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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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This supplementary material has been corrected. The corrected version first appeared at thelancet.com/oncology on May 28, 2024.

Supplementary Appendix

Supplemental methods....2
Supplementary tables....3
Table S1: Principal investigators and activated trial sites....3
Table S2: Study inclusion and exclusion criteria....10
Table S3: Grading for Tumor Treating Fields (TTFields) device-related skin adverse events....12
Table S4: Discontinuations of active participation....13
Table S5: Treatments received by patients following progression on study treatment....14
Table S6: Multivariable analysis of overall survival using a Cox proportional hazards regression model....15
Table S7. All grade 3 to 5 adverse events....16
Table S8. Serious adverse events....23
Table S9 Therapy-related serious adverse events....27
Table S10. TTFields device-related adverse events....29
Supplementary figures....30
Figure S1: The Tumor Treating Fields (TTFields) medical device used in thoracic cancer....30
Figure S2: Study design and major protocol amendment....31
Figure S3: Tumor Treating Fields array layouts....32
Figure S4: Overall survival in patients with squamous and non-squamous disease....33
Figure S5: Progression-free survival in patients receiving an ICI or docetaxel....34
Figure S6: Health-related quality of life Global Health Status scores....35
REFERENCES....36
Clinical Study Protocol....37
Statistical Analysis Plan....111

Supplemental methods

Follow-up visits

Follow-up visits were conducted every 6 weeks (± 1 week) for radiological assessment of disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria for patients receiving docetaxel, or immune-related (ir)RECIST for patients receiving an immune checkpoint inhibitor. Visits also included computed tomography, positron emission tomography, or magnetic resonance imaging scans, review of Tumor Treating Fields (TTFields) therapy usage time, adverse event reporting, physical examination, and laboratory testing. After 1 year of follow-up, imaging examinations were performed once every 12 weeks. Further follow-up to monitor survival was carried out every 4 weeks (± 1 week) during a visit to the study centre or telephone call. After progression in the thorax and/or liver, additional follow-up visits took place 30, 60, and 100 days (all ± 1 week) after disease progression.

Concomitant medication

During treatment, a high potency topical steroid (eg, clobetasol) or antibiotic ointment could be prescribed and applied by the patient/caregiver (after removing the arrays and cleaning skin with baby oil and medical alcohol) if skin irritation/abrasion occurred with TTFields therapy.

Supplementary tables

Table S1: Principal investigators and activated trial sites

Country	Site name	Location	Principal Investigator
Austria	Ordensklinikum Linz Krankenhaus der Elisabethinen Linz GmbH	Linz	Michael Schumacher
Austria	Medical University Salzburg, State Hospital, University hospital for internal medicine III / PMU	Salzburg	Richard Greil
Belgium	Jules Bordet Institute	Brussels	Thierry Berghmans
Belgium	Clinic André Renard André Renard Clinic and Polyclinic Herstal	Herstal	Faycal Bali
Belgium	Clinic André Renard André Renard Clinic and Polyclinic Herstal	Herstal	Lionel Bosquee
Belgium	Clinic André Renard André Renard Clinic and Polyclinic Herstal	Herstal	Frederique Bustin
Belgium	Hospital AZ Sint Maarten	Mechelen	Marc Lambrechts
Bulgaria	Complex Oncology Center	Plovdiv	Ivan Tonev
Canada	McGill University Health Centre	Montreal, QC	Scott Owen
Canada	CHUS/CIUSSS	Sherbrooke, QC	Nicole Bouchard
Canada	Allan Blair Cancer Center	Regina, SK	Mussawar, Iqbal
China	Beijing Cancer Hospital	Beijing, BJ	Jun Zhao
China	Sun Yat-sen University Cancer Center (SYSUCC)	Guangzhou, GD	Li Zhang
China	Affiliated Cancer Hospital and Institute of Guangzhou Medical University	Guangzhou, GD	Yanfang Zheng
China	Henan Provincial People's Hospital	Zhengzhou, HA	Shundong Cang
China	Henan Cancer Hospital	Zhengzhou, HA	Yanqiu Zhao
China	PKUCare Luzhong Hospital	Zibo, SD	Xiaohua Chen
China	Sir Run Run Shaw Hospital, Zhejiang University School of Medicine	Hangzhou, ZJ	Yong Fang
China	Zhejiang Cancer Hospital	Hangzhou, ZJ	Yun Fan
Croatia	University Hospital Centre Zagreb	Zagreb	Miroslav Samarzija
Czech Republic	Vítkovice Hospital	Ostrava-Poruba	Jaromir Roubec
Czech Republic	Pneumo-Oncology Clinic, Thomayer Hospital	Prague	Libor Havel

Czech Republic	Department of Oncology, General University Hospital in Prague	Prague	Lubos Petruzelka
France	Institut Bergonié – Centre Régional de Lutte Contre le Cancer	Bordeaux	Sophie Cousin
France	Institut Bergonié – Centre Régional de Lutte Contre le Cancer	Bordeaux	Sylvestre Le-Moulec
France	Groupe Hospitalier Bretagne Sud	Lorient	Regine Lamy
France	Groupe Hospitalier Bretagne Sud	Lorient	Jacky Crequit
France	Service de Pneumologie, CHU Caremeau	Nîmes	Sylvie Van-Hulst
France	AH-HP Hôpital Saint Louis	Paris	Bonnet Clement
France	AH-HP Hôpital Saint Louis	Paris	Ludovic Doucet
France	AH-HP Hôpital Saint Louis	Paris	Safae Terrisse
France	Service de Pneumologie, Centre Hospitalier de Saint-Quentin	Saint-Quentin	Charles Dayen
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HK	Queen Mary Hospital	Hong Kong	Victor Lee
Hungary	Tolna County Balassa Janos Hospital	Szekszard	Yousuf Al-Farhat
Hungary	Jasz-Nagykun-Szolnok County Hospital	Szolnok, Jasz-Nagykun-Szolnok	Tibor Csoszi
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Israel	Tel Aviv Sourasky (Ichilov) Medical Center	Tel Aviv	Ofer Merimsky
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Italy	IRCCS Istituto Romagnolo per lo Studio dei Tumori “Dino Amadori” (IRST)	Meldola	Angelo Delmonte
Italy	Saronno Hospital	Saronno	Claudio Verusio
Netherlands	Ziekenhuis St Jansdal	Harderwijk	Lisenka Boom
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USA	Beverly Hills Cancer Center	Beverly Hills, CA	Michael Castro
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USA	Dignity Health Cancer Institute	Carmichael, CA	Sonia Reichert
USA	California Cancer Associates for Research and Excellence	Fresno, CA	Steven Hager
USA	Providence Medical Foundation (formerly St. Joseph Heritage Healthcare)	Fullerton, CA	David Park
USA	Banner MD Anderson Cancer Center at North Colorado Medical Center	Greeley, CA	Lin Hao
USA	Memorial Care Health System	Orange County, CA	Linda Chan
USA	Redlands Community Hospital Center for Cancer Care	Redlands, CA	Emad Ibrahim
USA	Compassionate Cancer Care Medical Group	Riverside, CA	Brian Choi
USA	Sutter Cancer Center	Sacramento, CA	Deepti Behl
USA	Innovative Clinical Research Institute/American Institute of Research	Whittier, CA	Rafael Ortiz
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USA	Orlando Health	Orlando, FL	Jennifer Tseng
USA	NeuroOncology Center, Florida Hospital Medical Group	Orlando, FL	Herbert Newton
USA	Boca Raton Clinical Research	Plantation, FL	Jason Tache
USA	University of Illinois Cancer Center	Chicago, IL	Lawrence Feldman
USA	Illinois Cancer Care, P.C.	Peoria, IL	Gregory Gerstner
USA	Simmons Cancer Institute, Southern Illinois University School of Medicine	Springfield, IL	Krishna Rao
USA	Cancer Care Group, P.C.	Indianapolis, IN	Michael Eaton
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USA	Tulane Cancer Centre	New Orleans, LA	Kendra Harris
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USA	Christus Cancer Treatment Center	Shreveport, LA	Neelima Chintapalli
USA	Tufts Medical Center	Boston, MA	Lori Pai
USA	Beth Israel Deaconess Medical Center	Boston, MA	Deepa Rangachari
USA	University of Maryland Medical Center	Baltimore, MD	Ranee Mehra
USA	University of Maryland Medical Center	Baltimore, MD	Christian Rolfo
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USA	St. Joseph Hospital – The Center for Cancer Prevention and Treatment	Ann Arbor, MI	Samir Narayan
USA	Barbara Ann Karmanos Cancer Hospital	Detroit, MI	Michael Dominello
USA	Detroit Clinical Research Center	Farmington Hills, MI	Craig Gordon
USA	Detroit Clinical Research Center	Lansing, MI	Tallat Mahmood
USA	Regions Cancer Care Center	St. Paul, MN	Arkadiusz Dudek
USA	Saint Luke's Cancer Specialists	Kansas City, MO	Vinay Gupta
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USA	CHI Health Nebraska (Alegent)	Omaha, NE	Hadi Zahra
USA	University of Nebraska Medical Center	Omaha, NE	Alissa Marr
USA	New Jersey Center for Cancer Research	Brick, NJ	Apurv Agrawal
USA	Presbyterian Cancer Center	Albuquerque, NM	Shantan Reddy
USA	OptumCare Cancer Care	Las Vegas, NV	Khawaja Jahangir
USA	Renow Regional Medical Center	Reno, NV	Garrett Green
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USA	Northern Westchester Hospital	Mt. Kisco, NY	Alfred Tinger
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USA	Stony Brook University	Stony Brook, NY	Roger Keresztes
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USA	Toledo Clinic Cancer Center	Toledo, OH	Rex Mowat
USA	Vita Medical Associates	Bethlehem, PA	Anna Niewiarowska
USA	Geisinger Cancer Services,	Danville, PA	Rajiv Panikkar
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USA	Texas Oncology – Paris	Paris, TX	Sucharu Prakash
USA	Texas Oncology – Plano West	Plano, TX	James Petrikas
USA	Huntsman Cancer Institute University of Utah	Salt Lake City, TX	Wallace Akerley
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Table S2: Study inclusion and exclusion criteria

Inclusion criteria
• Aged ≥22 years.
• Life expectancy 3 months or greater.
• Eastern Cooperative Oncology Group performance status of 0–2.
Histological or cytological diagnosis of squamous or non-squamous, inoperable, metastatic non-small cell lung cancer (NSCLC) made while on or after first platinum-based systemic therapy administered for advanced or metastatic disease. – Patients who developed metastatic disease within 6 months of completing adjuvant or neoadjuvant platinum-based chemotherapy (after surgery and/or radiation therapy) are also eligible. If longer than 6 months, then the patient must have also received platinum-based therapy in the advanced setting. – Platinum-based therapy must have been the most recent therapy prior to enrolment, aside from a maintenance therapy.
Able to operate the NovoTTF-200T device independently or with the help of a caregiver.
Provided signed informed consent.
Exclusion criteria
• Metastases to central nervous system (CNS) with clinical symptoms or evidence of new CNS metastases during screening. Note that patients with previously treated CNS metastases, that are stable and meet the following requirements are eligible: – Patients were neurologically returned to baseline (except for residual signs or symptoms related to CNS treatment). – Patients received no treatment (ie, surgery, radiotherapy, corticosteroid therapy) for CNS metastases during the screening period. – CNS lesions did not progress (by magnetic resonance imaging) within 14 days prior to randomisation. – There was no meningeal metastasis or spinal cord compression.
• Patients due to receive an immune checkpoint inhibitor had no contraindications to receive an immune checkpoint inhibitor.
• Patients due to receive docetaxel had no contraindications to receive docetaxel.
• Severe comorbidities: – Clinically significant (as determined by the investigator) haematological, hepatic, or renal dysfunction, defined as: Neutrophil count <1.5 x 10 9/L and platelet count <100 x 10 9/L; bilirubin >1.5 x upper limit of normal (ULN); aspartate transaminase and/or alanine transaminase > 2.5 x ULN or > 5 x ULN if patient has documented liver metastases; and serum creatinine >1.5 x ULN. – History of significant cardiovascular disease unless the disease is well controlled. Including: ▪ Second/third degree heart block. ▪ Significant ischaemia.

▪ Poorly controlled hypertension. ▪ Congestive heart failure of the New York Heart Association Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation, or dyspnoea). ▪ History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded. ▪ History of pericarditis. – History of interstitial lung disease. – A cerebrovascular accident within 6 months prior to randomisation or that is unstable. – Active infection or serious underlying medical condition that would impair the ability of the patient to receive study therapy. – History of any psychiatric condition that might impair understanding or compliance with the study or consent. – Any other malignancy requiring anti-tumour treatment in the past 3 years, excluding treated stage 1 prostate cancer, in situ cervical cancer, in situ breast cancer and non-melanomatous skin cancer
• Concurrent treatment with another experimental NSCLC treatment while in the study.
• Implanted electronic medical device (eg, pacemaker, defibrillator) in the upper torso.
• Known allergies to medical adhesives or hydrogel.
• Pregnancy or breast-feeding (patients with reproductive potential must use effective contraception methods throughout the entire study period, as determined by their investigator/gynaecologist).
• Admitted to an institution by administrative or court order.

Table S3: Grading for Tumor Treating Fields (TTFields) device-related skin adverse events

Grade 1 Asymptomatic or mild symptoms AND 1. No intervention required OR only topical treatment intervention indicated 2. Treatment interruption of <3 days may be required
Grade 2 Moderate symptoms AND Systemic therapy required OR event requiring interruption of TTFields for >3 days
Grade 3 Severe or medically significant but not immediately life threatening AND hospitalisation OR prolongation of existing hospitalisation indicated
Grade 4 Life threatening consequences AND urgent intervention indicated

Table S4: Discontinuations of active participation

	TTFields therapy with standard therapy	Standard therapy
No. patients randomised	137	139
Patients discontinued active participation	135 (98·5%)	135 (97·1%)
Progressive disease in thorax or liver	69 (50·4%)	72 (51·8%)
Death	10 (7·3%)	16 (11·5%%)
Patient request (excluding intolerable toxicity)	15 (10·9%)	7 (5·0%)
Withdrawal of consent	10 (7·3%)	10 (7·%2)
Adverse event/intolerable toxicity	10 (7·3%)	8 (5·8%)
Lack of compliance	3 (2·2%)	0
Other	18 (13·1%)	22 (15·8%)

Data are n (%). Standard therapy refers to an immune checkpoint inhibitor or docetaxel.

TTFields, Tumor Treating Fields.

Table S5: Treatments received by patients following progression on study treatment

	TTFields therapy with standard therapy	Standard therapy	TTFields therapy with an ICI	ICI	TTFields therapy with docetaxel	Docetaxel
Intention-to-treat population	137	139	66	68	71	71
Any systemic salvage therapy	41 (29·9%)	36 (25·9%)	18 (27·3%)	16 (23·5%)	23 (32·4%)	20 (28·2%)
Bevacizumab	0	4 (2·9%)	0	2 (2·9%)	0	2 (2·8%)
Carboplatin	7 (5·1%)	5 (3·6%)	4 (6·1%)	4 (5·9%)	3 (4·2%)	1 (1·4%)
Cisplatin	1 (0·7%)	1 (0·7%)	0	0	1 (1·4%)	1 (1·4%)
Crizotinib	0	2 (1·4%)	0	1 (1·5%)	0	1 (1·4%)
Docetaxel	15 (10·9%)	9 (6·5%)	11 (16·7%)	9 (13·2%)	4 (5·6%)	0
Erlotinib	0	1 (0·7%)	0	0	0	1 (1·4%)
Etoposide	1 (0·7%)	1 (0·7%)	0	0	1 (1·4%)	1 (1·4%)
Gemcitabine	12 (8·8%)	9 (6·5%)	3 (4·5%)	3 (4·4%)	9 (12·7%)	6 (8·5%)
Nab-paclitaxel	0	1 (0·7%)	0	1 (1·5%)	0	0
Nivolumab	3 (2·2%)	5 (3·6%)	2 (3·0%)	1 (1·5%)	1 (1·4%)	4 (5·6%)
Other	10 (7·3%)	15 (10·8%)	1 (1·5%)	8 (11·8%)	9 (12·7%)	7 (9·9%)
Paclitaxel	4 (2·9%)	1 (0·7%)	2 (3·0%)	1 (1·5%)	2 (2·8%)	0
Pembrolizumab	3 (2·2%)	1 (0·7%)	1 (1·5%)	0	2 (2·8%)	1 (1·4%)
Pemetrexed	3 (2·2%)	5 (3·6%)	1 (1·5%)	2 (2·9%)	2 (2·8%)	3 (4·2%)
Vinorelbine	4 (2·9%)	4 (2·9%)	0	1 (1·5%)	4 (5·6%)	3 (4·2%)

Data are n (%). Standard therapy refers to an ICI or docetaxel.

ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Table S6: Multivariable analysis of overall survival using a Cox proportional hazards regression model

Parameter	Parameter value	HR	95% lower CI	95% upper CI	Two-sided p-value
Study arm	TTFields therapy with standard therapy vs standard therapy	0·73	0·55	0·97	0·03
Standard treatment	ICI vs docetaxel	0·64	0·48	0·85	0·002
Histology	Non-squamous vs squamous	0·89	0·66	1·20	0·45
Region	East Asia vs ROW	0·69	0·35	1·34	0·27
Age	Years	1·00	0·98	1·01	0·64
Sex	Male vs female	0·83	0·61	1·13	0·25
ECOG PS	0 vs 1	1·04	0·75	1·44	0·80
PD-L1	≥1% vs <1%	0·80	0·55	1·16	0·23
Smoking history	No vs yes	0·76	0·49	1·16	0·20

Standard therapy refers to an ICI or docetaxel. CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed cell death ligand 1 tumour proportion score; ROW, rest of the world.

