

Official Title of Protocol: EF-36/Keynote B36: A pilot, randomized, open-label study of Tumor Treating Fields (TTFields, 150 kHz) concomitant with pembrolizumab for first line treatment of advanced or metastatic non-small cell lung cancer

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EF-36/Keynote B36: A pilot, randomized, open-label study of Tumor Treating Fields (TTFields, 150 kHz) concomitant with pembrolizumab for first line treatment of advanced or metastatic non-small cell lung cancer

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Sponsor	Novocure GmbH Park 6 CH-6039 Root D4 Switzerland
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REVISION HISTORY

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LIST OF ABBREVIATIONS

<u>Abbreviation/Term</u>	<u>Definition</u>
1L	First line
7AAD	7-Aminoactinomycin D
A	Ampere
A549	Human squamous cell lung carcinoma
ADE	Adverse Device Effect
ADL	Activities of Daily Living
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASADE	Anticipated Serious Adverse Device Effect
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
B16F10	Mouse Malignant Melanoma Cell Line
β-HCG	Beta-human chorionic gonadotropin
BCG	Bacillus Calmette–Guérin
BMDC	Bone marrow-derived dendritic cell
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CP	Conditional power
CR	Complete response
CrCl	Calculated creatinine clearance
CRF	Case report form
CNS	Central nervous system
CT	Computed tomography
CT-26	Murine colon carcinoma
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
CVA	Cerebrovascular accident
DC	Dendritic cell
DCR	Disease Control Rate
DD	Device Deficiency
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response

<u>Abbreviation/Term</u>	<u>Definition</u>
DSS	Device Support Specialist
ECIs	Events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
F-98	Glioma Cells
FDA	Food and Drug Administration
FEM	Finite Element Method
F/T	Freeze/thawed
GBM	Glioblastoma
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GI	Gastrointestinal
Gy	Grey
H1299	Human Adenocarcinoma NSCLC
H520	Human lung squamous cell carcinoma
HBsAg	Hepatitis B soluble antigen
HCC827	Human Adenocarcinoma NSCLC
HCV	Hepatitis C
HEPG2	Human hepatocellular carcinoma
HIV	Human immunodeficiency virus
HMGB1	High mobility group box 1 (protein)
HR	Hazard Ratio
HTB 182	Human Squamous NSCLC
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
iCR	iRECIST complete response
iCPD	iRECIST confirmed progressive disease
IFU	Instructions for Use
IHC	Immunohistochemistry
ILE	Insulated Lung Electrodes
INR	International normalized ratio
IP	Intraperitoneal
irAEs	Immune-related adverse events
IRB	Institutional Review Board
iRECIST	Modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
iSD	iRECIST stable disease
ITT	Intent-to-treat
iUPD	=iRECIST unconfirmed progressive disease
IV	Intravenous
kg	Kilogram

<u>Abbreviation/Term</u>	<u>Definition</u>
kHz	Kilohertz
KLN205	Murine lung squamous cell carcinoma
LLC-1	Lewis Lung Carcinoma
mAB	Monoclonal antibody
MCV	Mean Corpuscular Volume
MG	Milligram
MG/KG	Milligram per kilogram
MGMT	O6-Methylguanin-DNS-Methyltransferase
MHC	Major Histocompatibility Complex
MOSE	Murine Ovarian Surface Epithelial
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
OTC	Over-the-counter
PBPK	Physiologically-based Pharmacokinetic
PD	Progressive disease
PD-1	Programmed cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PD-L2	Programmed Death-Ligand 2
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
PTT	Partial Thromboplastin Time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q9W	Every 9 weeks
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
RMS	Root mean square
RNA	Ribonucleic acid
RR	Response rate
RT	Radiation Therapy
SADE	Serious Adverse Device Effect
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase

<u>Abbreviation/Term</u>	<u>Definition</u>
SOP	Standard Operating Procedure
SUSAR	Serious Unexpected Suspected Adverse Reaction
T1DM	Type 1 diabetes mellitus
TKI	Tyrosine kinase inhibitors
TMDD	Target-mediated drug disposition
TMZ	Temozolomide
TPS	Tumor proportion score
TSH	Thyroid stimulating hormone
TTFields	Tumor Treating Fields
UADE	Unanticipated Adverse Device Effect
ULN	Upper limit of normal
USADE	Unanticipated Serious Adverse Device Effect
V/CM	Volt per Centimeter
VX-2	Rabbit Pleural Carcinoma Cell Line
WBC	White Blood Cell
WOCBP	Woman of Childbearing Potential

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (ICH GCP) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki, as required by the following: US Code of Federal Regulations (CFR) applicable to clinical studies (CFR Title 21), European Medical Device Regulation (2017/745) (MDR), EN ISO 14155 Clinical investigation of medical devices for human subjects, Ethics Committee (EC) / Institutional Review Board (IRB) requirements and applicable regional regulation in the various countries the study is conducted in.

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

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of the patients may proceed without prior approval by the Sponsor, the Ethics Committee (EC)/ Institutional Review Board (IRB) and the Competent Authority (CA). Such deviations shall be documented and reported to the Sponsor, the EC/IRB and the CA within the deadlines set by the local legal requirements.

The study is being funded by Novocure GmbH as confidentially described in the agreement with each investigation site.

