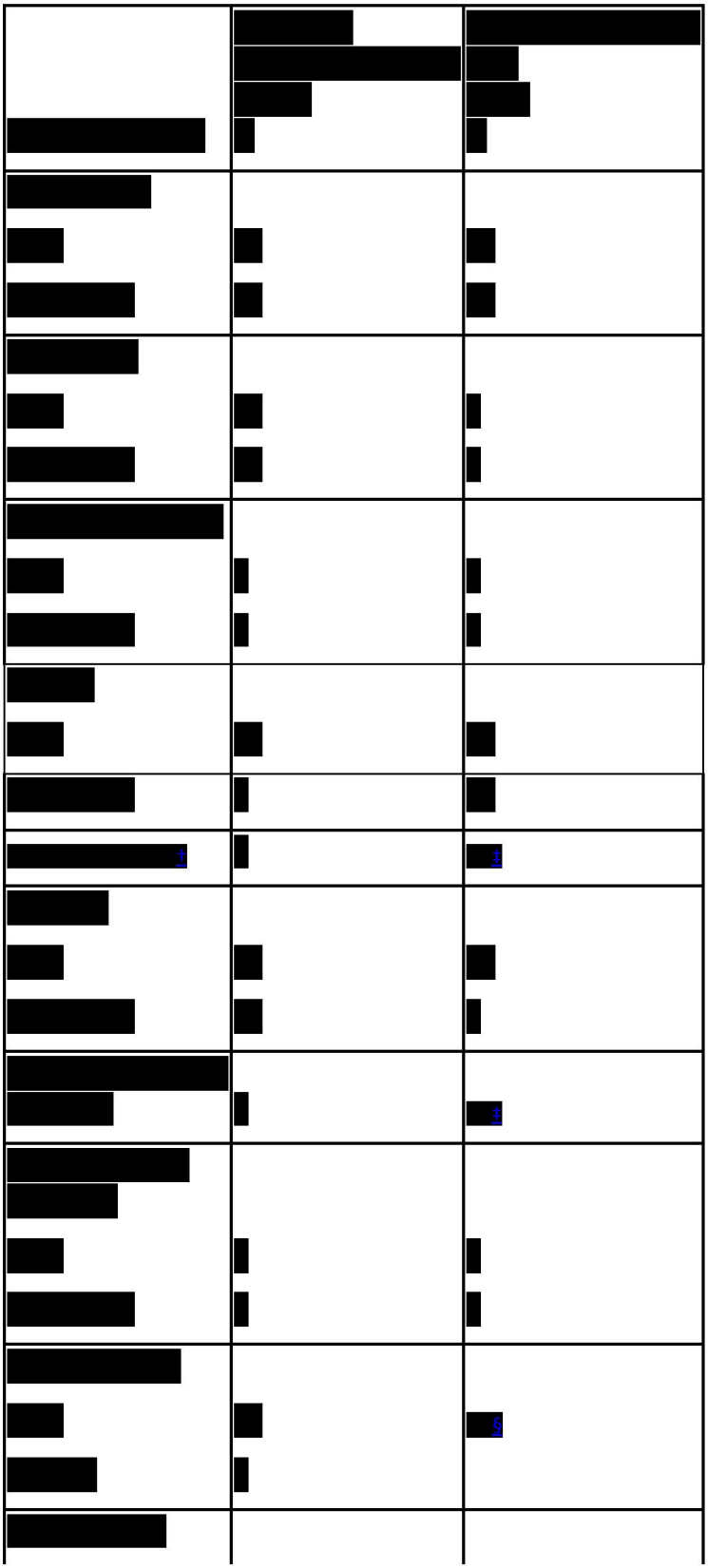
5.5 CLINICAL INVESTIGATION-RELATED