Table S7. All grade 3 to 5 adverse events

	TTFields therapy with an ICI (n=67)			ICI (n=66)			TTFields therapy with docetaxel (n=66)			Docetaxel (n=68)		
	Grade 3	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**Grade 5**
Any adverse event	29 (43·3%)	3 (4·5%)	5 (7·5%)	20 (30·3%)	6 (9·1%)	6 (9·1%)	22 (33·3%)	11 (16·7%)	8 (12·1%)	23 (33·8%)	16 (23·5%)	4 (5·9%)
Adverse events												
Blood and lymphatic system disorders												
Anaemia	4 (6·0%)	1 (1·5%)	0	2 (3·0%)	0	0	5 (7·6%)	0	0	9 (13·2%)	0	0
Leukopenia	1 (1·5%)	1 (1·5%)	0	0	2 (3·0%)	0	6 (9·1%)	10 (15·2%)	0	3 (4·4%)	14 (20·6%)	0
Febrile neutropenia	0	0	0	0	0	0	6 (9·1%)	0	0	3 (4·4%)	0	0
Thrombocytopenia	1 (1·5%)	0	0	0	0	0	2 (3·0%)	0	0	0	1 (1·5%)	0
Lymphopenia	2 (3·0%)	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Cardiac disorders												
Arrhythmia	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Myocardial infarction	0	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0
Pericardial effusion	1 (1·5%)	0	0	0	0	0	0	1 (1·5%)	0	0	0	0
Cardiac failure	0	0	0	0	0	0	1 (1·5%)	1 (1·5%)	0	0	0	0
Ventricular dysfunction	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Cardiac tamponade	0	0	0	0	0	0	0	1 (1·5%)	0	0	0	0
Coronary artery disease	0	0	0	0	0	0	0	0	1 (1·5%)	0	0	0
Endocrine disorders												
Thyroiditis	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Eye disorders												
Cataract	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0

Gastrointestinal disorders												
Diarrhoea	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Nausea	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Vomiting	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0	0	0	0
Mouth ulceration	0	0	0	0	0	0	2 (3·0%)	0	0	0	0	0
Colitis	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Rectal haemorrhage	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Ileus	1 (1·5%)	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Intestinal obstruction	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Intestinal perforation	0	0	1 (1·5%)	0	0	0	0	1 (1·5%)	0	0	0	0
Ascites	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Intestinal haemorrhage	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Esophagitis	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Pancreatic failure	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Pancreatitis	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
General disorders and administration site conditions												
Fatigue	2 (3·0%)	0	0	2 (3·0%)	0	0	3 (4·5%)	0	0	8 (11·8%)	0	0
Localised oedema	0	0	0	0	0	0	1 (1·5%)	0	0	2 (2·9%)	0	0
Pain	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0
Pyrexia	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
General physical health deterioration	1 (1·5%)	0	0	1 (1·5%)	1 (1·5%)	0	4 (6·1%)	0	0	0	0	0
Inflammation	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Euthanasia	0	0	0	0	0	0	0	0	0	0	0	1 (1·5%)

Multiple organ dysfunction syndrome	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Hepatobiliary disorders												
Cholelithiasis	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Liver disorder	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Cholangitis	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Cholecystitis	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Immune system disorders												
Drug hypersensitivity	0	0	0	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0
Infections and infestations												
Respiratory tract infection	2 (3·0%)	0	0	0	0	0	1 (1·5%)	0	1 (1·5%)	0	0	0
Pneumonia	4 (6·0%)	0	0	3 (4·5%)	2 (3·0%)	2 (3·0%)	9 (13·6%)	2 (3·0%)	0	7 (10·3%)	1 (1·5%)	0
Infection	0	0	0	0	0	0	2 (3·0%)	0	1 (1·5%)	0	0	0
Urinary tract infection	1 (1·5%)	0	0	1 (1·5%)	0	0	2 (3·0%)	0	0	0	0	0
Sepsis	0	1 (1·5%)	0	1 (1·5%)	1 (1·5%)	1 (1·5%)	0	3 (4·5%)	0	1 (1·5%)	1 (1·5%)	0
Herpes zoster	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Skin infection	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Abscess	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Gastroenteritis	0	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0
Bacteraemia	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Diverticulitis	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Encephalitis	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Pyelonephritis	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Pyopneumothorax	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0

Injury, poisoning and procedural complications												
Fracture	1 (1·5%)	0	0	0	0	0	0	1 (1·5%)	0	0	0	0
Investigations												
Hepatic enzyme increased	0	0	0	3 (4·5%)	0	0	0	0	0	1 (1·5%)	0	0
Weight decreased	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Blood bilirubin increased	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
C-reactive protein increased	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Forced expiratory volume decreased	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Metabolism and nutrition disorders												
Anorexia	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Hypoalbuminemia	0	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0
Hypokalaemia	1 (1·5%)	0	0	0	0	0	2 (3·0%)	0	0	0	0	0
Hyponatremia	0	1 (1·5%)	0	3 (4·5%)	0	0	2 (3·0%)	0	0	2 (2·9%)	0	0
Hypercalcemia	1 (1·5%)	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0	0	0	0
Dehydration	0	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0
Hyperglycaemia	2 (3·0%)	0	0	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0
Hyperkalaemia	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Hypertriglyceridaemia	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Refeeding syndrome	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Musculoskeletal and connective tissue disorders												
Musculoskeletal pain	1 (1·5%)	0	0	3 (4·5%)	0	0	3 (4·5%)	0	0	2 (2·9%)	0	0
Muscular weakness	0	0	0	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0

Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)												
Tumour pain	0	0	0	1 (1·5%)	0	0	2 (3·0%)	0	0	1 (1·5%)	0	0
Metastases to central nervous system	0	0	0	0	0	0	3 (4·5%)	0	0	2 (2·9%)	0	0
Metastases to bone	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Malignant ascites	0	0	0	0	0	0	0	0	0	1 (1.5%)	0	0
Adenocarcinoma of colon	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Metastases to skin	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Nervous system disorders												
Neuropathy peripheral	1 (1·5%)	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0	3 (4·4%)	0	0
Syncope	0	0	0	0	0	0	1 (1·5%)	0	0	2 (2·9%)	0	0
Brain oedema	0	0	0	0	0	0	0	0	0	0	1 (1·5%)	0
Cerebrovascular accident	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Dysarthria	1 (1·5%)	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Neurotoxicity	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Nervous system disorder	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Paresis	0	1 (1·5%)	0	0	0	0	0	0	0	1 (1·5%)	0	0
Seizure	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Neurologic neglect syndrome	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Cauda equina syndrome	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Motor dysfunction	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Psychiatric disorders												
Anxiety	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0

Confusional state	0	0	0	0	0	0	1 (1·5%)	0	0	0	1 (1·5%)	0
Renal and urinary disorders												
Micturition disorder	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders												
Dyspnoea	2 (3·0%)	0	0	1 (1·5%)	0	0	7 (10·6%)	0	0	2 (2·9%)	1 (1·5%)	0
Cough	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Pulmonary haemorrhage	2 (3·0%)	0	2 (3·0%)	0	0	0	0	0	3 (4·5%)	1 (1·5%)	0	0
Pleural effusion	1 (1·5%)	0	0	2 (3·0%)	0	0	2 (3·0%)	0	0	5 (7·4%)	0	0
Pneumonitis	1 (1·5%)	0	0	2 (3·0%)	0	0	0	1 (1·5%)	0	1 (1·5%)	0	0
Pulmonary embolism	1 (1·5%)	0	1 (1·5%)	2 (3·0%)	1 (1·5%)	0	3 (4·5%)	0	0	1 (1·5%)	0	0
Respiratory failure	0	0	1 (1·5%)	0	1 (1·5%)	2 (3·0%)	2 (3·0%)	0	2 (3·0%)	0	0	3 (4·4%)
Chronic obstructive pulmonary disease	1 (1·5%)	0	0	1 (1·5%)	0	1 (1·5%)	1 (1·5%)	0	0	1 (1·5%)	0	0
Hypoxia	0	0	0	0	0	0	1 (1·5%)	0	0	2 (2·9%)	0	0
Atelectasis	1 (1·5%)	0	0	0	0	0	0	0	0	2 (2·9%)	0	0
Bronchial obstruction	0	0	0	0	0	0	0	0	0	0	2 (2·9%)	0
Interstitial lung disease	0	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Bronchopleural fistula	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Oesophagobronchial fistula	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders												
Dermatitis	1 (1·5%)	0	0	0	0	0	2 (3·0%)	0	0	0	0	0
Alopecia	0	0	0	0	0	0	0	0	0	1 (1·5%)	0	0
Pruritus	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0

Rash	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Rash maculo-papular	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Skin ulcer	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0
Erythema	0	0	0	1 (1.5%)	0	0	0	0	0	0	0	0
Vascular disorders												
Hypertension	0	0	0	0	0	0	3 (4·5%)	0	0	0	0	0
Thrombosis	0	0	0	0	0	0	0	0	0	0	1 (1·5%)	0
Embolism	0	0	0	1 (1·5%)	0	0	1 (1·5%)	0	0	0	0	0
Deep vein thrombosis	1 (1·5%)	0	0	1 (1·5%)	0	0	0	0	0	0	0	0
Peripheral arterial occlusive disease	1 (1·5%)	0	0	0	0	0	0	0	0	0	0	0
Thromboembolic event	0	0	0	0	0	0	1 (1·5%)	0	0	0	0	0

Data is n (%). Adverse events were compiled from the safety population. In the population assigned to receive TTFields with docetaxel, one patient received TTFields with an ICI, and one received an ICI alone. In the population assigned to receive an ICI, one patient received docetaxel.

ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Table S8. Serious adverse events

Preferred term	TTFields with standard therapy (n=133)	Standard therapy (n=134)	TTFields therapy with an ICI (n=67)	ICI (n=66)	TTFields therapy with docetaxel (n=66)	Docetaxel (n=68)
Any serious adverse event	70 (52·6%)	51 (38·1%)	34 (50·7%)	23 (34·8%)	36 (54·5%)	28 (41·2%)
Adverse events						
Blood and lymphatic system disorders	**10 (7·5%)**	**9 (6·7%)**	**2 (3·0%)**	**0**	**8 (12·1%)**	**9 (13·2%)**
Febrile neutropenia	6 (4·5%)	2 (1·5%)	0	0	6 (9·1%)	2 (2·9%)
Leukopenia	2 (1·5%)	6 (4·5%)	0	0	2 (3·0%)	6 (8·8%)
Anaemia	2 (1·5%)	2 (1·5%)	2 (3·0%)	0	0	2 (2·9%)
Thrombocytopenia	0	1 (0·7%)	0	0	0	1 (1·5%)
Cardiac disorders	**6 (4·5%)**	**4 (3·0%)**	**1 (1·5%)**	**1 (1·5%)**	**5 (7·6%)**	**3 (4·4%)**
Arrhythmia	2 (1·5%)	2 (1·5%)	0	1 (1·5%)	2 (3·0%)	1 (1·5%)
Myocardial infarction	1 (0·8%)	1 (0·7%)	0	0	1 (1·5%)	1 (1·5%)
Pericardial effusion	2 (1·5%)	0	1 (1·5%)	0	1 (1·5%)	0
Cardiac failure	1 (0·8%)	0	0	0	1 (1·5%)	0
Cardiac tamponade	1 (0·8%)	0	0	0	1 (1·5%)	0
Coronary artery disease	1 (0·8%)	0	0	0	1 (1·5%)	0
Ventricular dysfunction	0	1 (0·7%)	0	0	0	1 (1·5%)
Endocrine disorders	**1 (0·8%)**	**0**	**1 (1·5%)**	**0**	**0**	**0**
Thyroiditis	1 (0·8%)	0	1 (1·5%)	0	0	0
Gastrointestinal disorders	**8 (6·0%)**	**5 (3·7%)**	**2 (3·0%)**	**2 (3·0%)**	**6 (9·1%)**	**3 (4·4%)**
Ileus	1 (0.8%)	1 (0.7%)	1 (1.5%)	0	0	1 (1.5%)
Intestinal perforation	2 (1.5%)	0	1 (1.5%)	0	1 (1.5%)	0
Vomiting	1 (0.8%)	1 (0.7%)	0	1 (1.5%)	1 (1.5%)	0
Colitis	1 (0.8%)	0	0	0	1 (1.5%)	0
Diarrhoea	1 (0.8%)	0	0	0	1 (1.5%)	0
Intestinal haemorrhage	0	1 (0.7%)	0	0	0	1 (1.5%)
Intestinal obstruction	0	1 (0.7%)	0	0	0	1 (1.5%)
Oesophagitis	1 (0.8%)	0	0	0	1 (1.5%)	0

Pancreatitis	0	1 (0.7%)	0	1 (1.5%)	0	0
Rectal haemorrhage	1 (0.8%)	0	0	0	1 (1.5%)	0
General disorders and administration site conditions	**6 (4·5%)**	**5 (3·7%)**	**2 (3·0%)**	**3 (4·5%)**	**4 (6·1%)**	**2 (2·9%)**
General physical health deterioration	2 (1.5%)	2 (1.5%)	1 (1.5%)	2 (3.0%)	1 (1.5%)	0
Pyrexia	1 (0.8%)	1 (0.7%)	0	1 (1.5%)	1 (1.5%)	0
Euthanasia	0	1 (0.7%)	0	0	0	1 (1.5%)
Fatigue	0	1 (0.7%)	0	0	0	1 (1.5%)
Localised oedema	1 (0.8%)	0	1 (1.5%)	0	0	0
Multiple organ dysfunction syndrome	1 (0.8%)	0	0	0	1 (1.5%)	0
Pain	1 (0.8%)	0	0	0	1 (1.5%)	0
Hepatobiliary disorders	**0**	**1 (0·7%)**	**0**	**0**	**0**	**1 (1·5%)**
Cholangitis	0	1 (0·7%)	0	0	0	1 (1·5%)
Infections and infestations	**27 (20·3%)**	**22 (16·4%)**	**9 (13·4%)**	**12 (18·2%)**	**18 (27·3%)**	**10 (14·7%)**
Pneumonia	14 (10·5%)	16 (11·9%)	4 (6·0%)	8 (12·1%)	10 (15·2%)	8 (11·8%)
Sepsis	4 (3·0%)	5 (3·7%)	1 (1·5%)	3 (4·5%)	3 (4·5%)	2 (2·9%)
Gastroenteritis	2 (1·5%)	1 (0·7%)	0	0	2 (3·0%)	1 (1·5%)
Infection	3 (2·3%)	0	0	0	3 (4·5%)	0
Urinary tract infection	2 (1·5%)	1 (0·7%)	1 (1·5%)	1 (1·5%)	1 (1·5%)	0
Respiratory tract infection	2 (1·5%)	0	1 (1·5%)	0	1 (1·5%)	0
Abscess	0	1 (0·7%)	0	1 (1·5%)	0	0
Bacteraemia	1 (0·8%)	0	0	0	1 (1·5%)	0
Diverticulitis	1 (0·8%)	0	0	0	1 (1·5%)	0
Encephalitis	1 (0·8%)	0	1 (1·5%)	0	0	0
Herpes zoster	0	1 (0·7%)	0	1 (1·5%)	0	0
Pyelonephritis	1 (0·8%)	0	1 (1·5%)	0	0	0
Pyopneumothorax	0	1 (0·7%)	0	0	0	1 (1·5%)
Skin infection	1 (0·8%)	0	0	0	1 (1·5%)	0
Injury, poisoning and procedural complications	**3 (2·3%)**	**0**	**2 (3·0%)**	**0**	**1 (1·5%)**	**0**
Fracture	3 (2·3%)	0	2 (3·0%)	0	1 (1·5%)	0
Investigations	**1 (0·8%)**	**1 (0·7%)**	**0**	**1 (1·5%)**	**1 (1·5%)**	**0**

C-reactive protein increased	1 (0.8%)	0	0	0	1 (1.5%)	0
Hepatic enzyme increased	0	1 (0.7%)	0	1 (1.5%)	0	0
Metabolism and nutrition disorders	**3 (2·3%)**	**1 (0·7%)**	**1 (1·5%)**	**0**	**2 (3·0%)**	**1 (1·5%)**
Hyponatraemia	1 (0·8%)	1 (0·7%)	1 (1·5%)	0	0	1 (1·5%)
Hypercalcaemia	1 (0·8%)	0	0	0	1 (1·5%)	0
Hypokalaemia	1 (0·8%)	0	0	0	1 (1·5%)	0
Musculoskeletal and connective tissue disorders	**0**	**1 (0·7%)**	**0**	**1 (1·5%)**	**0**	**0**
Musculoskeletal pain	0	1 (0·7%)	0	1 (1·5%)	0	0
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	**7 (5·3%)**	**2 (1·5%)**	**2 (3·0%)**	**0**	**5 (7·6%)**	**2 (2·9%)**
Metastases to central nervous system	3 (2·3%)	2 (1·5%)	0	0	3 (4·5%)	2 (2·9%)
Metastases to bone	2 (1·5%)	0	1 (1·5%)	0	1 (1·5%)	0
Adenocarcinoma of colon	1 (0·8%)	0	1 (1·5%)	0	0	0
Tumour pain	1 (0·8%)	0	0	0	1 (1·5%)	0
Nervous system disorders	**6 (4·5%)**	**4 (3·0%)**	**5 (7·5%)**	**2 (3·0%)**	**1 (1·5%)**	**2 (2·9%)**
Headache	2 (1·5%)	0	2 (3·0%)	0	0	0
Brain oedema	0	1 (0·7%)	0	0	0	1 (1·5%)
Cerebrovascular accident	1 (0·8%)	0	1 (1·5%)	0	0	0
Dysarthria	1 (0·8%)	0	1 (1·5%)	0	0	0
Nervous system disorder	0	1 (0·7%)	0	1 (1·5%)	0	0
Neuropathy peripheral	0	1 (0·7%)	0	1 (1·5%)	0	0
Neurotoxicity	1 (0·8%)	0	1 (1·5%)	0	0	0
Paresis	1 (0·8%)	0	1 (1·5%)	0	0	0
Seizure	1 (0·8%)	0	0	0	1 (1·5%)	0
Syncope	0	1 (0·7%)	0	0	0	1 (1·5%)
Renal and urinary disorders	**1 (0·8%)**	**1 (0·7%)**	**0**	**0**	**1 (1·5%)**	**1 (1·5%)**
Acute kidney injury	1 (0·8%)	0	0	0	1 (1·5%)	0
Micturition disorder	0	1 (0·7%)	0	0	0	1 (1·5%)
Respiratory, thoracic, and mediastinal disorders	**25 (18·8%)**	**21 (15·7%)**	**15 (22·4%)**	**10 (15·2%)**	**10 (15·2%)**	**11 (6·2%)**
Respiratory failure	4 (3·0%)	6 (4·5%)	1 (1·5%)	3 (4·5%)	3 (4·5%)	3 (4·4%)
Pleural effusion	4 (3·0%)	5 (3·7%)	3 (4·5%)	2 (3·0%)	1 (1·5%)	3 (4·4%)

Pulmonary haemorrhage	7 (5·3%)	2 (1·5%)	4 (6·0%)	1 (1·5%)	3 (4·5%)	1 (1·5%)
Pulmonary embolism	2 (1·5%)	4 (3·0%)	2 (3·0%)	3 (4·5%)	0	1 (1·5%)
Chronic obstructive pulmonary disease	3 (2·3%)	2 (1·5%)	2 (3·0%)	1 (1·5%)	1 (1·5%)	1 (1·5%)
Pneumonitis	2 (1·5%)	3 (2·2%)	1 (1·5%)	2 (3·0%)	1 (1·5%)	1 (1·5%)
Dyspnoea	3 (2·3%)	0	1 (1·5%)	0	2 (3·0%)	0
Atelectasis	1 (0·8%)	1 (0·7%)	1 (1·5%)	0	0	1 (1·5%)
Bronchial obstruction	0	2 (1·5%)	0	0	0	2 (2·9%)
Bronchopleural fistula	1 (0·8%)	0	1 (1·5%)	0	0	0
Hypoxia	1 (0·8%)	0	0	0	1 (1·5%)	0
Interstitial lung disease	0	1 (0·7%)	0	1 (1·5%)	0	0
Oesophagobronchial fistula	1 (0·8%)	0	1 (1·5%)	0	0	0
Skin and subcutaneous tissue disorders	**2 (1·5%)**	**0**	**0**	**0**	**2 (3·0%)**	**0**
Dermatitis	2 (1·5%)	0	0	0	2 (3·0%)	0
Skin ulcer	1 (0·8%)	0	0	0	1 (1·5%)	0
Vascular disorders	**1 (0·8%)**	**0**	**1 (1·5%)**	**0**	**0**	**0**
Peripheral arterial occlusive disease	1 (0·8%)	0	1 (1·5%)	0	0	0

Data is n (%). Adverse events were compiled from the safety population. In the population assigned to receive TTFields with docetaxel, one patient received TTFields with an ICI, and one received an ICI alone. In the population assigned to receive an ICI, one patient received docetaxel.

ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Table S9 Therapy-related serious adverse events

	Standard therapy-related		TTFields therapy-related
Preferred term	**TTFields with standard therapy (n=133)**	**Standard therapy (n=134)**	**TTFields with standard therapy (n=133)**
Any therapy-related serious adverse event	25 (18·8%)	20 (14·9%)	4 (3·0%)
Therapy-related serious adverse events			
Blood and lymphatic system disorders			
Febrile neutropenia	6 (4·5%)	2 (1·5%)	0
Leukopenia	2 (1·5%)	6 (4·5%)	0
Anaemia	0	2 (1·5%)	0
Thrombocytopenia	0	1 (0·7%)	0
Endocrine disorders			
Thyroiditis	1 (0·8%)	0	0
Gastrointestinal disorders			
Colitis	1 (0·8%)	0	0
Diarrhoea	1 (0·8%)	0	0
Intestinal haemorrhage	0	1 (0·7%)	0
Intestinal perforation	1 (0·8%)	0	0
Oesophagitis	1 (0·8%)	0	0
Pancreatitis	0	1 (0·7%)	0
Vomiting	1 (0·8%)	0	0
General disorders and administration site conditions			
General physical health deterioration	1 (0·8%)	1 (0·7%)	0
Pyrexia	1 (0·8%)	0	0
Infections and infestations			
Pneumonia	5 (3.8%)	7 (5·2%)	0
Infection	2 (1.5%)	0	0
Bacteraemia	1 (0·8%)	0	0
Encephalitis	1 (0·8%)	0	0
Herpes zoster	0	1 (0·7%)	0
Skin infection	0	0	1 (0·8%)
Investigations			
Hepatic enzyme increased	0	1 (0·7%)	0
Nervous system disorders			
Cerebrovascular accident	1 (0·8%)	0	0

Headache	1 (0·8%)	0	0
Neuropathy peripheral	0	1 (0·7%)	0
Neurotoxicity	1 (0·8%)	0	0
Syncope	0	1 (0·7%)	0
Renal and urinary disorders			
Acute kidney injury	1 (0·8%)	0	0
Micturition disorder	0	1 (0·7%)	0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion	0	2 (1·5%)	0
Pneumonitis	0	2 (1·5%)	0
Bronchopleural fistula	1 (0·8%)	0	1 (0·8%)
Chronic obstructive pulmonary disease	1 (0·8%)	0	0
Interstitial lung disease	0	1 (0·7%)	0
Pulmonary haemorrhage	1 (0·8%)	0	0
Respiratory failure	1 (0·8%)	0	0
Skin and subcutaneous tissue disorders			
Dermatitis	0	0	2 (1·5%)
Skin ulcer	0	0	1 (0·8%)

Data are n (%). Serious adverse events were compiled from the safety population. In the population assigned to receive TTFields with systemic therapy, one patient received systemic therapy alone. Standard therapy refers to an immune checkpoint inhibitor or docetaxel.

Table S10. TTFields device-related adverse events

Preferred term	TTFields therapy with an ICI (n=67)		TTFields therapy with docetaxel (n=66)	
	All grades	Grade 3*	All grades	Grade 3*
Any TTFields device-related adverse event	49 (73·1%)	3 (4·5%)	46 (69·7%)	5 (7·6%)
Any serious TTFields device-related adverse event	1 (1·5%)		3 (4·5%)	
TTFields device-related adverse event leading to device discontinuation	8 (11·9%)		11 (16·7%)	
TTFields device-related adverse event leading to death	0		0	
TTFields device-related adverse events†				
General disorders and administration site conditions				
Pain	2 (3·0%)	1 (1·5%)	1 (1·5%)	0
Infections and infestations				
Skin infection	0	0	3 (4·5%)	1 (1·5%)
Respiratory, thoracic, and mediastinal disorders				
Bronchopleural fistula	1 (1·5%)	1 (1·5%)	0	0
Skin and subcutaneous tissue disorders				
Dermatitis	31 (46·3%)	1 (1·5%)	24 (36·4%)	2 (3·0%)
Pruritus	10 (14·9%)	0	7 (10·6%)	1 (1·5%)
Rash	8 (11·9%)	0	4 (6·1%)	0
Skin ulcer	7 (10·4%)	0	5 (7·6%)	1 (1·5%)
Maculo-papular rash	2 (3·0%)	0	7 (10·6%)	0
Erythema	2 (3·0%)	0	5 (7·6%)	0

Data is n (%). Adverse events are compiled from the safety population. In the population assigned to receive TTFields with docetaxel, one patient received TTFields with an ICI, and one received an ICI alone.

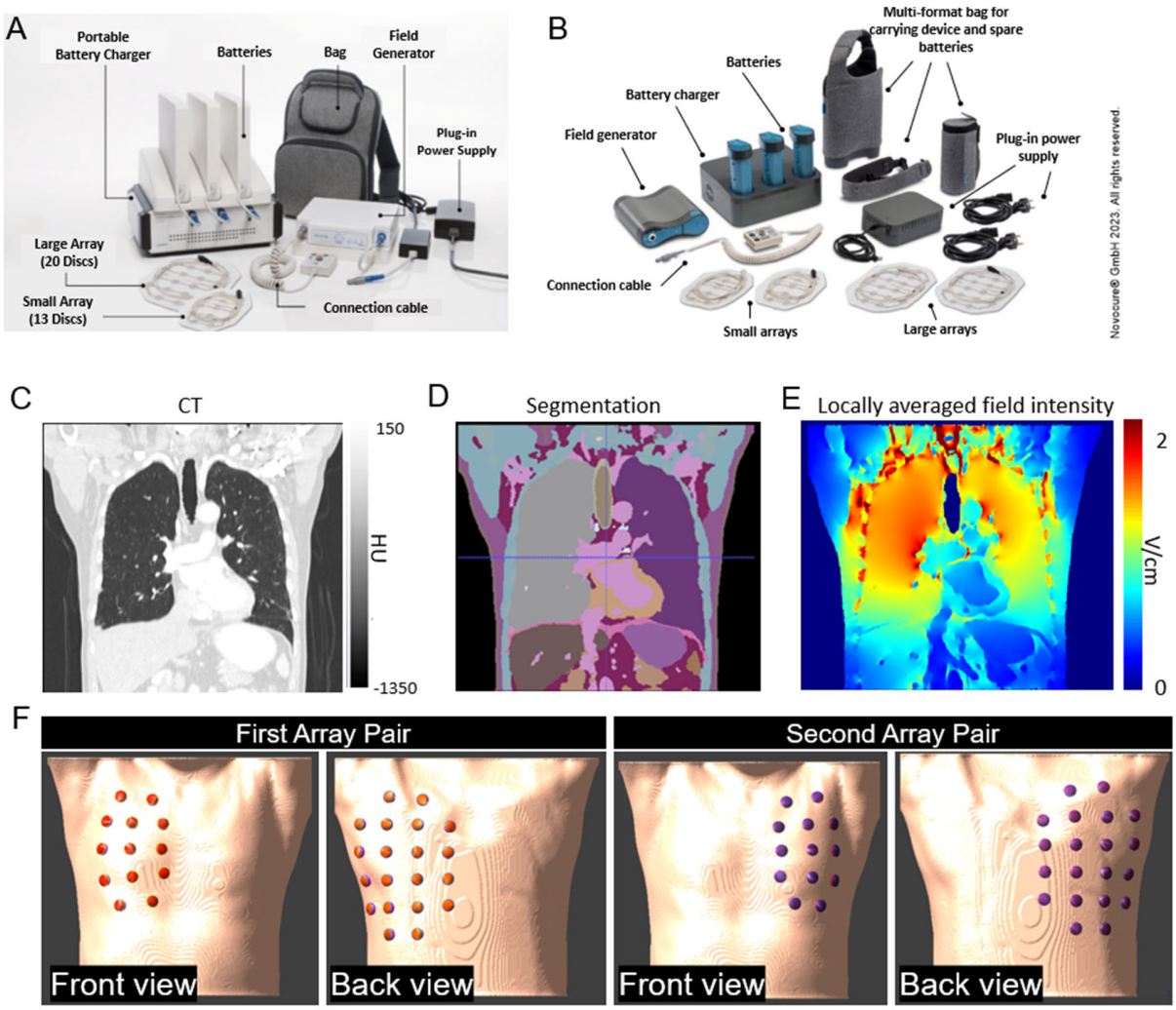
*There were no TTFields device -related grade 4 or 5 adverse events.

†5% of patients in any group and all grade 3 to 5 adverse events.

ICI, immune checkpoint inhibitor; TTFields, Tumor Treating Fields.

Supplementary figures

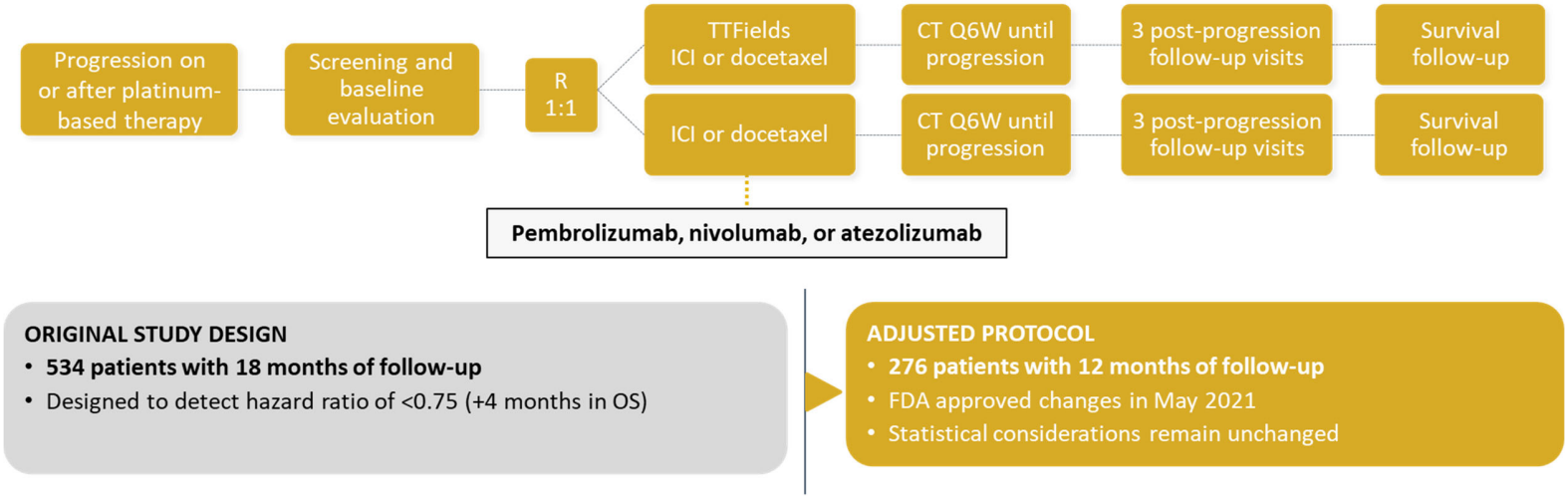
Figure S1: The Tumor Treating Fields (TTFields) medical device used in thoracic cancer



(A & B) components of the wearable first-generation (NovoTTF-100L) and second-generation (NovoTTF-200T) devices that generate and deliver TTFields. The lighter weight (1·2 kg vs 2·7 kg) NovoTTF-200T device was introduced during the course of patient enrolment, and patients were eligible to use either device.[1,2] (C) a representative CT scan of the upper thoracic region of an individual with non-small cell lung cancer, (D) segmentation of the upper thoracic region, (E) simulated locally averaged field intensity and distribution (V/cm) with 2.6A p2p normalised current and array layouts as shown in (F). Other array layouts are shown in figure S3. A & B Reused with permission from © 2023 Novocure GmbH-all rights reserved. C–F © 2023 Novocure GmbH-all rights reserved.

CT, computed tomography; HU, Hounsfield unit.

Figure S2: Study design and major protocol amendment

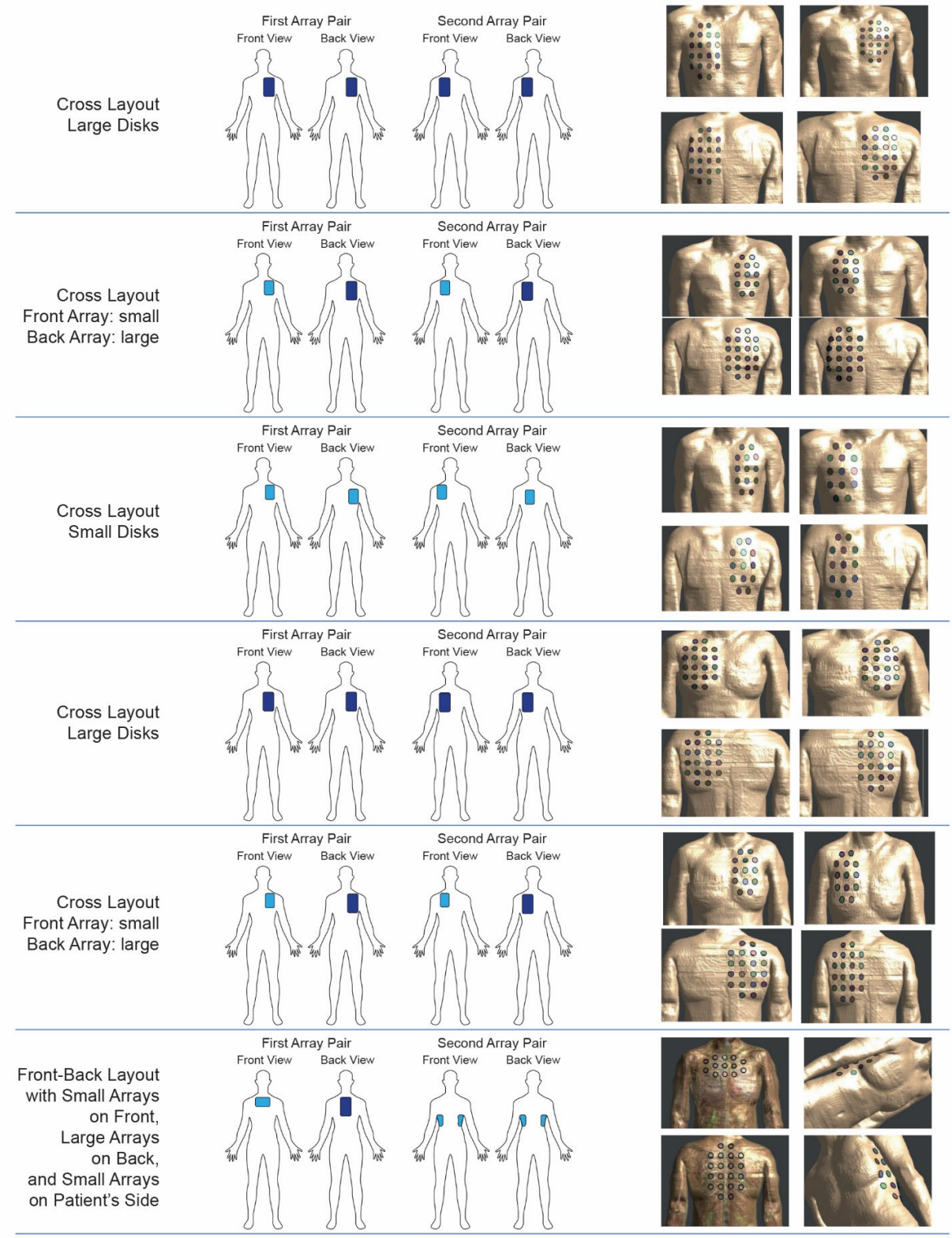


The protocol originally assigned patients to the NovoTTF-100L system but was updated (October 5, 2020) to allow use of the smaller and lighter second-generation NovoTTF-200T system. Six patients (4%) switched devices and received TTFields therapy with the NovoTTF-200T system (ICI subgroup: n=3; docetaxel subgroup: n=3).

Following prespecified annual review of safety and overall survival data by the Data Monitoring Committee March 31, 2021), the committee recommended that study endpoints could be analysed using a reduced sample size of 276 patients and 12-month follow-up.