1.0 STUDY SUMMARY

Abbreviated Title	Randomized pilot study of Tumor Treating Fields (TTFields, 150 kHz) concomitant with Pembrolizumab (MK-3475) for First Line Treatment of Advanced or Metastatic NSCLC (EF-36/Keynote B36)
Study Phase	Pilot
Clinical Indication	PD-L1 positive (TPS≥1%), previously untreated metastatic or current advanced NSCLC
Study Type	Interventional
Type of control	Active control
Route of administration	TTFields: Non-invasive application. Pembrolizumab: Intravenous
Study Blinding	Unblinded Open-label
Treatment Groups	TTFields at 150 kHz to the thorax, continuous application for at least 18 hours a day on average, using the NovoTTF-200T System. AND Pembrolizumab (MK-3475) 200 mg intravenous (IV) every 3 weeks (Q3W). OR Pembrolizumab (MK-3475) 200 mg intravenous (IV) every 3 weeks (Q3W).
Number of Sites enrolling participants:	[REDACTED]
Number of study subjects	[REDACTED]
Estimated duration of study	[REDACTED]
Duration of Participation	[REDACTED]

2.0 STUDY DESIGN

2.1 Study Design

This is a multicenter, randomized, open-label study of Tumor Treating Fields (TTFields) at 150 kHz to the thorax using the NovoTTF-200T System concomitant with IV pembrolizumab (also known as MK-3475) in subjects previously untreated for their metastatic or current advanced, PD-L1 positive (TPS $\geq$ 1% [tumor proportion score]) non-small cell lung cancer (NSCLC). Approximately 100 subjects with NSCLC, whose tumors are classified as TPS $>$ 1% and in whom EGFR or ALK-directed therapy is not indicated, are projected to be randomized in this study for examination of the effectiveness and safety of TTFields concomitant with pembrolizumab. Subjects will be randomized in a 1:1 ratio after a Screening Phase of up to 28 days to receive TTFields at 150 kHz to the thorax using the NovoTTF-200T System for at least 18 hours a day on average concomitant with pembrolizumab 200 mg IV Q3W or pembrolizumab 200 mg IV Q3W alone. Each subject

will participate in the study for approximately 2 years from the time the subject signs the Informed Consent Form (ICF) through the final contact.

[REDACTED]

[REDACTED]

The primary endpoint of the study is PFS by RECIST 1.1. Secondary endpoints include overall survival (OS), ORR, DOR, DCR and safety. [REDACTED]

[REDACTED]

PD-L1 expression status will be evaluated by the site local laboratory prior to randomization [REDACTED]

[REDACTED]



Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the Study Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Study Procedures.

[REDACTED]

[REDACTED]

3.0 OBJECTIVE(S) & HYPOTHESIS

3.1 Primary Objective & Hypothesis

- (1) **Objective:** To compare the progression-free survival (PFS) by RECIST 1.1 in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab to those treated with pembrolizumab alone.

Hypothesis: TTFields concomitant with Pembrolizumab administered as 1L, improves PFS by RECIST 1.1 in subjects with $TPS \geq 1\%$, metastatic/current advanced NSCLC compared to those treated with pembrolizumab alone.

3.2 Secondary Objectives

- (2) **Objective:** To evaluate the overall survival (OS) in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab and of those treated with pembrolizumab alone.
- (3) **Objective:** To evaluate the objective response rate (ORR) by RECIST 1.1 in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab and of those treated with pembrolizumab alone.
- (4) **Objective:** To evaluate the duration of response (DOR) by RECIST 1.1 in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab and of those treated with pembrolizumab alone.
- (5) **Objective:** To evaluate the disease control rate (DCR) by RECIST 1.1 in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab and of those treated with pembrolizumab alone.

Objective: To evaluate the safety and tolerability profile of TTFields concomitant with Pembrolizumab and of those treated with pembrolizumab alone in subjects with TPS

To investigate the relationship between PFS, and TTFields dose delivered to the tumor in subjects with $TPS \geq 1\%$, 1L metastatic/current advanced NSCLC treated with TTFields concomitant with pembrolizumab and of those treated with pembrolizumab alone.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on TTFields and pembrolizumab.

4.1.1 Background of TTFields

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 Food and Drug Administration (FDA) in the United States and have obtained a CE mark in Europe for the same indications

[REDACTED]

[REDACTED]

[REDACTED]

4.1.1.1 Preclinical Studies

4.1.1.1.1 In vivo Effects of TTFields

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1.1.1.2 Pre-clinical Results with TTFields in NSCLC

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1.1.1.3 TTFields and Immune Checkpoint Inhibitors

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.1.1.1.4 Metastasis Prevention Using TTFields

[REDACTED]

4.1.1.1.5 Delivery of TTFields to the Upper Torso

[REDACTED]