PROCEDURES

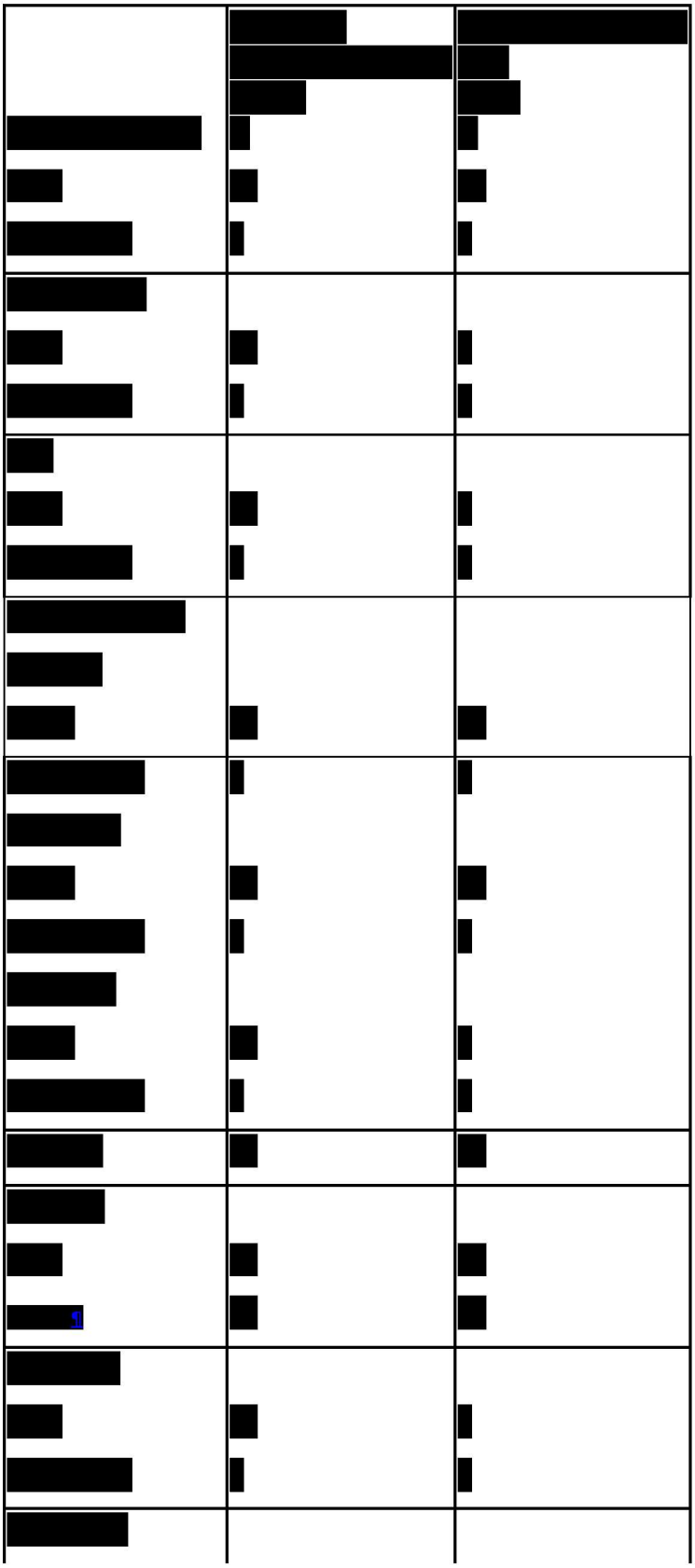
[redacted]