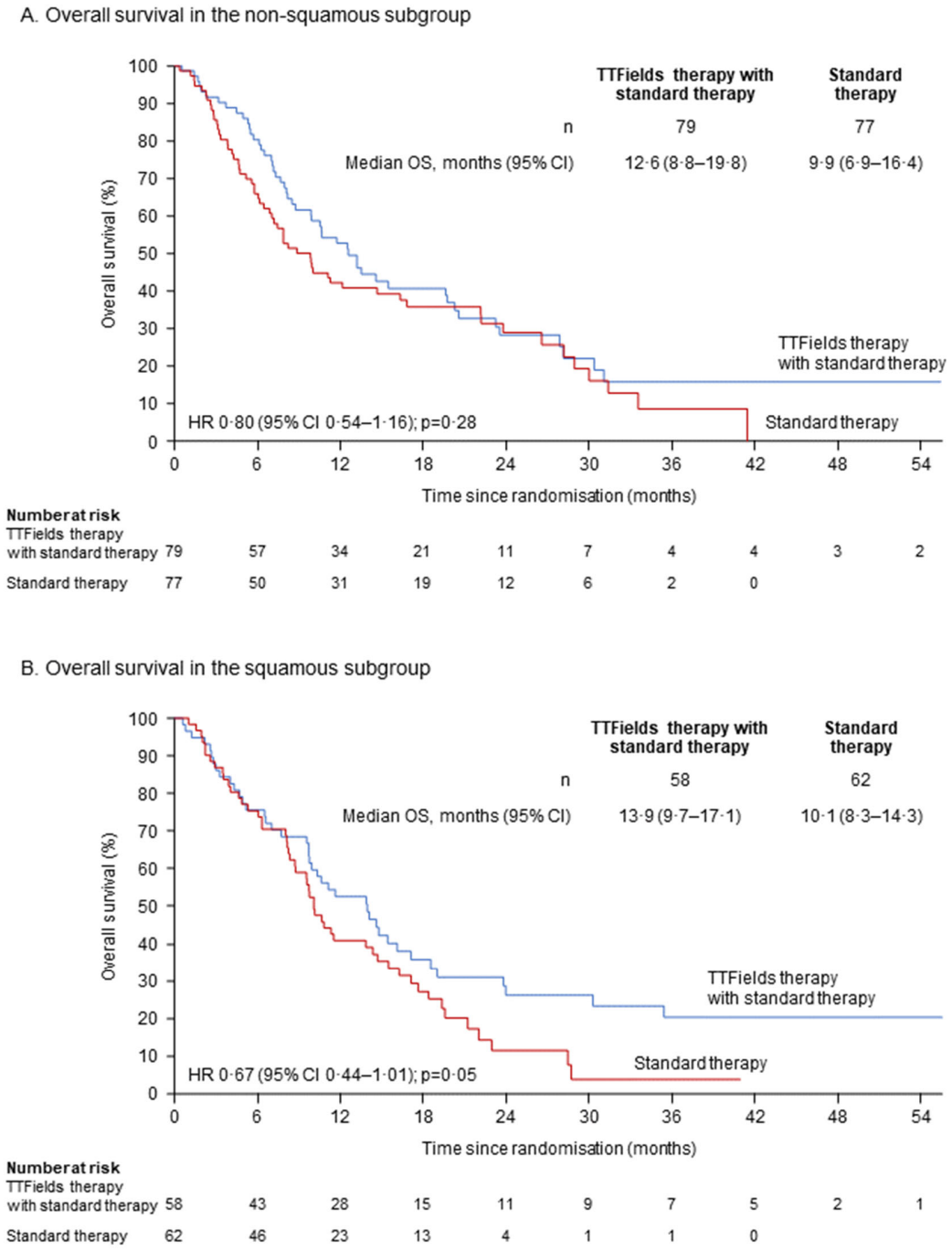
CT, computed tomography; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor, OS, overall survival; Q6W, every 6 weeks; R, randomisation; TTFields, Tumor Treating Fields.

Figure S3: Tumor Treating Fields array layouts



Large arrays are in dark blue, and small arrays in light blue.

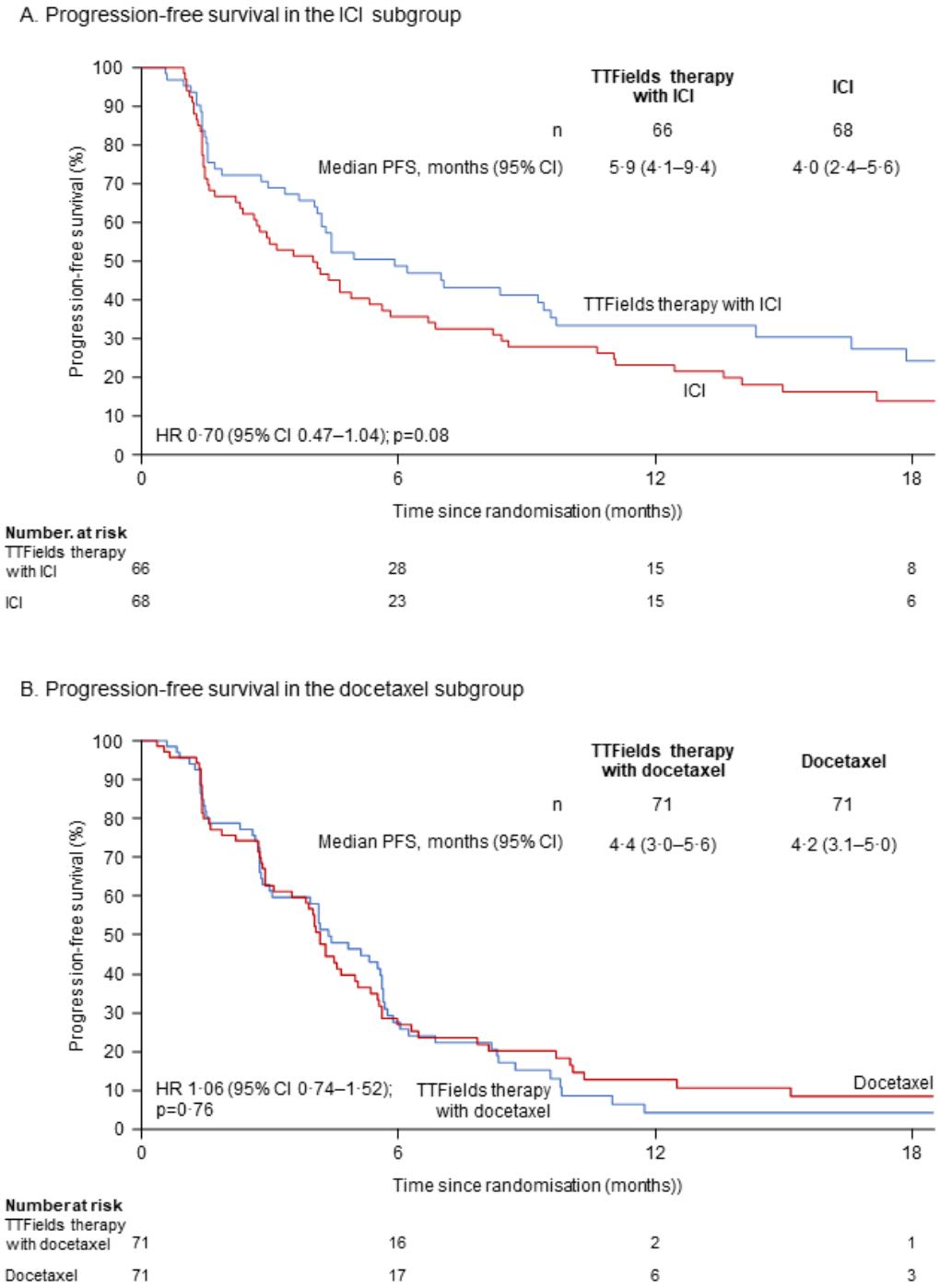
Figure S4: Overall survival in patients with squamous and non-squamous disease



Standard therapy refers to an immune checkpoint inhibitor or docetaxel.

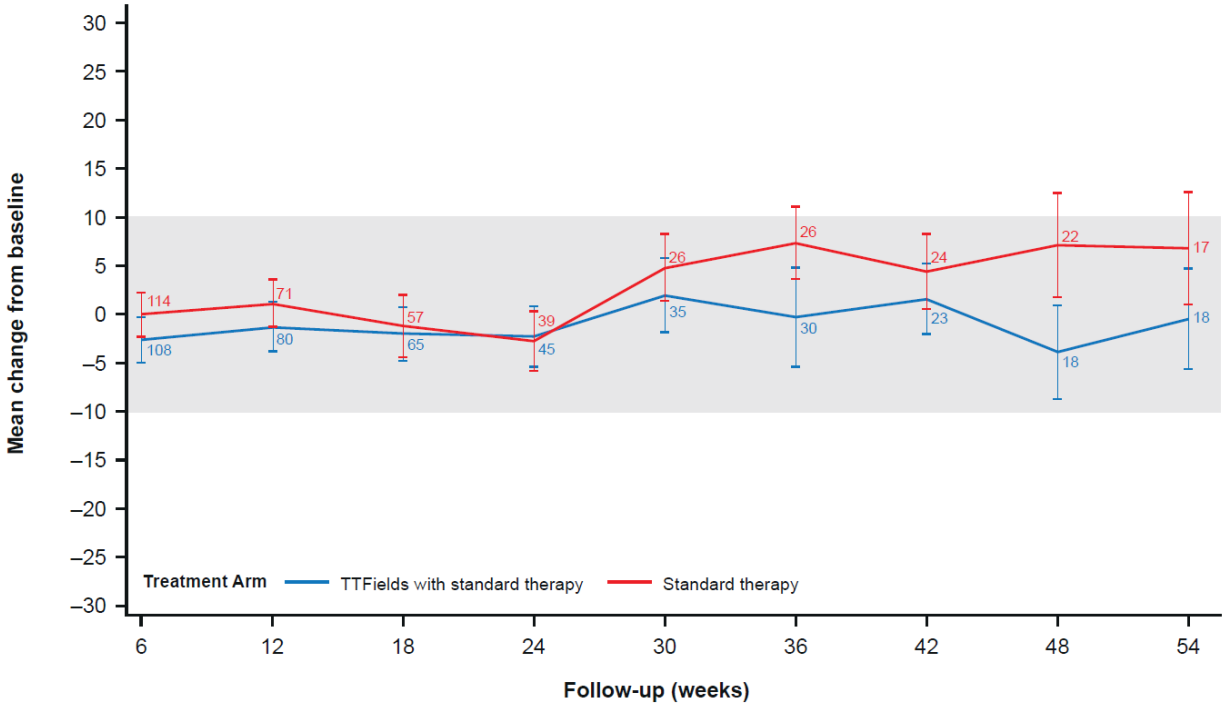
CI, confidence interval; HR, hazard ratio; OS, overall survival; TTFields, Tumor Treating Fields.

Figure S5: Progression-free survival in patients receiving an ICI or docetaxel



CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; PFS, progression-free survival; TTFields, Tumor Treating Fields.

Figure S6: Health-related quality of life Global Health Status scores



Plot shows mean and standard error of the change from baseline in EORTC QLQ-C30 Global Health Status score for patients receiving TTFields therapy with standard therapy, or standard therapy alone. A change of 10 points or more was considered clinically significant. Values show the number of patients returning scores at each follow-up visit.
Shading highlights that the mean change from baseline did not exceed 10 points at all timepoints and in both treatment arms.
Mean (standard error) baseline scores were 59·5 (2·0; n=109) and 59·3 (1·8; n=115) for patients receiving TTFields therapy with standard therapy and standard therapy alone, respectively.
Standard therapy refers to an immune checkpoint inhibitor or docetaxel. EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, quality of life questionnaire C30; TTFields, Tumor Treating Fields

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1. Novocure. Optune®: instructions for use. https://www.optune.com/Content/pdfs/Optune_IFU_8.5x11.pdf (accessed November 9, 2022).

2. Novocure. NovoTTF™-100L system: instructions for use for unresectable pleural malignant mesothelioma. https://www.novottf100l.com/pdfs/NovoTTF-100L_MPM_IFU.pdf (accessed July 10, 2022).

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	**CIP-SD-420**
Version	**7**

Revision history:

Version Number	Version Date	List of Changes	Approved by	Date of Approval
1.0	September 9, 2016	Initial Release	[redacted]	September 9, 2016
1.1	November 7th, 2016	Time for post progression visit in the study schema	[redacted]	November 7th, 2016
2.0	October 8, 2017	Modifications based on FDA interactive review comments from 6 October 2017 Limit to grade 4 NSCLC Include only patients after platinum failure Atezolizumab added as a standard of care immune checkpoint inhibitor	[redacted]	October 8th, 2017
2.1	October 25, 2017	Editorial changes : Correction of the address of the sponsor rep. In EU Post progression follow up added to study schema Correction of typos in times for treatment initiation (Vs. Randomization), period of AE collection, survival follow up frequency and baseline MRI	[redacted]	October 25th, 2017
3	NA*	Some revision information is now part of the signature manifest in the last page, Release date is the date of release in the electronic documentation system; Change of clinical study sponsor (cover page); Document formatting and section numbering changed; List of abbreviations edited; Editing text to clarify that this study is conducted with an investigational device. The same device has CE mark for a similar indication (section 1.1); EU authorized representative omitted since new sponsor is in Switzerland; Schematic of study design updated; "Compliance" was replaced with "usage" in relation to TTFields throughout the protocol; Replaced throughout the protocol the phrase “in combination with” with “concomitant with” to describe TTFields treatment given concomitant with standard of care therapies; Updated background information (section 2) Adding the fact that NovoTTF-100L is approved for treatment of MPM by FDA (section 2.2); Updated STELLAR data in risks (section 3); Randomization window was updated to 28 days from signing ICF, patients for which criteria to continue treatment through RECIST-defined radiological progression specified (section 5.1, 6.2); Inclusion criterion #3 “stage IV” replaced with “metastatic”, inclusion criterion #4 edited to further specify patient population, inclusion criterion #5 removed, exclusion	NA*	NA*

		criterion # was edited to allow specific patients with metastases to CNS (section 5.2); Adding to each drug section the sentence "For additional and updated information, please refer to the relevant country's approved package insert", changes to drugs recommended dosage (section 5.5); Regions for stratification changed (sections 6.2, 8.4) ; Added Urea, INR and aPTT as alternatives to BUN, PT and PTT (section 6.3) Changed window of the 100 day post PD visit (section 6.4); Updates to 15.2 including name and contact information of the Safety Officer for Novocure; Appendix A edited; Study calendar and footnotes updated (Appendix B); Other wording changes for greater protocol accuracy and comprehension		
4	NA*	Change in device model from the NovoTTF-100L to the smaller light-weight device model NovoTTF-200T (All TTFields parameters are the same between the two device models)	NA*	NA*
5	NA*	The need to re-consent when continuing treatment through RECIST-defined radiological progression clarified (section 5.1); Inclusion criterion 4.c. clarified (section 5.2); List of abbreviations updated; Enrollment plan updated (section 5.4); Administration time for drugs may vary (section 5.5); Changes have been made to allow treatment initiation out of hospital/clinic (section 5.5.3); Physical exam details added (section 6); Stratification factor region updated (section 6.2 and 8.4); Timing of post disease progression and survival follow up visits clarified (sections 6.4 and 6.5); Number and regional distribution of participating sites updated (section 8.3); Device accountability section 12 updated; Corrections in study calendar for consistency with protocol (Appendix B); Other changes for accuracy.	NA*	NA*
6	NA*	Sample size reduction to approximately 276 patients with a minimal follow up of 12 months, based on an interim analysis performed by the DMC (section 8.3); Removal of accrual in Asia (section 6.2, 8.4). Other wording changes consistent with the above. Statistical forms for two secondary endpoints added	NA*	NA*
7	NA*	Detailing the participating regions in Enrollment Plan including China (section 5.4); Minor edits for accuracy.	NA*	NA*

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

Table of Contents

LIST OF ABBREVIATIONS 7

SYNOPSIS OF THE CLINICAL STUDY 9

STUDY SCHEMA 11

1 CLINICAL STUDY BACKGROUND AND RATIONALE 12

1.1 Description of the Investigational Device and its Intended Purpose 12

1.2 The Manufacturer of the Investigational Device 12

1.3 System Parts and Their Identification 13

1.4 Traceability 13

1.5 Materials that will be in Contact with Tissues 14

1.6 Training Patients on Using the NovoTTF-200T System 14

2 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATIONAL PLAN 15

2.1 Advanced Non-small Cell Lung Cancer (NSCLC) 15

2.2 Tumor Treating Fields (TTFields) Overview 18

2.3 Preclinical Results with TTFields in NSCLC 18

2.4 TTFields and Immune Checkpoint Inhibitors 21

2.5 Delivery of TTFields to the Upper Torso 24

2.6 Clinical Results with Optune™ in Glioblastoma 25

2.7 Clinical Results with TTFields applied to the thorax 27

2.7.1 TTFields in NSCLC 27

2.7.2 TTFields in Mesothelioma 27

2.8 Rationale for Conducting the Clinical Investigation 28

2.9 Rationale for Design of Clinical Investigation 28

3 RISKS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION 29

4 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION 30

4.1 Purpose and Objectives 30

4.1.1 Purpose 30

4.1.2 Primary Objective 30

4.1.3 Key Secondary Objectives 30

4.1.4 Additional Secondary Objectives 30

5 DESIGN OF THE CLINICAL INVESTIGATION 31

5.1 General 31

5.2 Eligibility Criteria 32

5.2.1 Inclusion Criteria: 32
5.2.2 Exclusion Criteria 33
5.3 Criteria for Removal from Study Treatment 34
5.4 Enrollment Plan 34
5.5 Clinical Investigation-related Procedures 35
5.5.1 Docetaxel 35
5.5.2 Immune checkpoint Inhibitors 39
5.5.3 NovoTTF-200T System Treatment 43
5.5.4 Supportive Therapy 44
5.5.5 Salvage Therapy 44
6 PATIENT EVALUATIONS AND FOLLOW UP PLAN 44
6.1 Pre-treatment Evaluation (Baseline) 44
6.2 Randomization Visit 45
6.3 Follow-up Visit 46
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) 46
6.5 Survival Follow-up 47
7 MONITORING PLAN 47
8 STATISTICAL CONSIDERATIONS 48
8.1 Study Endpoints 48
8.1.1 Primary Endpoint 48
8.1.2 Key Secondary Endpoints 48
8.1.3 Additional Secondary Endpoints 48
8.2 Statistical Hypothesis Testing 49
8.3 Sample Size Assessment 50
8.4 Randomization and Stratification 52
8.5 Data Monitoring Committee 52
9 DATA MANAGEMENT 52
10 AMENDMENTS TO THE PROTOCOL 53
11 DEVIATIONS FROM THE PROTOCOL 53
12 DEVICE ACCOUNTABILITY 53
13 STATEMENTS OF COMPLIANCE 53
14 INFORMED CONSENT PROCESS 54