4.1.1.2 Clinical Studies

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

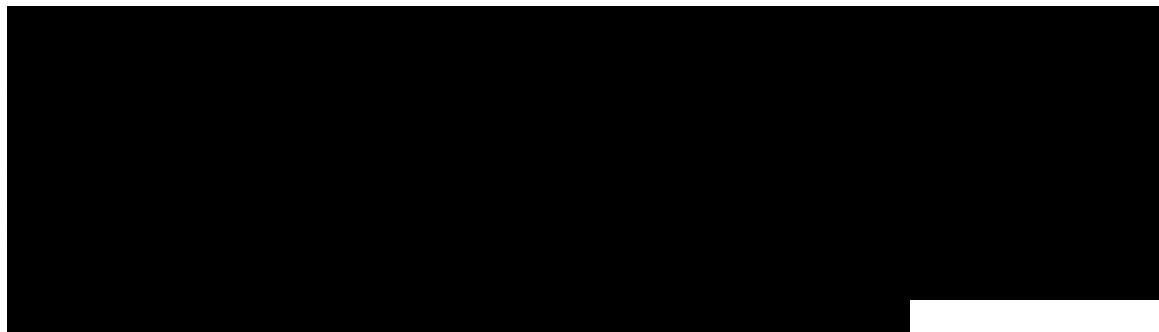
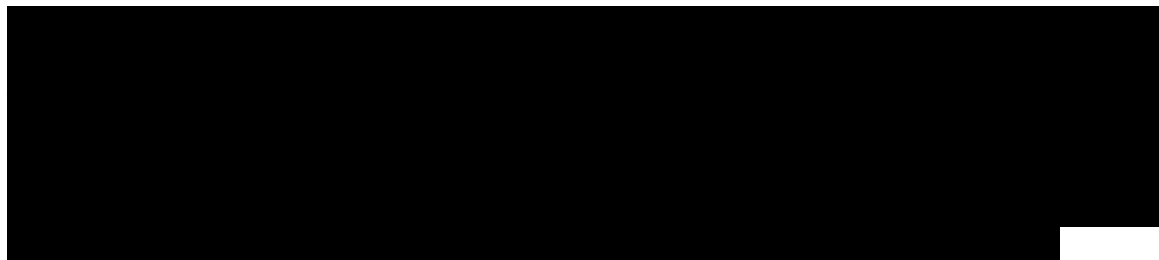
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]


4.1.2 Background of Pembrolizumab

4.1.2.1 Background

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda[®] (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475.

4.1.2.1.1 Pharmaceutical and Therapeutic Background

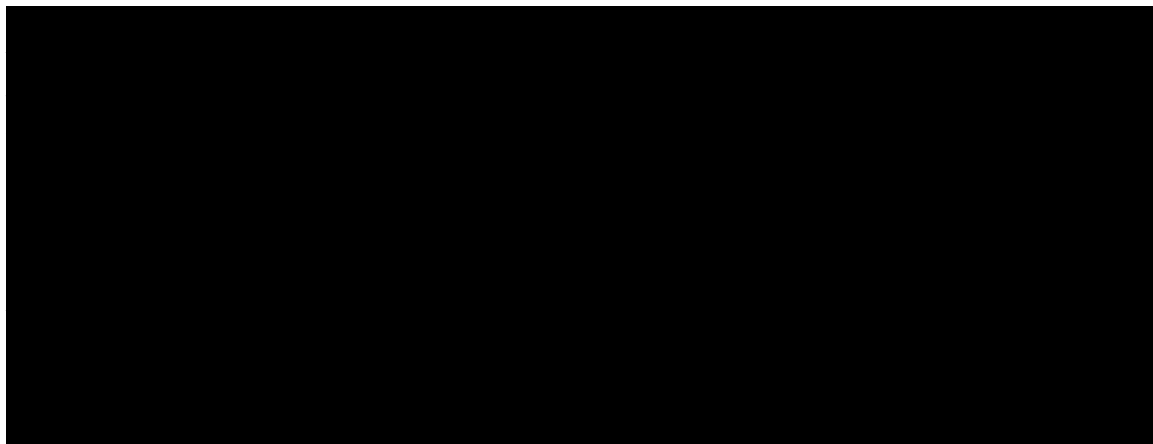
The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [Disis, 2010]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and

favorable prognosis in various malignancies. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺ effector T-cells/FoxP3⁺ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [Dudley et al., 2005; Hunder et al., 2008].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [Greenwald et al., 2005; Okazaki et al., 2001].

The structure of murine PD-1 has been resolved [Zhang et al., 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3 ζ), protein kinase C-theta (PKC θ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry et al., 2005; Francisco, 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in NSCLC.

4.1.2.1.1.1 Pre-clinical and Clinical Trials



[REDACTED]

4.1.2.1.1.2 Justification for Dose

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4.2 Rationale

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

5.0 METHODOLOGY

5.1 Study Enrollment and Withdrawal

5.1.1 Entry Criteria

[REDACTED]

[REDACTED]

5.1.1.2 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Type of Participant and Disease Characteristics

1. The participant (or legally acceptable representative if applicable) provides written informed consent for the study.
2.
 - a. Be ≥ 22 years of age on day of signing informed consent in the USA.
 - b. Be ≥ 18 years of age on day of signing informed consent out of the USA.

3. Have a histologically or cytologically confirmed diagnosis of stage III or metastatic NSCLC and not have an EGFR sensitizing (activating) mutation or an ALK translocation will be enrolled in this study.

Note: EGFR sensitizing mutations are those mutations that are amenable to treatment with TKIs including osimertinib, dacomitinib, erlotinib, gefitinib, or afatinib. Investigators must be able to produce the source documentation of the EGFR mutation and ALK translocation in all subjects with non-squamous histologies AND for subjects in whom testing is clinically recommended. If either an EGFR sensitizing mutation or ALK translocation is detected, additional information regarding the mutation status of the other molecule is not required.

Subjects with non-squamous histologies will not be randomized until EGFR mutation status and/or ALK translocation status is available in source documentation at the site.

4. Have a PD-L1 positive (TPS $\geq$ 1%) tumor as determined by immunohistochemistry at a local laboratory.

Note: Only PD-L1 positive (TPS $\geq$ 1%) subjects will be randomized. If the tumor specimen is not evaluable for PD-L1 expression by the local laboratory, the subject is not eligible to participate in the study.