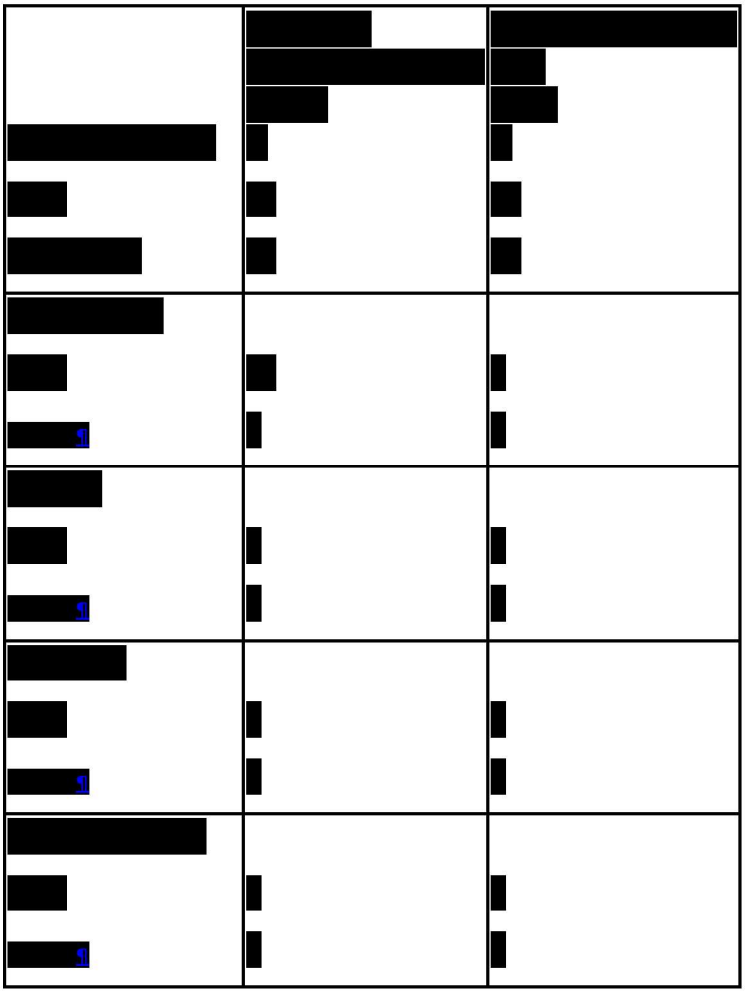
5.5.1 DOCETAXEL

[redacted]

Treatment Emergent Adverse Reactions Regardless of Relationship to Treatment in Patients Receiving docetaxel as Monotherapy for Non-Small Cell Lung Cancer Previously Treated with Platinum-Based Chemotherapy (Taxotere® package insert, http://products.sanofi.us/Taxotere/taxotere.html):







5.5.2 IMMUNE CHECKPOINT INHIBITORS

Nivolumab

[redacted]

The most common adverse reactions (reported in at least 20% of patients treated with nivolumab for their NSCLC) were fatigue, musculoskeletal pain, cough, decreased appetite, and constipation. The following list summarizes adverse reactions occurring more frequently in at least 10% of nivolumab-treated patients (http://packageinserts.bms.com/pi/pi_opdivo.pdf):

[redacted]

[redacted]

For additional and updated information about nivolumab, please refer to the most recent approved package insert. Please refer to the relevant country's approved package insert.

Pembrolizumab

[redacted]

[redacted]

The following summarizes adverse reactions that occurred in at least 10% of patients. The most common adverse reactions (reported in at least 20% of patients) were fatigue, decreased appetite, dyspnea, and cough. None of the AEs was reported as grade 4.
Adverse Event [% All Grades, % Grade 3)
(https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf):

[redacted]

The most updated prescription and safety data for pembrolizumab can be found in its FDA-approved package insert, and should be used as a reference for treatment and safety assessment on the study. For additional and updated information, please refer to the relevant country's approved package insert.

Atezolizumab

[redacted]

The most common (≥ 20%) adverse reactions in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen and received atezolizumab were fatigue (46%), decreased appetite (35%), dyspnea (32%), cough (30%), nausea (22%), musculoskeletal pain (22%), and constipation (20%). The most common Grade 3-4 adverse reactions (≥2%) were dyspnea, pneumonia, hypoxia, hyponatremia, fatigue, anemia, musculoskeletal pain, AST 395 increase, ALT increase, dysphagia, and arthralgia.