15 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES 55
15.1 Definitions 55
15.1.1 Adverse Event (AE) 55
15.1.2 Adverse Device Effect (ADE) 55
15.1.3 Device Deficiency (DD) 55
15.1.4 Serious Adverse Event (SAE) 55
15.1.5 Serious Adverse Device Effect (SADE) 56
15.1.6 Unanticipated serious adverse device effect (USADE) 56
15.1.7 Unanticipated adverse device effect (UADE) 56
15.2 Adverse Event Collection and Reporting 56
15.3 Grading of an Adverse Event 57
15.4 Determination of Causality of Adverse Events 58
15.5 Eliciting Adverse Event Information 58
15.6 Adverse Event Reporting Period 58
15.7 Follow-up of Unresolved Adverse Events 59
15.8 Reporting Procedures 59
15.8.1 Reportable Events 59
15.8.2 Reporting Timelines 59
15.8.3 Reporting of Pregnancy 60
16 VULNERABLE POPULATION 60
17 SUSPENSION OR PREMATURE TERMINATION OF THE CLINICAL INVESTIGATION 60
18 PUBLICATION POLICY 61
19 BIBLIOGRAPHY 62
20 INVESTIGATOR SIGNATURE PAGE 66
Appendix A Performance Status Criteria 67
Appendix B EF-24 Study Calendar 68
Appendix C Immune-Related Response Evaluation Criteria In Solid Tumors 71
Appendix D List of Investigators 72
Appendix E Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated Patients (thoracic malignancies) 73
Appendix F CTCAE Version 4.03 74

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

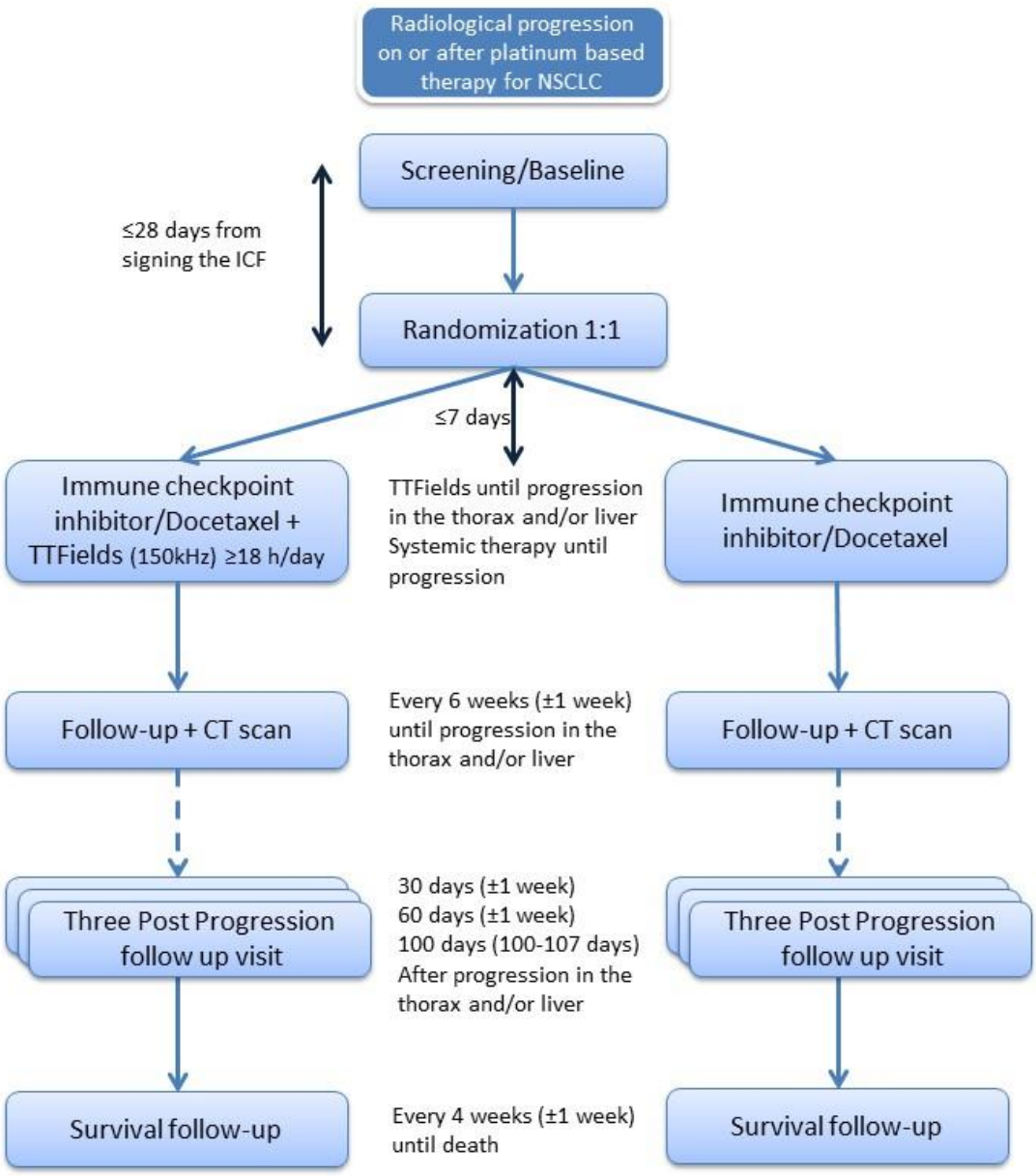
SYNOPSIS OF THE CLINICAL STUDY

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
Stratification	Standard of care therapy: 1) Immune checkpoint inhibitor 2) Docetaxel Histology: 1) Squamous 2) Non-Squamous
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.

The NovoTTF-100L, a previous version of the NovoTTF-200T device was granted a CE mark for the treatment of stage IV, non-squamous, non-small cell lung cancer, in combination with Pemetrexed (Alimta), after failure of first line treatments.

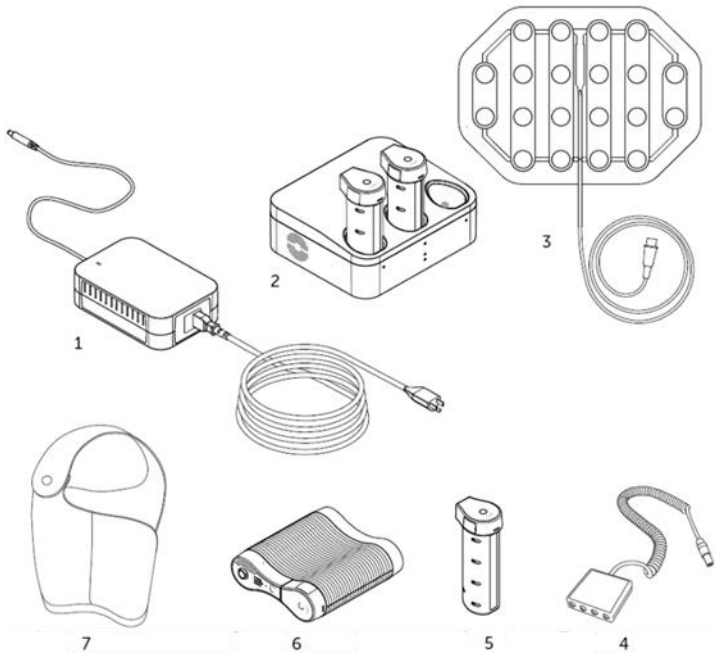
In the current study, NovoTTF-200T is an investigational device.

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

The NovoTTF-200T System is composed of several parts, which are shown in the picture below.



1 Plug in power supply and cord

2 Charger for portable batteries

3 Insulated transducer arrays

4 Connection cable and box

5 battery

6 NovoTTF-200T electric field generator

7 Shoulder bag and strap

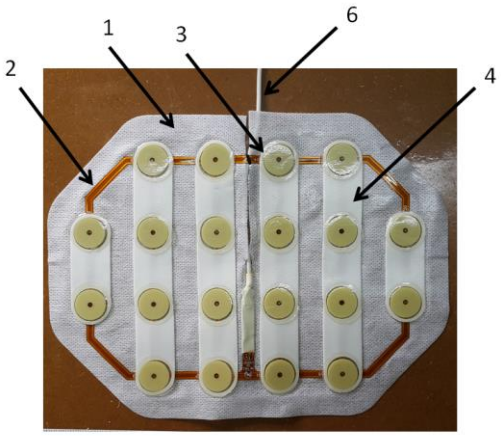
1.4 TRACEABILITY

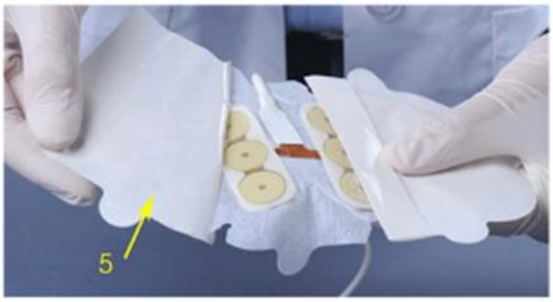
All parts of the NovoTTF-200T System are identified by a unique and personal serial number. Transducer arrays are identified by lot number. Novocure maintains traceability of all parts through paper documentation and SAP equipment management system (ERP):

Steps	**Traceability ensured by**
Manufacturing	EN ISO 13485 Vendor Quality System
Receiving	SOP-USOC-002 Incoming Inspection and SAP ERP
Storage	SOP-USOC-004 Stockroom and SAP ERP
Shipping	SOP-USOC-003 Shipping - Final release and SAP ERP
Use	SAP ERP

1.5 MATERIALS THAT WILL BE IN CONTACT WITH TISSUES

The Insulated Lung Electrode (ILE) transducer arrays are applied directly to the skin.





These arrays are sterile single use devices and incorporate the following:

	Part name	Functions
1	Cover tape	Provides adhesion of the array to patients' skin
2	ILE transducer array	The array delivers the treatment to the patient and measures the temperature
3	Conductive gel layers and Ceramic discs (beneath)	Gel: Ensures electric contact between the transducer array and the skin Ceramic disc: Used for the TTFields transmission
4	Mid-pads	Mechanically stabilizes the gel over the array
5	Overlapping liner	Covers the gel and the cover tape
6	Applied part cable with black connector or white connector	Connects the transducer array to the connection box

1.6 TRAINING PATIENTS ON USING THE NOVOTTF-200T SYSTEM

The NovoTTF-200T System is easy to use and a simple training by the Device Support Specialist (DSS) is sufficient for patients and the study team to apply the investigational device according to its intended use. No specific medical/surgical procedures are needed for the use of the investigational device.

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.

TTFields act by delivering low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields to the tumor using non-invasive transducer arrays placed on the skin around the region of the body containing the tumor. TTFields act predominantly during two phases of mitosis: 1) during metaphase, by disrupting the formation of the mitotic spindle, and 2) during cytokinesis, by dielectrophoretic dislocation of intracellular constituents resulting in apoptosis[28,29]. The efficacy of TTFields is frequency dependent on specific cell types. The anti-mitotic effect of TTFields has been shown in multiple cell lines when the appropriate frequency was utilized. This includes but not limited to the following tumor models: glioblastoma at 200 kHz[30], NSCLC at 150kHz[31]; breast carcinoma at 120kHz[32]; and melanoma at 100kHz[29].

The effect of TTFields is directional, *i.e.,* TTFields are most effective when applied in the direction of the division axis of the dividing cell[28,30]. In order to increase the efficacy of TTFields, two sequential field directions can be applied to tumors by using two perpendicular pairs of transducer arrays. Using two directional TTFields in pilot clinical testing demonstrated TTFields to be biologically active in human tumors.

2.3 PRECLINICAL RESULTS WITH TTFIELDS IN NSCLC

TTFields have demonstrated significant activity in *in vitro* and *in vivo* NSCLC pre-clinical models both as a single modality treatment and in combination with chemotherapies[30,31,33,34].

The effect of TTFields in vitro, using four human NSCLC cell lines (H1299, A549, HCC827, HTB-182) and two murine cell lines (LLC1, KLN205) was found to induce a frequency-dependent reduction in viability in all cell lines, with a peak at 150kHz. The anti-proliferative effect was demonstrated for both adenocarcinoma and squamous cell histologies.

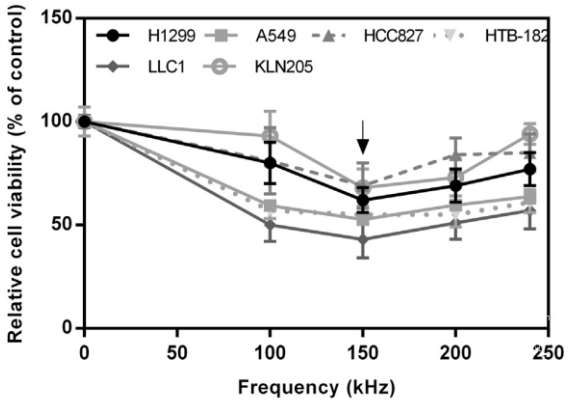


Figure 1: Effect of TTFields treatment, administered in different frequencies, on cell viability of various lung cancer cell lines (arrow indicates optimal frequency) (Giladi et al., *Semin Oncol, 2014*).

A reduction of 31-57% in the number of viable cancer cells, compared to control cultures, was seen following 72 hours of continuous TTFields treatment in these cell lines ($p<0.05$). TTFields were found to significantly impair the colony-forming ability of all tested cell lines in culture [24, 25].

The clonogenic potential of single cells after 150kHz TTFields treatment was compared with that of untreated cells. TTFields treatment was found to significantly impair the colony-forming ability of all tested cell lines in culture. Treatment efficacy was found to be positively correlated with TTFields intensities.

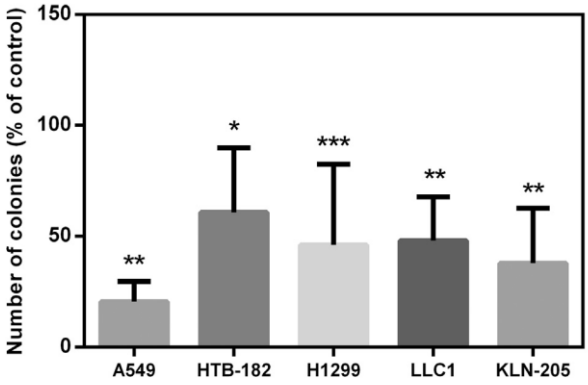


Figure 2: Clonogenic potential of various lung cancer cell lines after TTFields treatment at optimal frequency (150kHz). *P<.05,P<.01, and ***P<.001 versus control group (*Giladi et al., Semin Oncol, 2014*).**

Adding TTFields to pemetrexed led to a decrease in the number of viable cells for all tested concentrations in both H1299 and LLC1 cultures. These results suggest an additive effect for combining treatments. The combination of cisplatin, a commonly used first-line NSCLC treatment, and TTFields showed a similar pattern of augmented effect against NSCLC cell viability, including in the squamous cell lines HTB-182 and KLN205. TTFields therapy in combination with paclitaxel had the same additive effect and led to a decrease in the number of viable cells in cultures of both adenocarcinoma and squamous histology cells. The combined effect of TTFields and paclitaxel may be attributed to their shared cellular targets. NSCLC with activating EGFR mutations is highly responsive to EGFR tyrosine kinase inhibitors, including erlotinib, an approved agent for the treatment of locally advanced or metastatic NSCLC. Compared with exposure

to erlotinib alone, the combination of TTFields and erlotinib led to a significant reduction in HCC827 (EGFR mutant) cell viability.

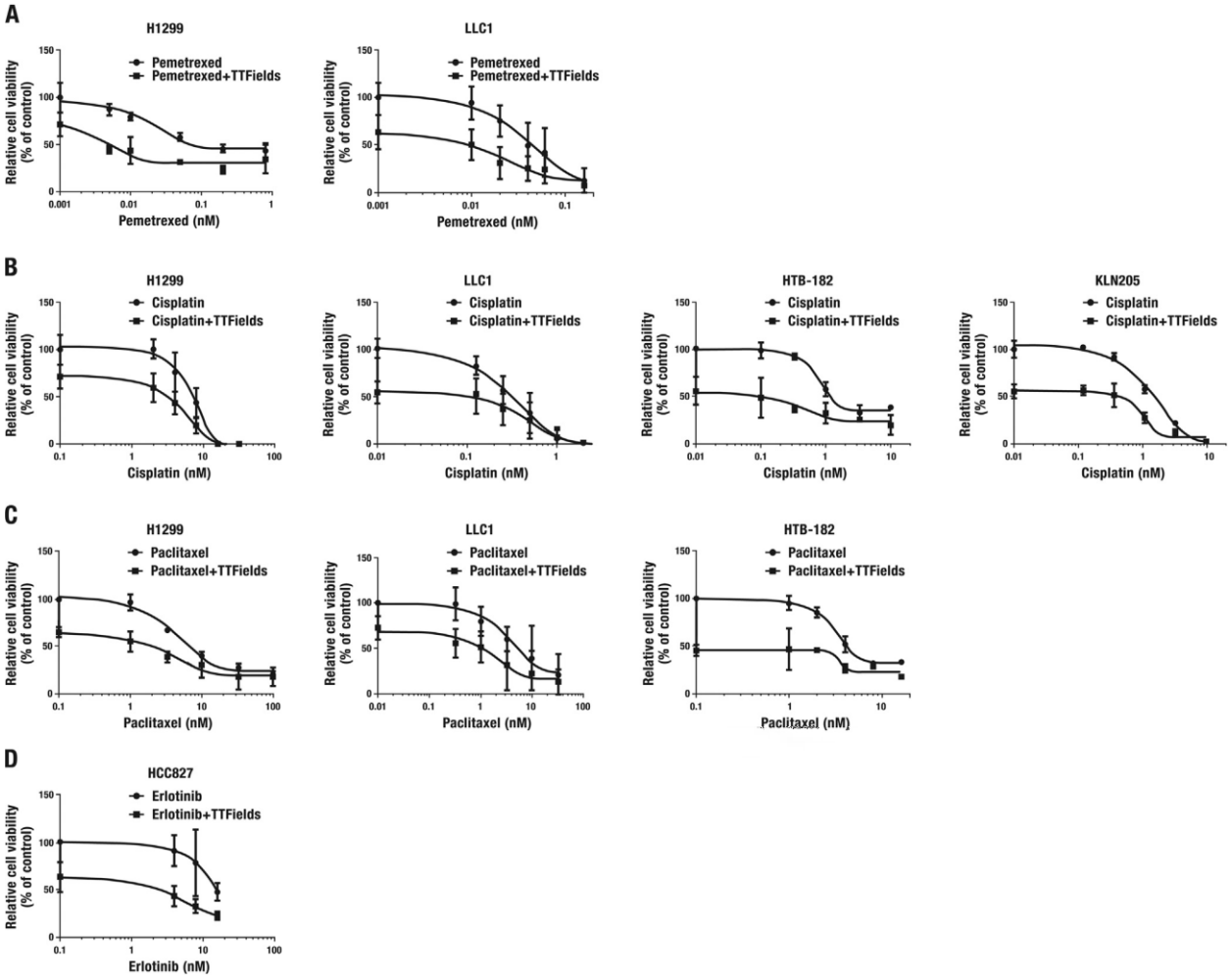


Figure 3: Dose–response plots of (A) pemetrexed alone and in combination with TTFields on H1299 (adenocarcinoma) and LLC1 (Lewis lung carcinoma 1) cells; (B) cisplatin alone and in combination with TTFields on H1299, LLC1, KLN205 (squamous cell carcinoma), and HTB-182 (squamous cell carcinoma) cells; (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*).