TPS will be determined by utilizing PD-L1 IHC 22C3 antibody-based kit

5. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:
 - a. Not a woman of childbearing potential (WOCBP)
 - b. A WOCBP who agrees to use two adequate barrier methods or a barrier method plus a hormonal method during the treatment period and for at least 120 days after the last dose of pembrolizumab. Such methods of contraception, or true abstinence from heterosexual activity, when this is in line with the preferred and usual lifestyle of the subject, are required (periodic abstinence, e.g., calendar, ovulation, symptothermal, post-ovulation methods and withdrawal are not acceptable methods of contraception).
6. Have evaluable (measurable or non-measurable) disease in the thorax per RECIST 1.1 as assessed by the local site investigator/radiology.
7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.
8. Have a life expectancy of at least 3 months.
9. Have not received prior treatments for their metastatic or current advanced NSCLC. Palliative treatment is allowed (e.g. radiation therapy without a curative intent, stent

placement or ablative procedures for airway patency, analgesia, steroids). Subjects who received adjuvant, neoadjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease are eligible if the therapy was completed at least 12 months prior to the development of metastatic or current advanced disease.

10. Have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 10 days prior to randomization.

[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] [REDACTED] [REDACTED]
[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	

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5.1.1.3 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Disease Characteristics

1. Has known active or untreated CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to randomization.
2. Has an EGFR sensitizing mutation and/or ALK translocation.

Note: For subjects enrolled who are known to have a tumor of predominantly squamous histology, molecular testing for EGFR mutation and ALK translocation will not be required as this is not standard of care and is not part of current diagnostic guidelines.

3. The subject's NSCLC can be treated with curative intent with either surgical resection and/or chemoradiation.
4. Is expected to require any other form of systemic or localized antineoplastic therapy while on study (including maintenance therapy with another agent for NSCLC, radiation therapy, and/or surgical resection).

Medical Conditions

Pregnancy Exclusion:

5. A WOCBP who has a positive urine pregnancy test (within 72 hours) prior to randomization. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

6. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137) in the past 12 months prior to the development of metastatic or current advanced disease.
7. Has received prior systemic anti-cancer therapy including investigational agents for metastatic or current advanced NSCLC. However, subjects who received adjuvant, neoadjuvant chemotherapy or chemoradiotherapy with curative intent for non-metastatic disease are eligible if the therapy was completed at least 12 months prior to the development of metastatic or current advanced disease.
8. Has received prior radiotherapy for NSCLC. Palliative radiotherapy is allowed. Participants receiving palliative radiotherapy must have recovered from all

radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is required for palliative radiation.

9. Has received radiation therapy to the lung that is >30Gy within 6 months of randomization.
10. Had any major surgery within 3 weeks of randomization or has not recovered from any effects of any major surgery.
11. Has received a live vaccine within 30 days prior to the randomization. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

Prior/Concurrent Clinical Study Experience

12. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to randomization.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Diagnostic assessments

13. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the randomization.
14. Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, superficial bladder cancer, or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

15. Has severe hypersensitivity ($\geq$ Grade 3) to pembrolizumab and/or any of its excipients.
16. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

17. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
18. Has an active infection requiring systemic therapy.
19. Has a known history of human immunodeficiency virus (HIV), Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

20. Has implantable electronic medical devices in the torso (thorax, abdomen or pelvis).
21. Has 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).
22. Has 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.
23. Has history of cerebrovascular accident (CVA) within 6 months prior to signing the informed consent or that is not stable.
24. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
25. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
26. Is unable to follow the protocol for medical, psychological, familial, geographic or other reasons, or comply with the requirements of the study or to provide consent.

Other Exclusions

27. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through last TTFIELDS treatment or 120 days after the last dose of pembrolizumab, the later of the two.
28. Has had an allogeneic tissue/solid organ transplant.

29. Has been admitted to an institution by administrative or court order.

5.1.2 Participant Withdrawal or Termination

[REDACTED]

[REDACTED]

5.1.2.1 Discontinuation of Study Treatments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.2 Study Treatments

The treatment(s) to be used in this study are outlined below:

Pembrolizumab (MK-3475)

Dosage Formulation	[REDACTED]	[REDACTED]	[REDACTED]	Regimen/ Treatment Period
Solution for infusion	[REDACTED]	[REDACTED]	[REDACTED]	Day 1 of each 21-day cycle

[REDACTED]

[REDACTED]

[REDACTED]

TTFields (NovoTTF-200T)

Frequency	[REDACTED]	[REDACTED]	[REDACTED]	Regimen/ Treatment Period
150 kHz	[REDACTED]	[REDACTED]	[REDACTED]	Continuous, 18 hours per day (monthly average)

5.2.1 Study Device

5.2.1.1 The NovoTTF-200T System (investigational device)

5.2.1.1.1 The NovoTTF-200T System and its Intended Use

The NovoTTF-200T System is an investigational medical device delivering 150 kHz TTFields to the thorax for the treatment of adult patients with PD-L1 positive (TPS $\geq$ 1%), previously untreated metastatic or current advanced NSCLC, concomitant with pembrolizumab. It is intended to be used for at least 18 hours per day on a monthly average and exclusively by patients in a clinical study.

The device is a portable, battery operated system which delivers TTFields at 150 kHz to the thorax by means of insulated [REDACTED]

5.2.1.1.2 The Manufacturer of the NovoTTF-200T System

The NovoTTF-200T System is manufactured by Novocure GmbH Park 6/Platz 10, CH-6039 Root D4 Switzerland.

[illegible]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]
■	[REDACTED]	[REDACTED]

[REDACTED]

5.2.1.2 Training Subjects on Using the NovoTTF-200T System

[REDACTED]

5.2.1.3 Appearance, Labeling and Storage Conditions

See the Investigator Brochure and patient's User Manual.