Additional information may be found on the atezolizumab package insert:
https://www.gene.com/download/pdf/tecentriq_prescribing.pdf

The most updated prescription and safety data for atezolizumab can be found in its FDA-approved package insert, and should be used as a reference for treatment and safety assessment on the study. For additional and updated information, please refer to the relevant country's approved package insert.

Immunotherapy drug dose modifications and treatment of drug related adverse events:

For Nivolumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf

For Pembrolizumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf

For Atezolizumab

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761041s000lbl.pdf

5.5.3 NOVOTTF-200T SYSTEM TREATMENT

- Treatment planning:
- Patient training:
- Treatment initiation: It is the responsibility of the investigator to oversee the treatment start supported by the Novocure Device Support Specialist (DSS).
- Treatment duration: TTFields application will be continuous
- Transducer Array replacement:
- Usage time assessment:

8. The following skin care guidelines should be closely adhered to:

[redacted]

5.5.4 SUPPORTIVE THERAPY

Patients on both arms of the study should also receive the best supportive care available at each site. All medications used throughout the study will be documented. [redacted]

5.5.5 SALVAGE THERAPY

Following progression patients may be offered standard NSCLC-directed therapy and salvage therapy based on local practice at each site. Salvage therapy should be recorded in the CRFs. [redacted]

6 PATIENT EVALUATIONS AND FOLLOW UP PLAN

A table of the study procedure calendar for this study is provided in **Appendix B**.

6.1 PRE-TREATMENT EVALUATION (BASELINE)

The following will be performed within [redacted] of randomization:

[redacted]

[redacted]

The following will be performed within [redacted] of randomization:

[redacted]

6.2 RANDOMIZATION VISIT

[redacted]

6.3 FOLLOW-UP VISIT

The following procedures will be performed for all study patients once every [redacted] until [redacted]:

[redacted]

6.4 FOLLOW-UP AFTER DISEASE PROGRESSION IN THE THORAX AND/OR LIVER PER RECIST OR IRRECIST (DEPENDING IF THE PATIENT IS RECEIVING DOCETAXEL OR IMMUNE CHECKPOINT INHIBITOR, RESPECTIVELY)

[redacted]

[redacted]

6.5 SURVIVAL FOLLOW-UP

Following the post progression visits, patients will be followed every [redacted] for survival ([redacted]). Patient death date will be captured in the CRFs.

All imaging study media for scans performed throughout the entire study will be de-identified and collected from all study subjects as part of the CRFs.

7 MONITORING PLAN

Study monitoring will be performed by [redacted] and according to a detailed monitoring plan. Study monitoring functions will be in compliance with recognized Good Clinical Practices, EN ISO 14155, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. § 812.46. The principal function of the clinical monitor is to observe and assess the quality of the clinical study. The monitor's duties include: [redacted]

On-site monitoring visits will take place at each center, during the course of the study ([redacted]), at the frequency defined in the monitoring plan, and a final visit at the close of the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure [redacted]:

[redacted]

4. [redacted]

[redacted]

[redacted]

[redacted]

8 STATISTICAL CONSIDERATIONS

8.1 STUDY ENDPOINTS

8.1.1 PRIMARY ENDPOINT

Overall survival of patients treated with TTFields concomitant with docetaxel or immune checkpoint inhibitors compared to patients treated with docetaxel or immune checkpoint inhibitors alone (superiority). Overall survival will be measured from time of randomization.

8.1.2 KEY SECONDARY ENDPOINTS

The following endpoints will be tested only if the primary endpoint is met in order to avoid multiplicity in type I error:

1. Overall survival of patients treated with docetaxel + TTFields compared to overall survival of patients treated with docetaxel alone (superiority).
2. Overall survival of patients treated with Immune checkpoint inhibitors + TTFields compared to overall survival of patients treated with Immune checkpoint inhibitors alone (superiority).