LLC1 and KLN205-T1 cells were implanted into the left lung of C57BL/6 mice and KLN205-T1 cells were implanted into DBA/2 mice. LLC1 tumors exposed to TTFields (1.86+/-0.67 V/cm RMS) in combination with chemotherapy were smaller than tumors treated with chemotherapy alone. Similar results were observed for KLN205-T1 tumors.

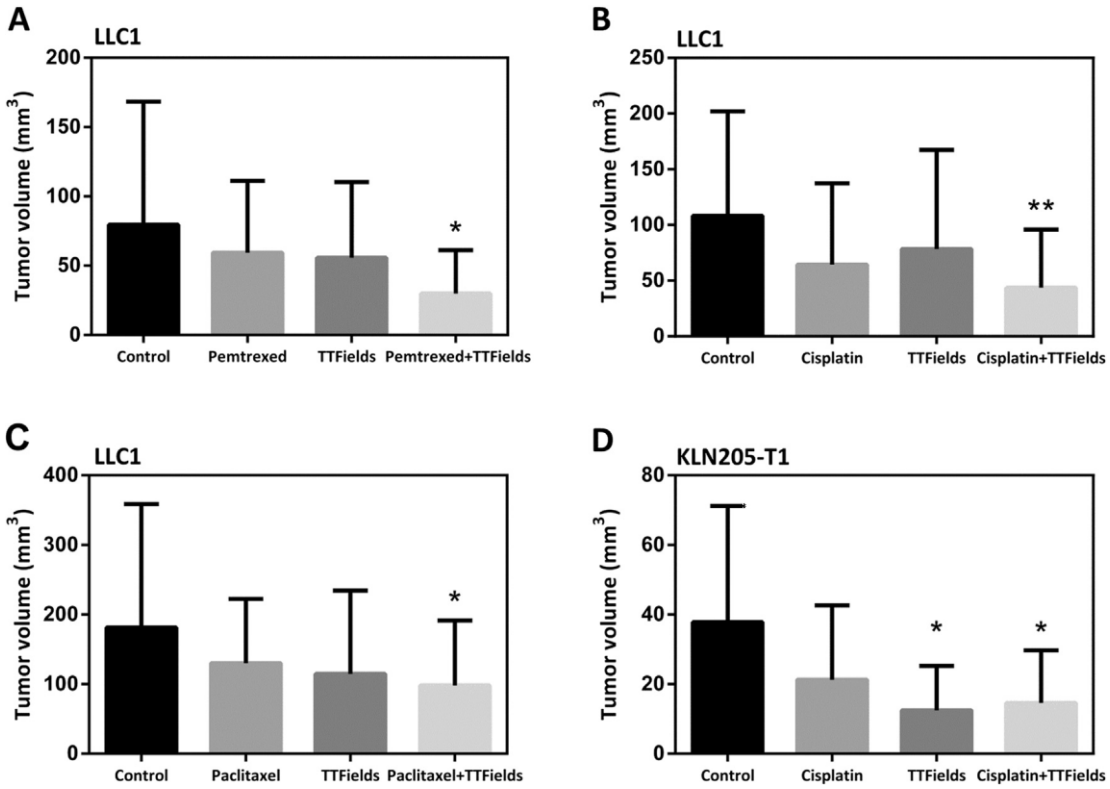


Figure 4: In vivo effects of treatment combination of TTFields therapy and chemotherapy. Volume of LLC1 (Lewis lung carcinoma 1) or KLN205-T1 (murine squamous cell carcinoma cells derived from DBA/2 mice lung tumors) tumors in mice treated with (A) pemetrexed, (B,D) cisplatin,and (C) paclitaxel.*P<.05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

2.4 TTFIELDS AND IMMUNE CHECKPOINT INHIBITORS

Various experiments have demonstrated abnormal mitotic process outcomes, which can lead to different forms of cellular death. These included abnormal chromosome segregation, ER stress, and autophagy. Lewis lung carcinoma (LLC-1) and murine ovarian surface epithelial (MOSE-L) cells treated with TTFields for 24-72 hours at optimal frequency (150 and 200 kHz, respectively), showed elevation of early apoptotic cells (Annexin V+/7AAD-) and late apoptotic cells (Annexin V+/7AAD+)[35]. The same cells had a significantly higher exposure of calreticulin on cells' surface, and higher release of the chromatin-binding protein HMGB1, an indicator of intracellular ATP levels in cells. All of the above are hallmark features of immunogenic cell death, suggesting that TTFields can potentially generate or augment a systemic anticancer immune response.

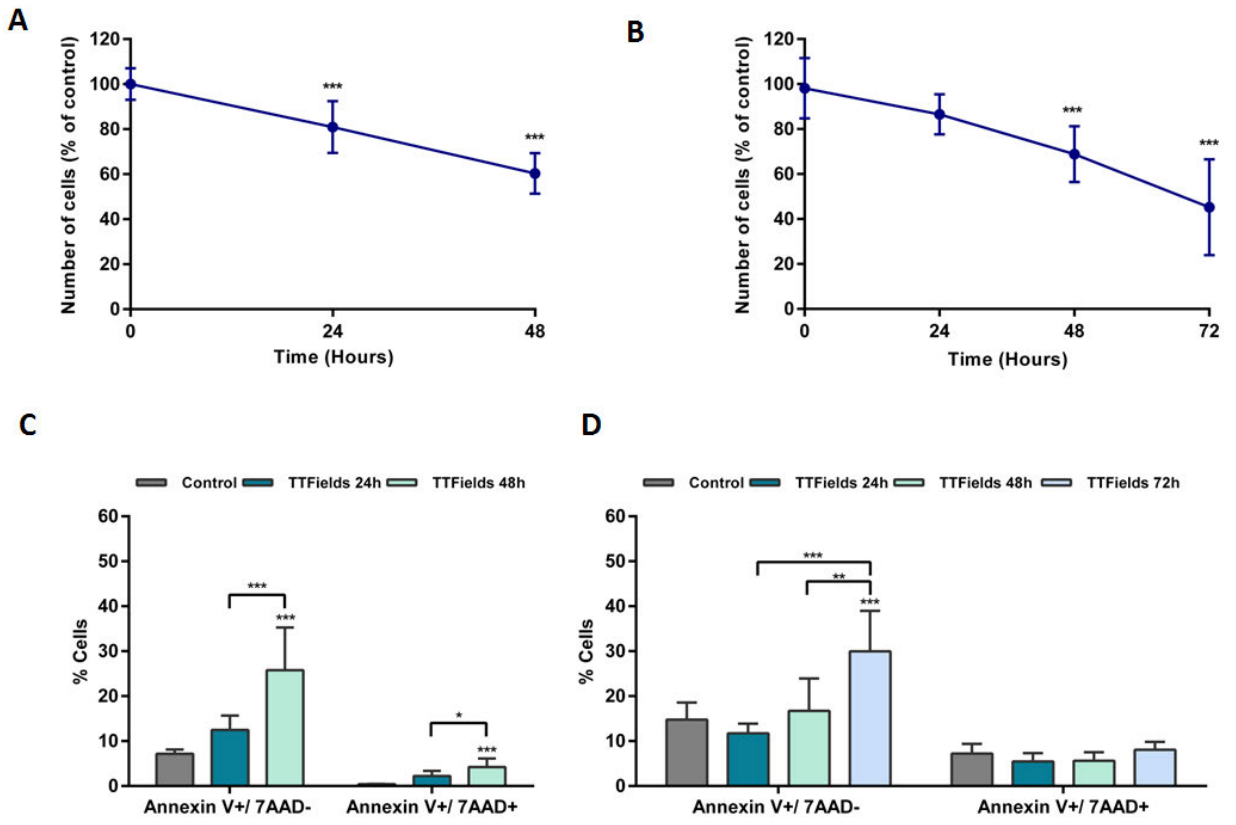


Figure 5: Lewis lung carcinoma (LLC-1; A, C) and murine ovarian surface epithelial (MOSE-L; B, D) cells were treated with TTFields for 24-72 hours at optimal frequency (150 and 200 kHz, respectively). Effect of TTFields treatment on cell counts (A-B). C, D show elevation (%) of early apoptotic cells (Annexin V+/7AAD-) and late apoptotic cells (Annexin V+/7AAD+). Mean ± SD (.05> **P*>.01, ***P*<.01, ****P*<.001) from control group.

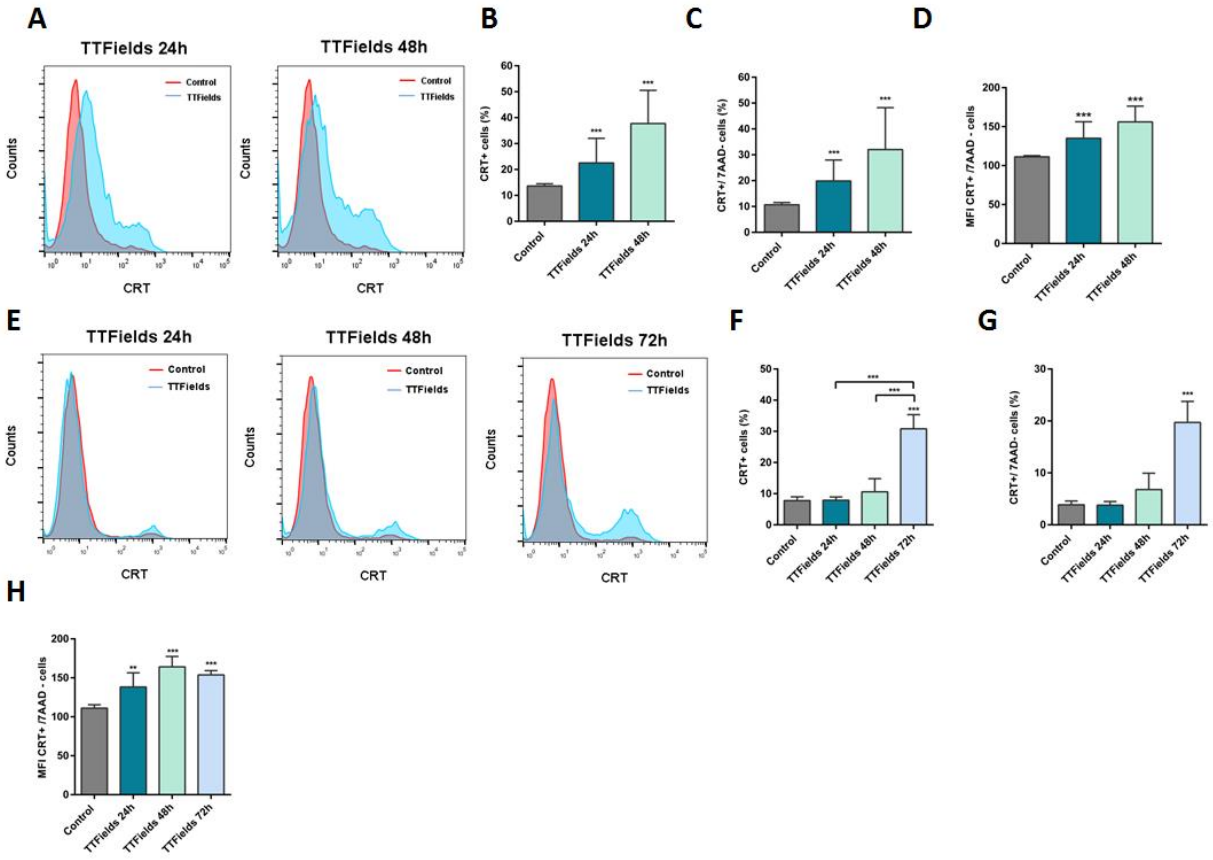


Figure 6: LLC-1 (A-D) and MOSE-L (E-H) cells were treated with TTFields for 24-72 hours at optimal frequency. A quantitative analysis of CRT surface exposure was performed using flow cytometry. Representative histograms of CRT surface exposure (A, E). Total CRT+ cells (B, F). CRT surface exposure among viable cells (7AAD-) (C, G). Mean fluorescence intensity (MFI) of CRT in viable cells (D, H). Mean ± SD (.05 > **P*>.01, ***P*<.01, and ****P*<.001) from control group

In an in-vivo experiment, C57Bl/6 mice were injected directly into the lungs with LLC-1 cells. Application of TTFields to the mouse lungs was maintained for 7 days and parallel to the ongoing I.P. injection of anti-PD-1. The combined treatment of TTFields and anti-PD-1 led to a significant decrease in tumor volume as compared to control mice and to mice treated with anti-PD-1 alone. The percentages and PD-L1 expression levels of tumor infiltrating CD45+ cells, dendritic cells (CD11b+/CD11c+), and macrophages (CD11b+/F4/80+) were higher in tumors from the combined treatment group, compared to infiltrating immune cells in the control group. This suggests an enhanced antitumor immunity as a result of applying the combined treatment of PD-1 inhibitors and TTFields.

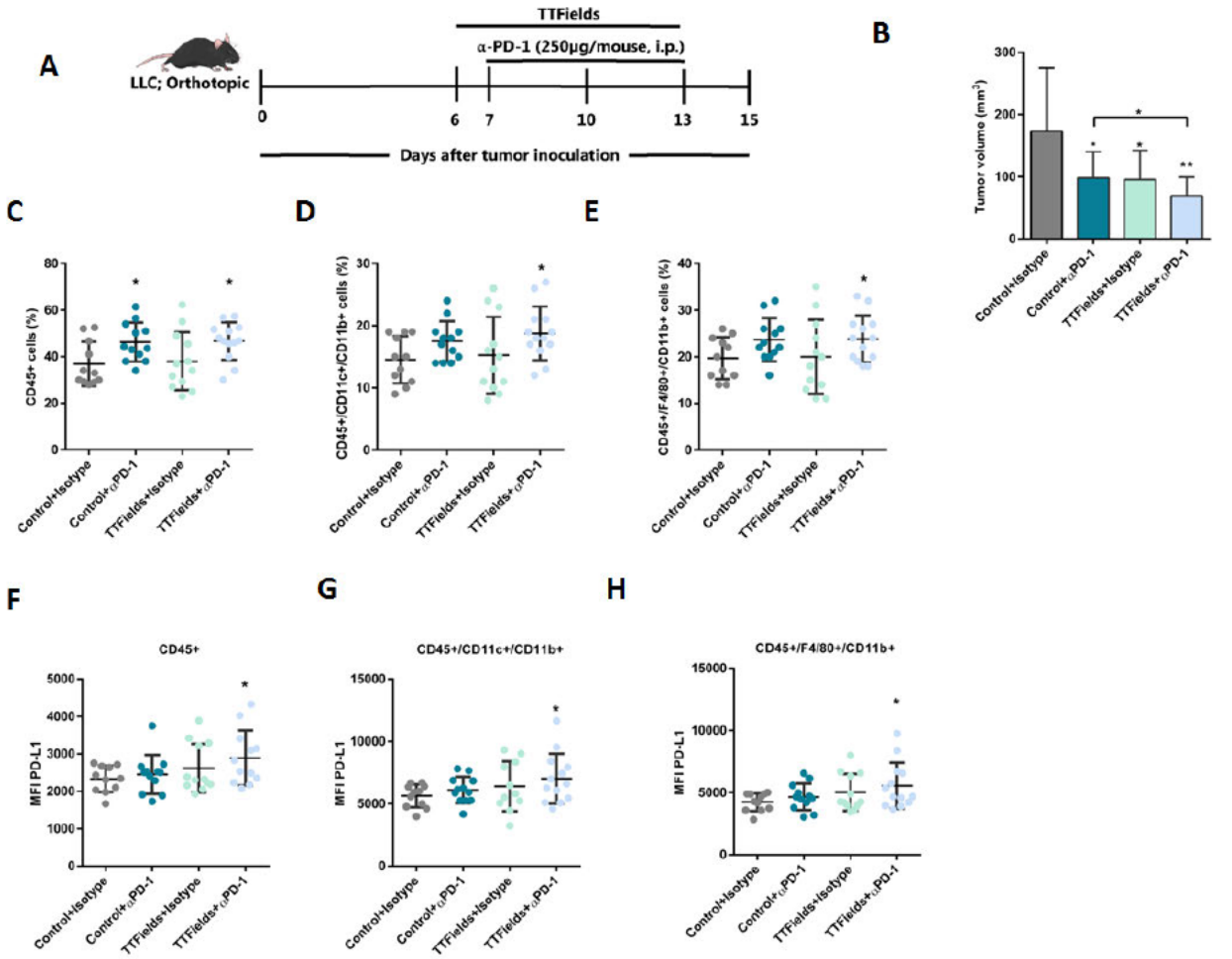


Figure 7: 10-12-week-old male C57Bl/6 mice were injected directly into the lungs with Lewis lung carcinoma (LLC-1; 3x103 cells) (A). Application of TTFields to the mouse lungs was initiated 6 days afterwards and was maintained for 7 days. Mice received an I.P. injection of anti-PD-1. The combined treatment of TTFields and anti-PD-1 led to a significant decrease in tumor volume as compared to control mice and to mice treated with anti-PD-1 alone (B). The percentages (Figures C-E) and PD-L1 expression levels (F-H) of tumor infiltrating CD45+ cells (C, F), dendritic cells (CD11b+/CD11c+) (D, G), and macrophages (CD11b+/F4/80+) (E, H). CD45+ and specifically CD11b+/CD11c+ and CD11b+/F4/80+ cells from tumor in the combined treatment group exhibited both higher tumor infiltration and elevated PD-L1 expression, as compared to infiltrating immune cell in the control group. Mean ± SD; *P<.05, **P<.01 from control group.

2.5 DELIVERY OF TTFIELDS TO THE UPPER TORSO

The distribution of TTFields within the thorax was investigated using a simulation of a realistic human thorax[36,37]. The frequency used for the calculations was 150 kHz and the potential difference between paired arrays was 200 V peak-to-peak. The intensity of fields applied through this simulation were above the therapeutic threshold of 1 V/cm, indicating the feasibility of delivering TTFields to the thorax using the NovoTTF-100L System. A cross-chest array configuration was found to allow for the strongest fields throughout the entire thorax, with 98% of the lungs receiving maximal field intensity of over 2 V/cm.

2.6 CLINICAL RESULTS WITH OPTUNE™ IN GLIOBLASTOMA

Based on promising pilot data in both recurrent and newly diagnosed glioblastoma, a phase III trial was conducted in the United States and Europe to test the safety and efficacy of 200 kHz TTFields alone versus active chemotherapy in patients with recurrent glioblastoma[38]**.** The primary endpoint was overall survival. Patients (median age 54 years (range 23-80), Karnofsky performance status 80% (range 50-100)) were randomized to 200 kHz TTFields alone (n=120) or active chemotherapy control (n=117). The active chemotherapy control arm included "physician choice" chemotherapy that predominantly included bevacizumab based regimens, irinotecan or nitrosurea. The median number of prior treatments was 2 (range 1-6).