5.2.1.4 Applying TTFields using the NovoTTF-200T System

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED] to thorax
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

5.2.1.5 Duration of Therapy

TTFields at 150 kHz to the thorax will be continuous [REDACTED]

[REDACTED]

[REDACTED]

5.2.1.6 Skin Care Guidelines

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.2.1.7 Device Specific Considerations

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.2.1.8 Risks of NovoTTF-200T System

[REDACTED]

[REDACTED]

5.2.2 Pembrolizumab

5.2.2.1 Dose Selection/Modification

5.2.2.1.1 Dose Selection

The rationale for selection of dose to be used in this study is provided in Section 4.0 – Background & Rationale. Details on the dose calculation, preparation and administration are provided in the Pharmacy Manual.

5.2.2.1.2 Dose Modification (Escalation/Titration/Other)

5.2.2.1.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy,

skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids [REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. [REDACTED]

[REDACTED]

--

5.2.2.1.4 Other allowed dose interruption for pembrolizumab

[REDACTED]

5.2.3 Timing of Dose Administration

[REDACTED]

5.2.4 Study Blinding/Masking

This study is being conducted as an open-label study (i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each patient is randomized and treatment is assigned).

5.3 Randomization

[REDACTED]

[REDACTED]

Arm I: Subjects receive TTFields using the NovoTTF-200T device concomitant with pembrolizumab.

Arm II: Subjects receive pembrolizumab.

5.4 Stratification

[REDACTED]

[REDACTED]

[REDACTED]

5.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy may be

required. The investigator should discuss any questions regarding this with the Sponsor Medical Monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5.6 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.0 STUDY FLOW CHART

6.1 Treatment Phase

[illegible]

27.

6.2 Crossover Phase

Only applicable for subjects in the control arm who have disease progression in the thorax and are clinically stable as defined in section 5.1.2.1. Subject may receive NovoTTF-200T treatment for up to 24 months and pembrolizumab for up to total of 35 treatments.

[illegible]



7.0 STUDY PROCEDURES

7.1 Study Procedures

The Study Flow Chart - Section 6.0 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below.

7.1.1 Administrative Procedures

7.1.1.1 Informed consent

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in the study as outlined in Section 14.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use,

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication,

[REDACTED]

7.1.1.5 Non-Small Cell Lung Cancer (NSCLC) Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain NSCLC disease details.

7.1.1.5.2 Prior Treatment

A previous treatment for NSCLC is an exclusion criterion for this study [REDACTED]

7.1.1.5.3 Subsequent Antineoplastic Therapy Status

The investigator or qualified designee will review all new antineoplastic therapy [REDACTED]

7.1.1.6 Assignment of Subject Number

All screened subjects will be given a unique subject number that will be used to identify the subject for all procedures that occur throughout the study. [REDACTED]

Specific details on the screening visit requirements (screening) are provided in Section 7.1.5.1.

7.1.1.7 Study Compliance

Pembrolizumab

NovoTTF-200T System

7.1.2 Clinical Procedures/Assessments

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 4 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

[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]	[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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.1.4 Other Procedures

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2 Adverse Events, Serious Adverse Events and Other Reportable Events

[REDACTED]

[REDACTED]

[REDACTED]

7.2.1 Definitions

7.2.1.1 Adverse Events (AE)

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 and whether anticipated or unanticipated. 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 the use of the investigational medical devices.

7.2.1.2 Serious Adverse Events (SAE)

An adverse event that led to any of the following criteria/outcomes is classified as serious:

- death,
- serious deterioration in health of the subject, user, or other persons as defined by one or more of the following:
 - a life-threatening illness or injury, or
 - a permanent impairment of a body structure or a body function including chronic diseases, 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.
- fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2.1.3 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. This includes ‘comparator’ if the comparator is a medical device.

7.2.1.4 Device Deficiency (DD)

Inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. This includes malfunctions, use error, or inadequacy in the information supplied by the manufacturer including labeling. This includes device deficiencies related to the investigational medical device or the comparator.

7.2.1.5 Serious Adverse Device Effect (SADE)

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

7.2.1.6 Serious Health Threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

7.2.1.7 Unanticipated Serious Adverse Device Effects (USADE)

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 assessment.

7.2.1.8 Unanticipated Adverse Device Effect (UADE)

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.

7.2.1.9 Suspected Adverse Reaction

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

7.2.1.10 Unexpected Adverse Event or Unexpected Adverse Reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.2.1.11 Serious Unexpected Suspected Adverse Reaction (SUSAR)

Adverse events that meet the following criteria:

- Suspected adverse reaction
- Serious
- Unexpected

7.2.1.12 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2.1.13 Treatment of Overdose

[REDACTED]

[REDACTED]

7.2.2 Adverse Event Collection and Reporting

The adverse event collection and reporting will be handled as required and in accordance with the applicable national regulations in all participating countries.

The investigator will record every adverse event and observed device deficiency, together with an assessment.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.2.3 Classification of an Adverse Event

7.2.3.1 Severity (grading) of Event

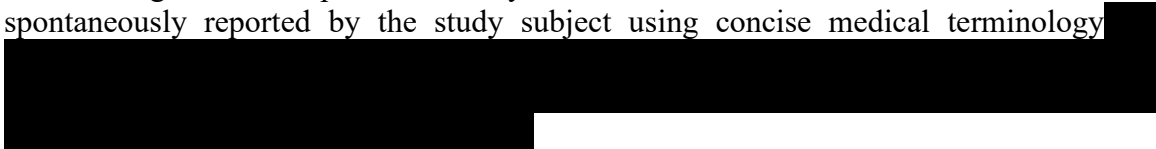
The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for assessing severity of adverse events. If the toxicity is not characterized adequately by the NCI toxicity scale, the investigator will use the adjectives MILD, MODERATE, SEVERE, LIFE-THREATENING and FATAL to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
MODERATE	Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)
SEVERE	Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or



7.2.4.1 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject using concise medical terminology



7.2.5 Reporting Procedures

7.2.5.1 Reportable Events

- Any SAE that has a causal relationship with the investigational device, the comparator or the investigation procedure or where such causal relationship is reasonably possible
 - 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
 - Any SUSAR
- 

7.2.5.2 Reporting Timelines

The Investigator is to report all SAEs, reportable events as defined in section 7.2.5.1 and ECIs immediately but not later than 1 business day after awareness of the event.