8.1.3 ADDITIONAL SECONDARY ENDPOINTS

1. Overall survival of patients treated with docetaxel + TTFields compared to overall survival of patients treated with Immune checkpoint inhibitors alone (non-inferiority). Overall survival will be measured from time of randomization.
2. Progression-free survival of patients treated with docetaxel or Immune checkpoint inhibitors + TTFields compared to progression-free survival of patients treated with docetaxel or Immune checkpoint inhibitors alone, based on RECIST.
3. Overall radiological response rate (based on RECIST) of patients treated with docetaxel or Immune checkpoint inhibitors + TTFields compared with that of patients treated with docetaxel or Immune checkpoint inhibitors alone.
4. Quality of life of patients treated with docetaxel or Immune checkpoint inhibitors concomitant with TTFields compared to that of patients who are treated with docetaxel or Immune checkpoint inhibitors without TTFields, using the EORTC QLQ C30 questionnaire with LC13 addendum.
5. Analyses of the effects of NovoTTF-200T with each type of immune checkpoint inhibitor on OS and PFS will be performed.
6. Analysis of the effects of NovoTTF-200T on OS and PFS will be tested within each histological subgroup (squamous and non-squamous).

7. The effect of treatment usage time with NovoTTF-200T (as calculated from the device log file) will be tested to determine whether average monthly usage time of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.
8. Adverse events, severity and frequency, in patients treated with docetaxel or Immune checkpoint inhibitors concomitant with TTFields using the NovoTTF-200T System compared to patients treated with docetaxel or Immune checkpoint inhibitors alone.

8.2 STATISTICAL HYPOTHESIS TESTING

In the EF-15 study [redacted], the Sponsor chose a Hazard ratio of 0.75 for the sample size assessment in the current protocol. [redacted]

The primary endpoint is overall survival. Overall survival will be tested using two sided proportional hazards [redacted] The hazard rate for standard of care of Docetaxel or immune checkpoint inhibitor (SOC) is represented by h_{SOC} and the hazard for TTFields with SOC is represented by $h_{SOC+TTF}$. with the null hypothesis being $H_0 \geq 0.75$ and the alternate hypothesis being $H_A < 0.75$. The comparison itself is defined between h_{SOC} and $h_{SOC+TTF}$, as follows:

H0: Hazard Ratio = $h_{SOC+TTF} / h_{SOC} \geq 0.75$
HA: Hazard Ratio = $h_{SOC+TTF} / h_{SOC} < 0.75$

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

The key secondary endpoints will be tested hierarchically if the primary endpoint is met to preserve type I error. The key secondary endpoints will examine survival in components of SOC (either docetaxel or Immune checkpoint inhibitors) compared to those components together with TTFields. The components of SOC will be combined by therapeutic class so there are only 2 subgroups (Immune checkpoint inhibitors or Docetaxel), [redacted]

1. Superiority of TTFields + Docetaxel vs Docetaxel alone

The hazard rate for standard of care of Docetaxel is represented by $h_{Docetaxel}$ and the hazard for TTFields with Docetaxel is represented by $h_{TTF+Docetaxel}$. With the null hypothesis being $H_0 \geq 0.75$ and the alternate hypothesis being $H_0 < 0.75$.

The comparison itself is defined between $h_{Docetaxel}$ and $h_{TTF+ Docetaxel}$, as follows:

H_0: Hazard Ratio = $h_{TTFields + Docetaxel} / h_{Docetaxel} \geq 0.75$

H_A: Hazard Ratio = $h_{TTFields + Docetaxel} / h_{Docetaxel} < 0.75$

2. Superiority of TTFields + Immune checkpoint inhibitors vs Immune checkpoint inhibitors alone

The hazard rate for standard of care of immune checkpoint inhibitor is represented by h_{immune} and the hazard for TTFields with immune checkpoint inhibitor is represented by $h_{TTF+immune}$ checkpoint inhibitor. With the null hypothesis being $H_0 \geq 0.75$ and the alternate hypothesis being $H_0 < 0.75$.