In the intent to treat (ITT) population which included all randomized subjects (Optune=120, BSC=117), overall survival in subjects treated with Optune was comparable to that observed in subjects treated with Best Supportive Care (BSC) (median OS=6.3 vs. 6.4 months; p=0.98). Significantly higher overall survival (p=0.0447) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months). The one-year survival was similar in the Optune and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS-6) was the same in the ITT population across groups (21.4% vs. 15.2%). Radiological response rates from the subset of patients evaluated were reported as 14% for the Optune group compared to 9.6% for the BSC group in the ITT population. Median time to progression (TTP) was 9.3 weeks for Optune vs. 9.6 weeks for BSC.

The characteristic adverse events of almost all chemotherapies were seen in a significantly higher proportion of BSC control subjects than in Optune subjects: gastrointestinal (30% vs. 8%), hematological (19% vs. 4%) and infectious (12% vs. 4%). Mild to moderate skin irritation beneath the device transducer arrays was observed in 16% of Optune subjects; none of these cases were assessed as severe by the investigator, all resolved after discontinuing treatment, and all were treated with topical steroids and periodic shifting of transducer array positions.

Quality of life analyses favored TTFields in most domains. Specifically, cognitive and emotional functions were reported to be much better in the TTFields treated patients than with chemotherapy.

The results of this phase III trial demonstrated comparable efficacy with this chemotherapy-free treatment (200 kHz TTFields) to chemotherapy (including bevacizumab) in recurrent glioblastoma with a more favorable safety profile and quality of life and supported FDA approval of TTFields in recurrent glioblastoma in 2011 and a CE mark in Europe.

Registry data from 457 recurrent GBM patients who started Optune™ prescribed by the treating physician in the US between October 2011 and November 2013 showed an even higher median overall survival of 9.6 months, with baseline characteristics similar to those of patients treated under the pivotal clinical trial. The 2-year survival rate in this population was 30% (compared to 9% in Optune™-treated patients on the clinical trial). Compliance was a clear predictor of survival on Optune™, and patients treated with the device for at least 18 hours per day had significantly longer survival time. No new safety signals have been detected in this registry dataset and the only common adverse event related to Optune™ was skin reaction.

Based on this clinical data in recurrent GBM and a pilot trial in newly diagnosed GBM with Optune™ in combination with temozolomide (TMZ) that demonstrated favorable safety profile and promising efficacy,

an international phase III trial in newly diagnosed GBM, evaluating the role of Optune™ in combination with maintenance temozolomide after surgery and chemoradiation versus temozolomide alone was conducted[39]. In the ITT population, which included all randomized subjects (Optune/TMZ=210, TMZ alone=105), PFS at the interim analysis met the predefined threshold for statistical significance at the time of the interim analysis. The difference of more than 3 months in median PFS is highly clinically significant. The Hazard Ratio for PFS was 0.621, which translates into a 37.9% decrease in the risk of progression when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 695 patients (Optune/TMZ=466, TMZ alone=229), PFS was also highly significant with a hazard ratio of 0.694. Median PFS in the PP (per protocol) population was identical to the ITT population at the interim analysis and slightly longer than the ITT population at the final analysis. Notably, median PFS remained significantly higher in the Optune/TMZ group than in the TMZ alone group in the PP population at both the interim and final analyses.

Overall survival (OS) was a powered secondary analysis in the trial. The threshold for superior OS at the interim analysis was predefined in the protocol at 0.00598 according to the Lan-DeMets O'Brien-Fleming alpha spending function, and was to be tested in the PP population. In the PP population, which analyzed patients according to the treatment they actually received (as treated: Optune/TMZ=196, TMZ=84), OS was also significantly longer in the Optune/TMZ arm compared to the TMZ alone arm. An increase of almost 5 months as seen here is highly significant clinically. The hazard ratio for OS was 0.666. This translates into a 33.4% decrease in the risk of death when using Optune/TMZ compared to TMZ alone. At the final analysis, which included 609 patients (Optune/TMZ=429, TMZ alone=180), OS was also highly significant with a hazard ratio of 0.683.

In addition, although not a pre-specified endpoint, 1- and 2-year survival were also analyzed in the ITT population at the interim analysis. In the ITT population, 1-year survival was 75% in the Optune/TMZ group and 70% in the TMZ alone group (p-value=0.162) at the interim analysis. 2-year survival in the ITT population at the interim analysis was 48% in the Optune/TMZ group and 34% in the TMZ alone group (p-value=0.0122).

Quality of Life assessments were based on the interim analysis cohort of 315 subjects. Quality of life, cognitive function and functional status were all maintained throughout treatment with the device, leading to the clear conclusion that use of Optune does not harm patients' quality of life, cognitive function or ability to perform activities of daily living.

Safety was assessed on all patients at the final analysis who received any treatment at the time of the analysis (Optune/TMZ=437, TMZ alone=207). A slightly higher incidence of grade 1-2 adverse events was seen in some of the systems in the Optune/TMZ arm of the study. This is most likely a reflection of the longer duration of TMZ treatment in these patients (median of 6 cycles versus 4 cycles in the control arm) due to the increase in PFS seen in the treatment group. Grade 3-5 adverse events were well balanced between arms. None of the grade 3-5 adverse events in these body systems were considered related to Optune by any of the investigators except for 1% grade 3 skin irritation.

Based on the data submitted to FDA from this newly diagnosed GBM study, FDA approved Optune™ in combination with temozolomide for the treatment of adult patients with newly diagnosed GBM on October 5, 2015. In the US, Optune™ with TMZ is indicated for the treatment of adult patients with newly diagnosed, supratentorial glioblastoma following maximal debulking surgery and completion of radiation therapy together with concomitant standard of care chemotherapy.

2.7 CLINICAL RESULTS WITH TTFIELDS APPLIED TO THE THORAX

2.7.1 TTFIELDS IN NSCLC

In a single arm pilot study (phase I/II), 42 inoperable stage IIIB (with pleural effusion) and IV NSCLC patients who had had tumor progression after at least one line of prior chemotherapy received pemetrexed 500mg/m^2 intravenously every 3 weeks together with continuous daily 150 kHz TTFields (for 12 hours per day) applied to the chest and upper abdomen until disease progression[40]. The primary endpoint was time to "in-field" progression. Median age was 63 years, 76% had stage IV disease, 78% had adenocarcinoma and 17% had an Eastern Cooperative Oncology Group (ECOG) performance status of 2.

The median time to in-field progression was 28 weeks and the median time to progression was 22 weeks. Six patients (14.6 %) had a partial response (PR) and 20 (48.8%) had stable disease (SD). The median overall survival was 13.8 months (compared to the historical control of 8.3 months reported in the phase III study of pemetrexed alone compared to docetaxel[24]) and the 1 year survival rate was 57% (compared to the historical control of 30% reported for pemetrexed alone). Given that it is now known that pemetrexed has no benefit for squamous histology, it is interesting to note that in an exploratory analysis of histology subsets, patients with tumors of adenocarcinoma histology had an overall survival of 12.8 months (n=35) and patients with tumors of squamous cell histology had an overall survival of 13.8 months (n=7). The combination was well tolerated and, compared to a pemetrexed historical control, there was no increase in the adverse event rate, GI toxicity or hepatic toxicity and no device related cardiac arrhythmias were reported. There were also no TTFields-related serious adverse events. The only device-related adverse event was mild to moderate contact dermatitis in 14 patients, which was expected with use of the transducer arrays. Therapy usage time was very good with 85% of patients adhering to the recommended TTFields schedule.

2.7.2 TTFIELDS IN MESOTHELIOMA

A single arm study of TTFields in malignant pleural mesothelioma (MPM) accrued a total of 80 patients with unresectable, previously untreated MPM. Patients were treated with TTFields concomitant with pemetrexed and cisplatin or carboplatin. Continuous TTFields at 150 kHz for a minimum of 18 hours/day were applied to the thorax together with standard dosing of chemotherapy. Inclusion criteria include ECOG 0-1, pathological evidence mesothelioma and at least one measurable lesion according to modified RECIST criteria. Patients were followed q3 weeks (CT scan q6 weeks) until disease progression. The primary endpoint was overall survival (OS) and secondary endpoints were response rate, progression free survival (PFS) and treatment-emergent toxicity.

Median overall survival was 18·2 months (95% CI 12·1–25·8) compare to historic control of 12.1 months (Vogelzang et al.). 1-year overall survival was 62·2% (95% CI 50·3–72·0) and 2-year overall survival was 41·9% (28·0–55·2). Median progression-free survival was 7·6 months (95% CI 6·7–8·6). The most common grade 3 or worse adverse events were anaemia (nine [11%] patients), neutropenia (seven [9%]), and thrombocytopenia (four [5%]). Skin reaction was the only adverse event associated with TTFields and was reported as grade 1–2 in 53 (66%) patients, and as grade 3 in four (5%) patients. No treatment-related deaths were observed[41].

The STELLAR study demonstrated no safety concerns for the combination of TTFields to the thorax together with standard chemotherapy for previously untreated mesothelioma patients. The NovoTTF-

100L system (previous version of NovoTTF-200T) has recently been granted Humanitarian Device Exemption by the FDA for the treatment of MPM.

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. In addition, 80 patients with mesothelioma treated with TTFields concurrent with chemotherapy have raised no safety concerns and demonstrated clinical superiority compared to historical control. Delivery of TTFields to the upper torso is technically feasible and allows therapeutic level TTFields to be administered to the lungs and adjacent tissues (e.g. the liver), which are common metastatic sites of NSCLC. The application of TTFields in this region could potentially lead to clinical response with symptomatic relief and improved quality of life, prolonged PFS and ultimately to prolonged survival. TTFields have been demonstrated to act synergistically with taxanes in several tumor models and have been shown to be additive when combined with PD-1 inhibitors in lung cancer models. This was also accompanied by significantly higher expression of markers related to immunogenic cell death, as well as by higher infiltration of APCs into the tumor *in vivo.* These findings suggest that TTFields may augment the immune response against the tumor and reduce tolerance induced by tumor cells through PD-1/PD-L1 interactions. 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.

As mentioned above, it is important to understand that the standard of care in advanced NSCLC has been changing rapidly over the past couple of years, with the introduction of immune checkpoint inhibitors as treatment options for this disease [16–19]. The next few years will likely see additional changes in the standard of care for this disease. Specifically, the current approved subsequent treatment lines in NSCLC (without somatic mutations) include Docetaxel and Immune checkpoint inhibitors (Nivolumab, Pembrolizumab and Atezolizumab). Immune checkpoint inhibitors have been shown to significantly extend survival in second line advanced NSCLC when compared to Docetaxel, however, immune checkpoint inhibitors are not yet available or not a treatment option to all patients. This is due to some patients not being eligible for these drugs, the fact that many patients are receiving immune checkpoint inhibitors today also at 1st line (and thus are not likely to receive them again at subsequent treatment lines) and due to different approvals and reimbursement coverage status for these drugs in different countries.

Multiple clinical trials led by large pharma companies are currently testing the effect of immune checkpoint inhibitors in first line advanced NSCLC. In fact, immune checkpoint inhibitors are already approved for first line NSCLC by FDA either as monotherapy or in combination with other drugs. On the

contrary, in a large phase 3 trial, nivolumab did not show superior survival to standard platinum/taxane regimens in the first line setting. Therefore, the future use of immune checkpoint inhibitors and/or docetaxel in second line advanced NSCLC is uncertain. Several possibilities exist:

1. Immune checkpoint inhibitors continue to move to 1st line and docetaxel return to be the only standard of care following platinum failure.
2. Some immune checkpoint inhibitors do not move to 1st line and are used as subsequent treatments only, making docetaxel an option only in patients who are not eligible for immune checkpoint inhibitors or cannot receive them due to approval/reimbursement status in their country.
3. A mixture of the above two scenarios.

In summary, currently, patients with stage 4 NSCLC, after platinum failure, may receive either docetaxel or an immune checkpoint inhibitor despite the fact that immune checkpoint inhibitors have been shown to be superior to docetaxel. Future use of Docetaxel versus Immune checkpoint inhibitors in subsequent therapy of advanced NSCLC is uncertain.

The pivotal study of the NovoTTF-200T device in stage 4 NSCLC was planned in light of the above uncertainties. The following is the key rationale for the LUNAR study design:

1. Allows approved standards of care for stage 4 NSCLC who have failed platinum treatment on the study (immune checkpoint inhibitors and docetaxel)
2. The primary endpoint tests whether TTFields at 150kHz to the lung, mediastinum and liver added to standard of care increases overall survival. Success in this endpoint allows for improved outcomes for all patients receiving standard of care as it is given today.
3. The key secondary endpoints, which are tested hierarchically if the primary endpoint of superior overall survival is met, will help clarify whether TTFields improve survival of patients treated with docetaxel more or less profoundly than with immune checkpoint inhibitors.
4. An exploratory secondary endpoint will also test whether TTFields with docetaxel is non-inferior to immune checkpoint inhibitors (which have been proven to be superior to docetaxel).

3 RISKS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

The risks associated with use of the NovoTTF-200T are the same as those reported already for the use of the system in the EF-15 pilot study of NovoTTF-100L (an earlier version of NovoTTF-200T) with Pemetrexed compared to Pemetrexed alone and in the STELLAR study of NovoTTF-100L with Pemetrexed and platinum based therapy in first line therapy for 80 patients with unresectable MPM. There were no device-related serious adverse events reported, and the most common device related adverse event seen in patients was mild to moderate dermatitis under the transducer arrays. This was reported in about half of the patients and usually improved by the application of topical steroids.

Technical failure while being treated with TTFields is extremely unlikely due to stringent compliance with all standard design and manufacturing safety protocols. In addition, appropriate measures have been taken to minimize the risk to study subjects, including preclinical *in vitro* and *in vivo* testing to ensure safe operation of the device.

Considering the expected minimal toxicity, the efficacy reported in previous studies and in multiple preclinical NSCLC models, the possible benefits of TTFields using the NovoTTF-200T System exceed its potential risks.

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 within 28 days of signing the informed consent form (ICF):

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 (see **Appendix C**) 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.
- NovoTTF-200T treatment delivers TTFields to the thorax and liver. 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).
- NovoTTF-200T patients who must stop treatment with docetaxel or immune checkpoint inhibitors due to intolerable toxicity will be allowed to continue NovoTTF-200T either alone or with a next line of treatment according to local practice, based on the patient's wishes and investigator opinion.
- All study follow-up procedures will continue on both arms according to the study's protocol until PD in the thorax or liver per RECIST or irRECIST, after which only survival follow-up will be performed.

Criteria to continue treatment through RECIST-defined radiological progression of disease for immune checkpoint inhibitors and for NovoTTF-200T:

The criteria are applicable to the following patients:

1. Patients on both arms who receive immune checkpoint inhibitor and do not have disease progression per irRECIST criteria.
2. Patients on the device arm who do not have progression in the thorax and/or liver.

   Absence of clinical symptoms or signs indicating clinically significant disease progression:
   a. No decline in performance status;
   b. Absence of rapid disease progression or threat to vital organs or critical anatomical sites requiring urgent alternative medical intervention, e.g.:
      i. CNS metastasis
      ii. Respiratory failure due to tumor compression
      iii. Spinal cord compression
   c. No significant, unacceptable or irreversible toxicities related to study treatment

If the patient belongs to one of the groups (1 or 2) and meets the clinical criteria (a, b and c), a written consent should be obtained from patient acknowledging that continuation of treatment (TTFields and/or Immune Checkpoint Inhibitor) is not considered standard of care. A separate Informed Consent Form is available for this purpose.

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

1. Patient request – The patient may decide to stop the study treatment at any time, and irrespective of the reason.
2. Lack of compliance – The Sponsor or investigator may remove a patient from the treatment for lack of compliance with the study protocol.
3. Intolerable toxicity - Patients may be removed from study treatment for intolerable adverse events attributable to the device. Any serious adverse event deemed life threatening by the treating physician that is definitely related to the study device will be cause for immediate cessation of treatment. NovoTTF-200T patients who must stop treatment with docetaxel or immune checkpoint inhibitors due to intolerable toxicity will be allowed to continue NovoTTF-200T either alone or with a next line of treatment according to local practice, based on the patient's wishes and investigator opinion.
4. Progressive disease in the liver or thorax based on RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively).
5. Pregnancy

Follow-up per protocol will continue following removal from study treatment and until PD in the thorax or liver per RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively), as long as the patient does not withdraw consent from participating in the study follow up.

5.4 ENROLLMENT PLAN

a) Start Date of Enrollment

Enrollment of the first patient was in 2017.

b) Total Expected Duration of the Clinical Investigation

The study is expected to last for 66 months.

c) Expected Duration of Each Subject's Participation

Subject participation in the study is anticipated to be about 6-10 months.

d) Number of Subjects Required to be Included in the Clinical Investigation

A total of 276 patients (138 per treatment arm) will be accrued in this study.

e) Participating Regions

North America, Europe, Israel and China.

f) Estimated Enrollment Period

It is assumed that the accrual will take place over 54 months.

5.5 CLINICAL INVESTIGATION-RELATED PROCEDURES

Patients with available tissue from their initial diagnosis will be requested by the investigator prior to entering the study to give their consent for potential testing of genetic markers, which will be listed in a designated informed consent form and performed by a central lab. Providing a tissue sample is not mandatory in this study.

All patients receiving immune checkpoint inhibitors will have PD-L1 expression levels documented in the study CRFs. In addition, any available results of genetic testing performed on tumor tissue from the time of diagnosis will be recorded in the CRFs as well.

5.5.1 DOCETAXEL

Docetaxel is indicated as a single agent for locally advanced or metastatic NSCLC after platinum therapy failure. As a second line, single agent, docetaxel is administered at 75 mg/m^2 IV over 1 hour every 3 weeks.

Given the variability of infusion pumps from site to site, administration time may vary.

Patients with bilirubin greater than the upper limit of normal (ULN) should not receive docetaxel. Patients with AST and/or ALT greater than 1.5 x ULN concomitant with alkaline phosphatase greater than 2.5 x ULN should not receive docetaxel.

Docetaxel should not be administered until neutrophil count recovers to a level greater than 1500 cells/mm^3 and platelets recover to a level greater than 100,000 cells/mm^3. It should also not be administered in case of hypersensitivity to docetaxel or polysorbate 80.