[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.0 CLINICAL MONITORING

[REDACTED] Study monitoring functions will be in compliance with recognized Good Clinical Practices, EN ISO14155, FDA's IDE guidance documents, and as outlined in 21 CFR § 812.43(d) and 21 CFR § 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: on-site visits and review of study documents and results. [REDACTED]

[REDACTED]

[REDACTED]

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this study. Full detail is in the Statistical Analysis Plan (SAP) (Section 9.2).

Study Design Overview	A pilot, randomized, open-label study evaluating PFS of Tumor Treating Fields (TTFields, 150 kHz) concomitant with pembrolizumab compared to PFS of pembrolizumab alone for first line treatment of advanced or metastatic non-small cell lung cancer (NSCLC)
Analysis Populations	Efficacy: Intent to Treat (ITT) and modified ITT (exploratory) Safety: All-Subjects-as-Treated (ASaT)
Primary Endpoint(s)	Progression-free survival (PFS) by RECIST 1.1 in subjects with TPS $\geq$ 1%, 1L metastatic/current advanced NSCLC
Secondary Endpoints	• Overall survival (OS) in subjects with TPS$\geq$1%, 1L metastatic/current advanced NSCLC. • Objective Response Rate (ORR) by RECIST 1.1 in subjects with TPS$\geq$1%, 1L metastatic/current advanced NSCLC. • Duration of response by RECIST 1.1 in subjects with TPS$\geq$1%, 1L metastatic/current advanced NSCLC. • Disease control rate at 18 weeks by RECIST 1.1 in subjects with TPS$\geq$1%, 1L metastatic/current advanced NSCLC. • Safety and tolerability profile of TTFields concomitant with Pembrolizumab in subjects with TPS $>$1%, 1L metastatic/current advanced NSCLC.
Exploratory Endpoints	[REDACTED] • [REDACTED]
Statistical Methods for Efficacy	The primary hypothesis will be evaluated by comparing the difference between PFS in the study population receiving treatment with NovoTTF-200T concomitant with pembrolizumab compared to pembrolizumab [REDACTED] [REDACTED]

Treatment Assignment	The participants will be randomized in a 1:1 ratio into one of the following treatment arms – Treatment Group – NovoTTF-200T concomitant with pembrolizumab Control Group – pembrolizumab
Statistical Methods for Safety Analyses	[REDACTED]
Interim analysis	[REDACTED]
Multiplicity	No multiplicity adjustment is planned in this pilot study.
Sample Size and Power	[REDACTED]

9.1.1 Efficacy Analyses

The intent to treat (ITT) populations in subjects with TPS $\geq$ 1% will serve as the primary populations for the analyses of efficacy data in this study. [REDACTED]

[REDACTED] The primary efficacy endpoint is progression-free survival (PFS) (i.e., time from randomization to documented progressive disease or death due to any cause, whichever occurs first) per RECIST 1.1. The secondary efficacy endpoints are overall survival (OS) (i.e., the time from randomization to death due to any cause), objective response rate (ORR) (i.e., proportion of subjects who have a partial or complete response to therapy) per RECIST 1.1, duration of response (DOR) (i.e., the time from documented initial response and subsequent disease progression) per RECIST 1.1, disease control rate (DCR) at (i.e., percentage of subjects with complete response, partial response and stable disease per RECIST 1.1). [REDACTED]

An outline of the analysis strategy for key efficacy endpoints is presented in Table 6.

Table 6 Analysis Strategy for Key Efficacy Endpoints

Endpoint (Description, Time Point)	Statistical Method	[REDACTED]
Primary		
PFS	Testing: Log rank test p value Estimation: Kaplan-Meier	[REDACTED]
Secondary		
OS	Testing: Survival plots and descriptive statistics Estimation: Kaplan-Meier	[REDACTED]
DOR		
ORR	Testing: Descriptive statistics	[REDACTED]
DCR		

9.1.2 Safety Analyses

[REDACTED]



9.1.3 Multiplicity Adjustment

No multiplicity adjustment is planned in this pilot study.

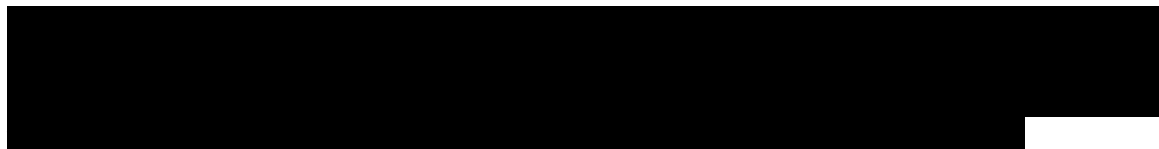
9.1.4 Power and Sample Size

The primary objective of this study is to test the null hypothesis (H0) that the PFS of each treatment arm is the same vs. the alternative hypothesis (H1) that the PFS of each treatment arm is not the same i.e.,

H0: $PFS_A \leq PFS_B$

H1: $PFS_A > PFS_B$

where PFS_A is the Kaplan-Meier (KM) PFS curve of the TTFelds + Pembrolizumab arm and PFS_B is the KM PFS curve of the Pembrolizumab arm.