The comparison itself is defined between h_{immune} and $h_{TTF+immune}$, as following:

H_0: Hazard Ratio = $h_{TTFields + Immune} / h_{Immune} \geq 0.75$

H_A: Hazard Ratio = $h_{TTFields + Immune} / h_{Immune} < 0.75$

[redacted]

Safety: Adverse events, severity and frequency based on Common Terminology Criteria for Adverse Events (CTCAE) V4.03 will be reported.

8.3 SAMPLE SIZE ASSESSMENT

The following assumptions were made in order to perform the sample size assessment for the protocol:

[redacted]

[redacted]	[redacted]					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Study duration: Patient accrual was planned to last 30 months and follow up was planned to last for an additional 18 months (48 month total study duration).

[redacted]

The assumptions used in the sample size calculations were planned to be evaluated at the interim analysis.

[redacted]

8.4 RANDOMIZATION AND STRATIFICATION

[redacted]

2. [redacted].

8.5 DATA MONITORING COMMITTEE

An independent Data and Monitoring Committee (DMC), comprised of [redacted] will be formed to monitor the safety data from the study. [redacted]

Specifically, DMC safety reviews will be performed once after [redacted] The DMC will also perform a safety review after [redacted] Subsequent DMC meetings will be held annually, or more often if necessary, to review the study safety data.

The DMC will base their recommendation to the Sponsor on an evaluation of data such as:

[redacted]

9 DATA MANAGEMENT

For all subjects enrolled in the study, site staff will [redacted]

Sites will retain organized subject, laboratory, and study device inventory records relating to the study for the period of time required by applicable federal law or regulation. [redacted]

[redacted]

10 AMENDMENTS TO THE PROTOCOL

All protocol amendments will be submitted to [redacted].

Amended protocols will be reviewed, approved and documented by the same method in which the original protocol was reviewed and approved. [redacted]

The final approved amended protocol will be distributed to participating investigator(s) at each site

11 DEVIATIONS FROM THE PROTOCOL

Investigators are not allowed to deviate from the protocol. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRBs/ECs. [redacted]

[redacted]

12 DEVICE ACCOUNTABILITY

[redacted]

[redacted]

13 STATEMENTS OF COMPLIANCE

The clinical investigation evaluated under this protocol shall be conducted at each participating sites in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The clinical

investigation will also be conducted in compliance with the ENISO 14155 and in compliance with national or regional regulations as appropriate.

The clinical investigation shall not begin before the appropriate IRBs/ECs and FDA/Competent Authority (CA) approval are obtained for the participating sites accordingly. Additional information required by the corresponding IRB/ EC as well as by the FDA and/or CA shall be delivered in a timely manner.

The appropriate insurance for subjects participating in this clinical study shall be arranged for each participating countries and sites. Participating subjects shall have the right to look at the insurance certificate and policy determined for this purpose.

14 INFORMED CONSENT PROCESS

[redacted]

Prior to carrying out any protocol-specific procedures, investigators or designated staff will [redacted]. All patients must provide written informed consent prior to registration and treatment.

The following points will be observed during the informed consent process:

[redacted]

[redacted]

Informed consent will comply with EN ISO 14155, 21 C.F.R 50 and other regional and national laws as applicable.

15 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

15.1 DEFINITIONS

15.1.1 ADVERSE EVENT (AE)

As defined by EN ISO 14155 (2011), an adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This includes events related to the investigational medical device or the comparator, events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

15.1.2 ADVERSE DEVICE EFFECT (ADE)

Adverse event related to the use of an investigational medical device. This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This includes any event resulting from use error or from intentional misuse of the investigational medical device.

15.1.3 DEVICE DEFICIENCY (DD)

Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

15.1.4 SERIOUS ADVERSE EVENT (SAE)

As defined by EN ISO14155 (2011), an adverse event that meets one or more of the following criteria/outcomes is classified as serious:

- led to a death,
- led to a serious deterioration in health of the subject that either resulted in:
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient hospitalization or prolongation of existing hospitalization, or
    - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

[redacted]

[redacted]

15.1.5 SERIOUS ADVERSE DEVICE EFFECT (SADE)

An SADE is any adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

15.1.6 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

As defined by EN ISO14155 (2011), serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

15.1.7 UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)

As defined by 21 CFR part 812.3, 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 subjects

15.2 ADVERSE EVENT COLLECTION AND REPORTING

The adverse event collection and reporting will be handled as required and in accordance with [redacted]

Safety evaluation and reporting will be managed through the following actions:

[redacted]

[redacted]

15.3 GRADING OF AN ADVERSE EVENT

The descriptions and grading scales found in the revised CTCAE version 4.03 will be utilized for assessing severity of adverse events. [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Modified Grading for TTFields-Related Skin Adverse Events:

[redacted]
[redacted]
[redacted]
[redacted]

[redacted]

15.4 DETERMINATION OF CAUSALITY OF ADVERSE EVENTS

The relationship of the adverse event to TTFields must be specified using the following definitions:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

15.5 ELICITING ADVERSE EVENT INFORMATION

[redacted]

15.6 ADVERSE EVENT REPORTING PERIOD

The adverse event reporting period will begin immediately following randomization. Adverse events will be collected for [redacted] following treatment termination, TTFields or systemic therapy, the later of the

two. All adverse events that occur in study patients during the adverse event reporting period specified in the protocol must be reported on the CRFs, [redacted]

15.7 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

[redacted]

[redacted]

15.8 REPORTING PROCEDURES

15.8.1 REPORTABLE EVENTS

- Any SAE
- Any Device Deficiency that might have led to a SAE if:
  - suitable action had not been taken or
  - intervention had not been made or
  - if circumstances had been less fortunate
- New findings/updates in relation to already reported events.
- Any UADE

[redacted]

15.8.2 REPORTING TIMELINES

The Investigator is to report reportable events immediately but not later than 1 business day after awareness of the event.

Novocure must report to [redacted]

[redacted]

[redacted]

15.8.3 REPORTING OF PREGNANCY

Pregnancy will be reported to Novocure immediately but not later than 1 business day after awareness of the pregnancy. [redacted]

16 VULNERABLE POPULATION

As described in the exclusion criteria, no vulnerable population will be included in this study.

17 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION

Novocure may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons. A Principal Investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible. If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, Novocure shall suspend the clinical investigation while the risk is assessed. Novocure shall terminate the clinical investigation if an unacceptable risk is confirmed.

Novocure shall consider terminating or suspending the participation of a particular investigation site or investigator in the clinical investigation if [redacted]

If, for any reason, Novocure suspends or prematurely terminates the investigation at an individual investigation site, Novocure shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the Principal Investigator or by Novocure. If the suspension or premature termination was in the interest of safety, Novocure shall inform all other Principal Investigators.

If suspension or premature termination occurs,

[redacted]

18 PUBLICATION POLICY

The results of the clinical investigation will be made publicly available in case of positive or negative results following the completion of the study.

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20 INVESTIGATOR SIGNATURE PAGE