[REDACTED]

9.1.5 Subgroup Analysis

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.1.6 Interim Analysis

One interim analysis for futility is planned in this study. [REDACTED]

[REDACTED]

[REDACTED]

9.2 Statistical Analysis Plan

9.2.1 Responsibility for Analyses

[REDACTED]

9.2.2 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

9.2.3 Analysis Endpoints

9.2.3.1 Efficacy Endpoints

Primary

Progression-Free Survival

Progression-free survival (PFS) is defined as the time from randomization to the first documented disease progression per RECIST 1.1 assessed by investigator or death due to any cause, whichever occurs first. For analysis of PFS, subjects will be censored at the last subject follow-up visit date that they are last known to be alive and progression-free (also if withdrawn or lost to follow-up) or at study closeout if they are still progression-free.

Secondary

Overall Survival

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the analysis will be censored at the date of the last follow-up.

Objective Response Rate

Objective response rate (ORR) is defined as the proportion of the subjects in the analysis population who have a confirmed complete response (CR) or partial response (PR) per RECIST 1.1 assessed by investigator.

Duration of response

Duration of response is defined as the time from documented initial response and subsequent disease progression per RECIST 1.1 assessed by investigator.

Disease control rate

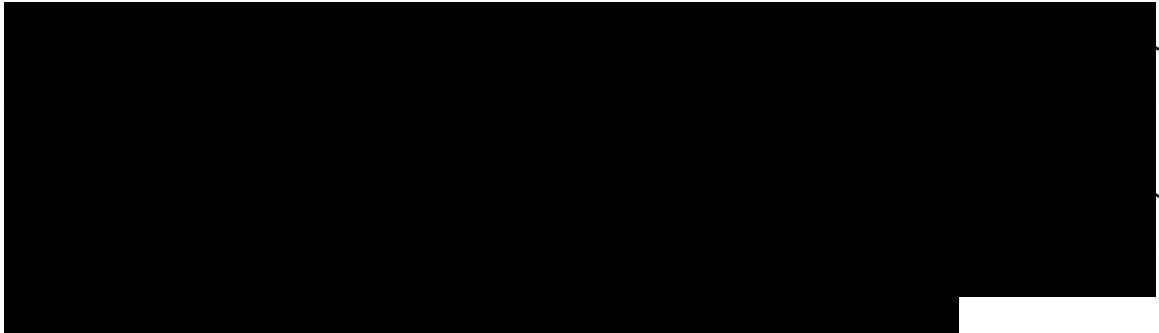
Disease control rate is defined as the percentage of subjects with complete response, partial response and stable disease per RECIST 1.1 assessed by investigator.

Exploratory

[REDACTED]

9.2.3.2 Safety Endpoints

[REDACTED]



9.2.4 Analysis Populations

9.2.4.1 Efficacy Analysis Population

The primary efficacy analysis will be carried out in the ITT population (i.e. all randomized patients, excluding patients enrolled prior to design change to a randomized controlled study).

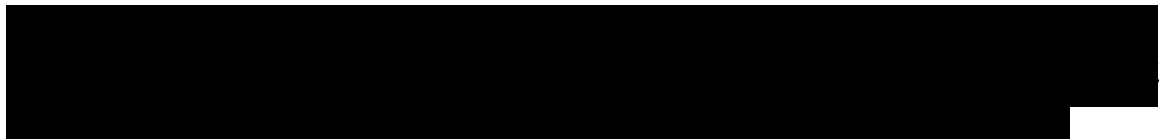


9.2.4.2 Safety Analysis Population



10.0 STUDY DEVICE ACCOUNTABILITY





11.0 STUDY DRUG LABELING, PACKAGING, STORAGE AND RETURN

For additional details refer to pembrolizumab Pharmacy Manual.

11.1 Study Drug

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of pembrolizumab in accordance with the protocol and any applicable laws and regulations.



11.2 Packaging and Labeling Information

Pembrolizumab will be affixed with a clinical label in accordance with regulatory requirements.



11.3 Study Drug Disclosure

The study is open-label; therefore, the subject, the study site personnel, the Sponsor and/or designee are not blinded. The product identification (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

11.4 Storage and Handling Requirements

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of pembrolizumab must be recorded by an authorized person at the study site.

Study drug may not be used for any purpose other than that stated in the protocol.

11.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the study drug received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the study.

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

11.6 Standard Policies

Study site personnel will have access to a central electronic system to allocate subjects and to manage the distribution of study drug.

12.0 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, recorded data from automated instruments, magnetic media, x-rays, and participant files and records kept at laboratories or other departments involved in the clinical study. It is acceptable to use CRFs as source documents.

It is not acceptable for the CRF to be the only record of a subject's participation in the study. This is to ensure that anyone who would access the subject medical record has adequate knowledge that the subject is participating in a clinical study.

For all subjects enrolled in the study, site staff will promptly complete and allow Novocure and/or its designees' access to all CRFs required for the study in the form supplied by the Sponsor or its designees. Site staff will not be required to disclose information in CRFs which would permit identification of a subject enrolled in, or a candidate for, the study. CRFs will be provided to Novocure or its designees in an electronic medium specified by Novocure or its designees. At the request of Novocure or its designees, sites will promptly correct any errors and/or omissions to the CRFs for the study and will make available to the Sponsor and/or its designees the corrected CRFs and supporting records for further verification. Investigator agrees to sign/e-sign a statement in each subject's study records or CRF attesting to his/her review of the CRF and verifying that the information included on such form is accurate and includes the treatment, care, and events surrounding such subject's involvement in the study.