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PI Name	Signature	Date

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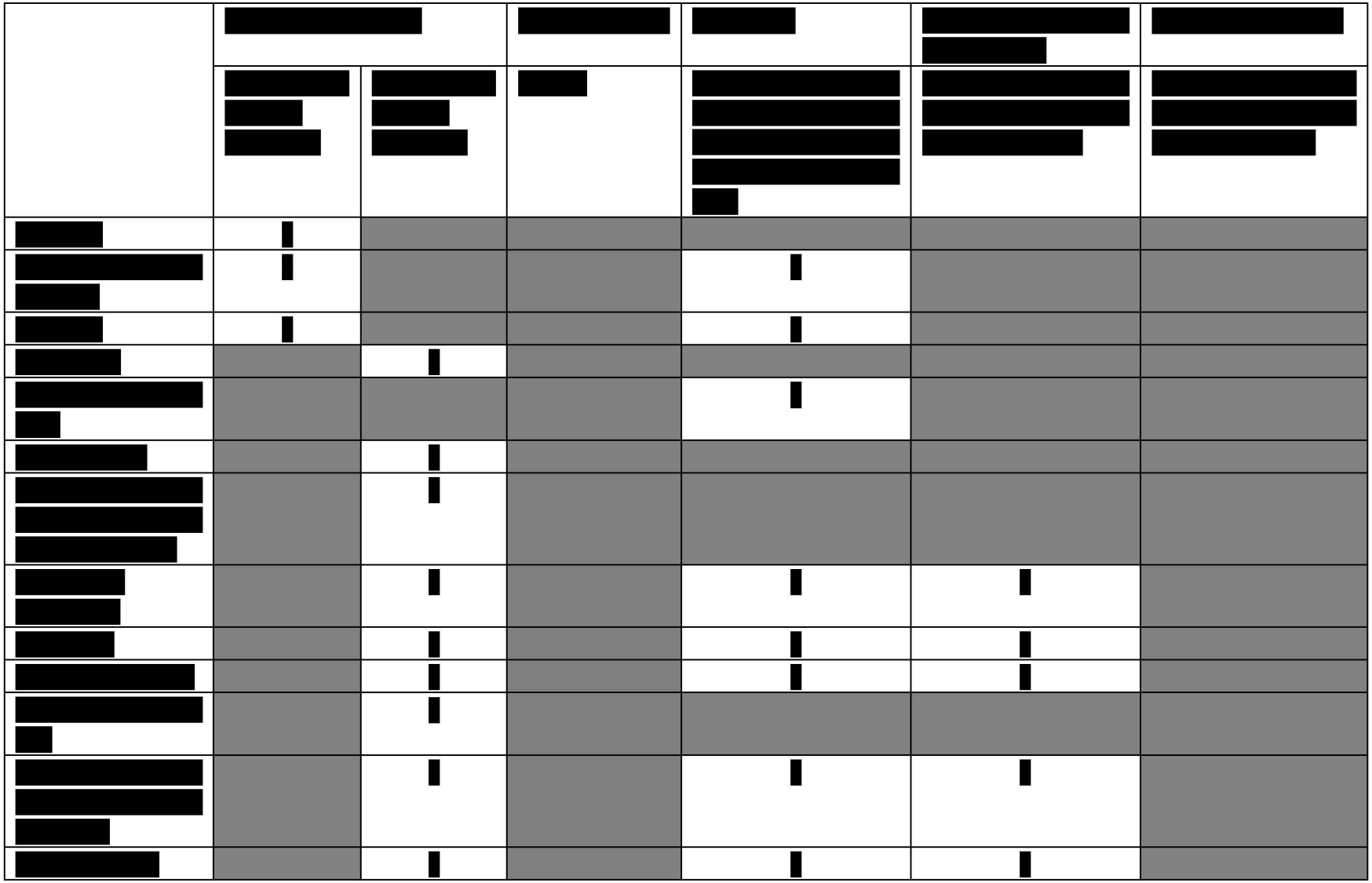
APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B EF-24 STUDY CALENDAR



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APPENDIX C IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

[redacted]

APPENDIX D LIST OF INVESTIGATORS

1) Principal Investigator(s),	
2) Coordinating Investigator, if appointed	
b) Name and address of the investigation site(s) in which the clinical investigation will be conducted.	
c) Name(s) and address(es) of other institutions involved in the clinical investigation.	
Note : The Sponsor shall maintain an updated list of principal investigators, investigation sites, and institutions. This list can be kept separately from the protocol. The definitive list shall be provided with the final clinical Investigation report.	

APPENDIX E CLINICAL PRACTICE GUIDELINES: OPTIMIZING THE TRANSDUCER ARRAY LAYOUT IN TTFIELDS-TREATED PATIENTS (THORACIC MALIGNANCIES)

APPENDIX F CTCAE VERSION 4.03

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