13.0 QUALITY ASSURANCE AND QUALITY CONTROL

QC procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all study related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

All protocol amendments will be submitted to relevant ECs, IRBs, FDA and other Competent Authorities as needed when any revision is made to the original protocol or subsequent version of the protocol that significantly affect the safety of subjects and/or any change is made that significantly affects the scope of investigation or scientific quality of the study.

Amended protocol will be reviewed, approved and documented by the same method in which the original protocol was reviewed and approved. Once the amended protocol and all associated documents are reviewed and approved, the protocol number and effective date will be changed on the title page. The final approved amended protocol will be distributed to participating investigators at each site.

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]

14.0 ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6, ISO 14155 and/or local regulations, whichever provides most protection to human subjects.

14.2 Institutional Review Board /Ethics Committee

The protocol, informed consent forms, recruitment materials, and all participant materials will be submitted to the IRB/EC for review and/or approval, as applicable to local requirements



14.3 Informed Consent Process

14.3.1 Consent Forms Provided to Participants

Consent forms describing in detail the study device, study drug, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting administering study device.

No vulnerable population will be included in this study.

14.3.2 Consent Procedures and Documentation

Prior to carrying out any protocol-specific procedures, investigators or designated staff will fully explain the details of the protocol, study procedures, and the aspects of subject privacy concerning research specific information. In addition to signing the IRB/EC Informed Consent, all subject must sign the Research Authorization component of the informed consent form where applicable. The Research Authorization requires a separate signature from the subject. The original signed documents will become part of the subject's medical record, and each subject will receive a copy of the signed documents. All subjects must provide written informed consent prior to registration and treatment.

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

- a) The Principal Investigator or his/her authorized designee conducts the informed consent process
- b) All aspects of the clinical investigation that are relevant to the subject's decision to participate will be included
- c) Any coercion or undue improper influence on, or inducement of, the subject to participate will be avoided
- d) The study does not waive or appear to waive the subject's legal rights
- e) Native non-technical language that is understandable to the subject will be used
- f) Ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation will be used

- g) Personally dated signatures of the subject and the Principal Investigator or an authorized designee responsible for conducting the informed consent process will be included in the informed consent form
- h) The subject will be provided with a copy of the signed and dated informed consent form and any other written information
- i) Important new information will be provided to new and existing subjects throughout the clinical investigation

Subjects that are unable to provide consent by their own will not be included as well as patients treated under emergencies circumstances.

Informed consent will comply with ENISO 14155, 21 CFR 50 and other regional and national laws as applicable.

14.4 Participant and Data Confidentiality

It is the responsibility of the Research Staff to ensure that protocol subjects have received the site's Notice of Privacy Practices, as applicable. If the subject has not already done so, personnel of the relevant participating site must try to obtain acknowledgment before the subject participates in this study. The site's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB/EC and Privacy Board.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor and its agents. 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 or representatives of the IRB/EC/competent authority may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the participants in this study. The clinical study site will permit access to such records.

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/EC and Institutional regulations. The DSS will keep the subject's contact information in order to provide technical support services to the subject throughout the study period.

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, CROs and Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived in a certified storage place.

15.0 DATA HANDLING AND RECORD KEEPING

15.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site PI. 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. Black or blue ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, initial and date the change and enter reason for correction. Do not erase, overwrite, or use correction fluid or tape on the original.

Data reported in the Electronic Case Report Form (eCRF) derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official study record.

Clinical data (including AEs, concomitant medications, and expected adverse event data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system. The data system will include password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

15.2 Study Records Retention

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

[REDACTED]

15.3 Protocol Deviations

[REDACTED]

[REDACTED]

15.4 Publication and Data Sharing 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. The study will be registered at www.clinicaltrials.gov. The data collected during this study are confidential and proprietary to Novocure

16.0 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

17.0 LIST OF REFERENCES

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18.0 APPENDICES

18.1 ECOG Performance Status

Grade	Description
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.
* As published in Am J Clin Oncol: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55. Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.	

18.2 Common Terminology Criteria for Adverse Events V5.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for adverse event reporting

(https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf).

18.3 Response Evaluation Criteria in Solid Tumors (RECIST) V1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1 will be used in this study for patient management. CT is the required imaging technique in this study. Details are provided in the Image Acquisition Guidelines.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

18.4 Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (see Table 4 and Figure 3). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to $\geq 20\%$ and ≥ 5 mm from nadir
 - Note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
 - For target lesions, worsening is a further increase in the sum of diameters of ≥ 5 mm, compared to any prior iUPD time point
 - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the “unequivocal” standard of RECIST 1.1
 - For new lesions, worsening is any of these:
 - An increase in the new lesion sum of diameters by ≥ 5 mm from a prior iUPD time point
 - Visible growth of new non-target lesions
 - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule.

The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is “reset”. This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 7.1.2.5.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
 - Sum of diameters reaches the PD threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudo-progression.
- Non-target lesions
 - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.

- If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
 - New lesions appear for the first time
 - Additional new lesions appear
 - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
 - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.

18.5 Clinical Practice Guidelines: Optimizing the Transducer Array Layout in TTFields-treated Patients (thoracic malignancies)

19.0 INVESTIGATOR SIGNATURE PAGE

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

_____	_____	_____
PI Name	Signature	Date

*Electronic Sponsor's signatures are available in the signature manifest on the last page of the protocol.