The following dose adjustments should be used during the clinical study:

- For patients initially dosed at 75 mg/m^2 and experiencing febrile neutropenia, neutrophils less than 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other grade 3 or 4 non-hematologic toxicities: treatment should be withheld until resolution of the toxicity and then be resumed at 55 mg/m^2.
- Patients developing a grade 3 or greater peripheral neuropathy should have docetaxel treatment discontinued entirely.

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):

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %
Neutropenia		
Any	84	14
Grade 3/4	65	12
Leukopenia		
Any	84	6
Grade 3/4	49	0
Thrombocytopenia		
Any	8	0
Grade 3/4	3	0
Anemia		
Any	91	55
Grade 3/4	9	12
Febrile Neutropenia†	6	NA‡
Infection		
Any	34	29
Grade 3/4	10	6
Treatment Related Mortality	3	NA‡
Hypersensitivity Reactions		
Any	6	0
Grade 3/4	3	0
Fluid Retention		
Any	34	ND§
Severe	3	
Neurosensory		

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %
Any	23	14
Grade 3/4	2	6
Neuromotor		
Any	16	8
Grade 3/4	5	6
Skin		
Any	20	6
Grade 3/4	1	2
Gastrointestinal		
Nausea		
Any	34	31
Grade 3/4	5	4
Vomiting		
Any	22	27
Grade 3/4	3	2
Diarrhea		
Any	23	6
Grade 3/4	3	0
Alopecia	56	35
Asthenia		
Any	53	57
Severe¶	18	39
Stomatitis		
Any	26	6
Grade 3/4	2	0
Pulmonary		

Adverse Reaction	TAXOTERE 75 mg/m^2 n=176 %	Best Supportive Care n=49 %
Any	41	49
Grade 3/4	21	29
Nail Disorder		
Any	11	0
Severe¶	1	0
Myalgia		
Any	6	0
Severe¶	0	0
Arthralgia		
Any	3	2
Severe¶	0	0
Taste Perversion		
Any	6	0
Severe¶	1	0

* Normal Baseline LFTs: Transaminases ≤1.5 times ULN or alkaline phosphatase ≤2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN

†Febrile Neutropenia: ANC grade 4 with fever >38°C with intravenous antibiotics and/or hospitalization

‡Not Applicable

§Not Done

¶COSTART term and grading system

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

5.5.2 IMMUNE CHECKPOINT INHIBITORS

Nivolumab

Nivolumab is indicated for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on therapy for these aberrations prior to receiving nivolumab. It should be administered at a dose of 240 mg every 2 weeks or 480 mg every 4 weeks or as a weight based dose, dosing to be as per local standard of care until disease progression or unacceptable toxicity.

Nivolumab should be withheld for any of the following cases:

- Grade 2 pneumonitis
- Grade 2 or 3 diarrhea or colitis
- Grade 2 or 3 hypophysitis
- Grade 2 adrenal insufficiency
- Grade 3 hyperglycemia
- Encephalitis, new-onset moderate or severe neurologic signs or symptoms
- Grade 3 rash
- AST or ALT >3-5 x ULN or total bilirubin >1.5-3 x ULN
- Serum creatinine >1.5-6 x ULN or >1.5 times baseline
- Any other severe or grade 3 treatment-related adverse reaction
- May resume treatment for patients whose adverse reactions recover to grade 0-1

Nivolumab should be permanently discontinued for any of the following

- Any life-threatening or grade 4 adverse reactions
- Grade 3 or 4 pneumonitis
- Grade 3 diarrhea or colitis (nivolumab in combination with ipilimumab)
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Grade 3 or 4 adrenal insufficiency
- Grade 4 hyperglycemia
- Immune-mediated encephalitis
- Grade 4 rash
- AST or ALT >5 x ULN or total bilirubin >3 x ULN
- Serum creatinine >6 x ULN
- Any severe or grade 3 treatment-related adverse reaction that recurs
- Inability to reduce corticosteroid dose to ≤10 mg/day of prednisone or equivalent within 12 weeks
- Persistent grade 2 or 3 treatment-related adverse reactions that do not recover to grade 0-1 within 12 weeks after the last dose

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):

- Cough (% of patients with all grades – 30%, % of patients with grades 3-4 – 0.3%)
- Decreased appetite (29%, 1.7%)

- Constipation (23%, 0.7%)
- Pruritus (11%, 0%)

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

Pembrolizumab is indicated for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.

Pembrolizumab should be administered in a dose of 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes, or as a weight based dose, dosing to be as per standard of care until disease progression or unacceptable toxicity.

Given the variability of infusion pumps from site to site, administration time may vary.

Pembrolizumab needs to be withheld in the following cases:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Grade 3 or 4 endocrinopathies
- Grade 2 nephritis
- Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
- AST or ALT greater than 3 and up to 5 times ULN or total bilirubin greater than 1.5 and up to 3 times ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Pembrolizumab should be permanently discontinued in the following cases:

- Any life-threatening adverse reaction
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- Grade 4 severe skin reactions or confirmed SJS or TEN
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN. For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

The most frequent serious adverse reactions reported in at least 2% of patients treated with pembrolizumab for NSCLC in a clinical trial were pleural effusion, pneumonia, dyspnea, pulmonary embolism, and pneumonitis.

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):

Fatigue (44, 4)
Pyrexia (12, 1)
Peripheral Edema (10, 0)
Decreased appetite (25, 1)
Dyspnea (23, 4)
Cough (29, <1)
Nausea (18, 1)
Diarrhea (15, 1)
Constipation (15, <1)
Vomiting (12, 1)
Arthralgia (15, 1)
Back pain (10, 2)
Anemia (12, 2)
Pruritus (12, 0)
Rash (18, <1)

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

Atezolizumab is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) who have disease progression during or following platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving atezolizumab.

The recommended dose of atezolizumab is 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks, administered as an intravenous infusion over 60 until disease progression or unacceptable toxicity, dosing to be as per standard of care. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Given the variability of infusion pumps from site to site, administration time may vary.

No dose reductions of atezolizumab are recommended.

Withhold atezolizumab for any of the following:

- Grade 2 pneumonitis
- AST or ALT greater than 3 and up to 5 times upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times ULN
- Grade 2 or 3 diarrhea or colitis
- Symptomatic hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism, or Grade 3 or 4 hyperglycemia
- Grade 2 ocular inflammatory toxicity
- Grade 2 or 3 pancreatitis, or Grade 3 or 4 increases in amylase or lipase levels (greater than 2 times ULN)
- Grade 3 or 4 infection
- Grade 2 infusion-related reactions
- Grade 3 rash

Atezolizumab may be resumed in patients whose adverse reactions recover to Grade 0–1.

Permanently discontinue atezolizumab for any of the following:

- Grade 3 or 4 pneumonitis
- AST or ALT greater than 5 times ULN or total bilirubin greater than 3 times ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis (all grades)
- Grade 3 or 4 ocular inflammatory toxicity
- Grade 4 or any grade of recurrent pancreatitis
- Grade 3 or 4 infusion-related reactions
- Grade 4 rash

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 please refer to section 2 (dose modification) and section 5 (warnings and precautions) of the Nivolumab US package insert found at:

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

For Pembrolizumab please refer to section 2 (dose modification) and section 5 (warnings and precautions) of the Pembrolizumab US package insert found at:

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

For Atezolizumab please refer to section 2 (dose modification) and section 5 (warnings and precautions) of the Atezolizumab US package insert found at:

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

5.5.3 NOVOTTF-200T SYSTEM TREATMENT

1. Treatment planning: Transducer array layout will be determined by the investigator based on the *Clinical Practice Guidelines: Optimizing the transducer array layout in TTFields-treated patients (thoracic malignancies)* (**Appendix E**). Array layout may be modified by the investigator throughout the TTFields treatment period, based on anatomical location of the disease in the thorax and liver. The array layout will be chosen to maximize the TTFields intensity in the area of maximal disease burden in the thorax and liver based on the baseline CT scan.
2. Patient training: Patients will be trained in the use of the device by the investigator, a designated health care provider (e.g., nurse) or a Device Support Specialist (DSS) trained by Novocure.
3. Treatment initiation: It is the responsibility of the investigator to oversee the treatment start supported by the Novocure Device Support Specialist (DSS). NovoTTF-200T will be initiated within 7 days of randomization, preferably concomitant to the administration of docetaxel / immune checkpoint inhibitors, and in any case between +/- 3 days of administering the systemic treatment. Patients with hair on the upper torso will be required to shave it prior to array placement, where arrays are planned to be applied. Array placement will be performed based on the Transducer Array Layout map planned by the investigator prior to treatment initiation, avoiding areas of skin damage such as wounds. The device cannot be used in shower, bath tub, sink or in heavy rain conditions.
4. Treatment duration: TTFields application will be continuous with for at least 18 hours a day on average. Patients may take breaks for personal needs (e.g. showering, array exchange) as long as the average treatment remains 18 hours per day. TTFields will be continued until progression in the thorax and/or liver according to RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively), or any of the treatment discontinuation conditions described under Criteria for Removal from Study Treatment above.
5. The NovoTTF-200T System will be programmed by Novocure to deliver 150kHz TTFields in two sequential, perpendicular field directions at a maximal intensity of 1414 mA RMS. There will be no adjustments made to the device by investigators or patients/caregivers.
6. Transducer Array replacement: Patients will replace the Transducer Arrays twice to three times per week with the help of a caregiver. At each array replacement the patient's skin will be re-shaved if needed, and treated according to the guidelines set out below.
7. Usage time assessment: The device will be inspected by a Novocure representative on a routine basis and usage time report based on device captured treatment time will be sent to the investigator on a monthly basis.
8. The following skin care guidelines should be closely adhered to:
    a. At the earliest time possible following initial evidence of skin inflammation (e.g. redness, edema, itchiness), a high potency topical steroid (e.g. clobetasol) should be prescribed to the patient. The patient or caregiver should apply the ointment after removing the arrays and cleaning the skin with baby oil and medical alcohol. The ointment should be left on

the skin for at least 30 minutes prior to washing the skin with a mild soap and applying a new set of arrays.

b. If the epidermis is breached (skin erosions, ulcers, open sores, punctate lesions, etc.) and in case of folliculitis, an antibiotic ointment (e.g. mupirocin) should be prescribed and used in place of the steroid ointment. Any evidence of infection should result in bacterial cultures being taken.
c. At each array replacement, the new set of arrays should be shifted by approximately 2 cm compared to the previous layout so that the array discs are placed between the areas of skin irritation. At the next array replacement, the arrays should be shifted back to their original location.
d. There will be no "dose" adjustments to the device for adverse events. Reasons for breaks in treatment for longer than 24 hours will be documented in the Case Report Forms (CRFs). The maximum duration of treatment break allowed for AEs related to TTFields is 3 weeks.

9. Patient on the study who initiated treatment with the NovoTTF-100L System will be offered to switch to the NovoTTF-200T System. After providing their consent, the patients will receive training on using the new device and the switch will be recorded in the CRFs

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. Patients should not receive any other anti-cancer therapy directed while on study (outside of protocol treatment) prior to disease progression on the study, after which they can receive standard NSCLC-directed therapy.

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. Surgery and radiation therapy are allowed prior to disease progression.

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 14 days of randomization:

1. Verification that an informed consent is signed
2. Medical history recording
3. PD-L1 expression level recording and local genetic test results (if applicable or available)
4. Concomitant medications recording
5. Performance Status assessment (ECOG Score)
6. Physical examination (head and neck, cardiac, pulmonary, abdominal, skin, extremities, neurological examinations) and vital signs (weight, temperature, respiratory rate, blood pressure, heart rate)
7. Serum pregnancy test (if applicable)

8. Complete blood count including differential
9. Serum chemistry panel, including:
    a. BUN/Urea, Creatinine
    b. Sodium, Potassium
    c. Glucose
    d. ALT, AST, ALP, Bilirubin
10. Coagulation tests (PT/INR, aPTT/PTT)
11. MRI of brain
12. Quality of Life questionnaire (EORTC QLQ C30 with LC13 addendum)

The following will be performed within 28 days of randomization:

1. CT scan of chest and abdomen - CT/PET scan may be used in lieu of CT scan as long as the CT scan is of diagnostic quality
2. Bone scan (as indicated)

Patients with available tissue from their initial diagnosis will be requested by the investigator prior to entering the study to give their consent for potential testing of genetic markers (not mandatory for enrollment in the study). Submission of the following material is required for tissue evaluation:

- Representative formalin-fixed and paraffin-embedded (FFPE) tumor tissue blocks. Slides are not desirable but optional in case no tissue blocks are available for testing.
- In case tissue samples are collected from study subjects, they will be kept at the Central Pathologist site until the molecular testing has been performed. After the end of the study, the tissue blocks will be returned to the local pathologists or centers.
- On specific request for medical reasons by the investigator or pathologist the block is shipped promptly back to the site.
- Shipping supplies and lab detailed specifications will be provided by Novocure for each site.
- The shipment should be accompanied by an anonymized copy of the local pathology report or a completed Local Pathology Form documenting and identifying the submitted material. This will include protocol number, local institution information, patient identifier and pathological data. The patient's name and/or other identifying information should be removed from the form.
- Every effort should be made to obtain FFPE tumor tissue block for a patient from a referral center.

If the assessments listed above were performed by participants before signature of ICF in accordance with local routine practice and within the screening/baseline windows as defined above, such assessments do not need to be repeated.

6.2 RANDOMIZATION VISIT

Randomization will be performed within 28 days of signing the informed consent form for patients who met all eligibility criteria. At the time of randomization, Patients will be stratified by tumor histology (non-squamous vs. squamous) and standard of care chosen (immune checkpoint Inhibitor or Docetaxel).

Patients are centrally randomized using an IxRS system at a 1:1 ratio to 2 treatment arms:

1. Arm I: Patients receive TTFields using the NovoTTF-200T System together with Immune checkpoint inhibitors or Docetaxel.
2. Arm II: Patients receive Immune checkpoint inhibitors or Docetaxel.

6.3 FOLLOW-UP VISIT

The following procedures will be performed for all study patients once every 6 weeks (±1 week) until PD in the thorax and/or liver per RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively):

1. Adverse Event and device deficiency collection and recording
2. Concomitant medications recording
3. Performance Status assessment (ECOG Score)
4. Review of treatment usage time with the patient
5. Physical examination (head and neck, cardiac, pulmonary, abdominal, skin, extremities, neurological examinations) and vital signs (temperature, respiratory rate, blood pressure, heart rate)
6. Complete blood count including differential
7. Serum chemistry panel, including:
    a. BUN/Urea, Creatinine
    b. Sodium, Potassium
    c. Glucose
    d. ALT, AST, ALP, Bilirubin
8. Coagulation tests (PT/INR, aPTT/PTT) – only if clinically relevant
9. CT scan of chest and abdomen - CT/PET scan may be used in lieu of CT scan as long as the CT scan is of diagnostic quality
10. CT scan or MRI of brain (as indicated)
11. Bone scan (as indicated)
12. For all patients – radiological assessment per RECIST Criteria
13. For patients treated with immune checkpoint inhibitors – radiological assessment per irRECIST in addition to assessment per RECIST Criteria
14. Quality of Life questionnaire (EORTC QLQ C30 with LC13 addendum)

Follow up after TTFields and/or systemic therapy discontinuation for any reason will continue in both arms according to the above until PD in the thorax and/or liver per RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively), excluding review of TTFields treatment usage time for patients on the device arm.

After 1 year of follow-up in the absence of PD, imaging examinations may be performed every 12 weeks.

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)

The following procedures will be performed for all study patients 30 days (±1 week), 60 days (±1 week) and 100 days (100-107 days) after disease progression (PD) in the thorax and/or liver per RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively). This follow up is not required if a study follow up visit took place more than 100 days after last study treatment.

1. Adverse Event and device deficiency collection and recording

2. Concomitant medications recording
3. Performance Status assessment (ECOG Score)
4. Physical examination (head and neck, cardiac, pulmonary, abdominal, skin, extremities, neurological examinations) and vital signs (temperature, respiratory rate, blood pressure, heart rate)
5. Complete blood count including differential
6. Serum chemistry panel, including:
    a. BUN/Urea, Creatinine
    b. Sodium, Potassium
    c. Glucose
    d. ALT, AST, ALP, Bilirubin
7. Coagulation tests (PT/INR, aPTT/PTT) – only if clinically relevant

6.5 SURVIVAL FOLLOW-UP

Following the post progression visits, patients will be followed every 4 weeks (±1 week) for survival (this can include telephone call follow-up and does not require a clinical visit at the study center). 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 a CRO assigned this responsibility by the Sponsor 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: on-site visits and review of study documents and results. The CRO will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits will take place at each center, during the course of the study (as long as there are patients in follow up at the site), 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 that the Investigators:

1. have appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
2. have the approval of the supervising Institutional Review Board (IRB) or Ethics Committee (EC) for the Investigational Plan;
3. have all study documentation and required records on site; and
4. assume responsibility for the investigation at their center.

Visits during the study are intended to assess Investigators' adherence to the Investigational Plan, maintenance of records, reports and investigational devices, and review of source documents for accuracy, completeness, and legibility. During these study visits, the monitor is required to assess the progress of the study toward meeting study objectives, and to identify any concerns that stem from observations of device performance and/or review of the Investigator's patient records, study

management documents, and informed consent documents, and to ensure accountability of all patients that have been treated under the study.

The monitor's final on-site visit at completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the Investigators and their staff members. Reports of the on-site visits will be made by the monitor and should include resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, the monitor will prepare a final report.

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 of NovoTTF-100L with Pemetrexed compared to Pemetrexed alone, overall survival was 13.8 vs. 8.3 months, respectively, corresponding to a Hazard ratio of 0.60. Since the EF-15 study was a non-randomized trial, it is possible the effect size of NovoTTF-100L was overestimated. Therefore, the Sponsor chose a Hazard ratio of 0.75 for the sample size assessment in the current protocol. Such a hazard ratio is considered highly significant clinically in oncology trials.

The primary endpoint is overall survival. Overall survival will be tested using two sided proportional hazards at an alpha of 0.05. 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), each tested at the 0.05 (two-sided) level:

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 = $h_{TTFields + Immune} / h_{Immune} < 0.75$

In addition, an exploratory analysis will be performed to test non-inferiority of TTFields with docetaxel compared to checkpoint inhibitors alone. Immune checkpoint inhibitors have been shown to extend survival with a HR of 0.67 compared to Docetaxel; a non-inferiority margin of 50% is equal to an upper bound of the HR Confidence interval of 1.25. If the confidence interval excludes 1.25 then the Sponsor can generate the hypothsis that TTFields with SOC of Docetaxel are non-inferior to SOC of Immune checkpoint inhibitors.

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:

1. 25% of patients will have squamous histology and 75% non-squamous histology
2. Standard of care treatments in both arms will consist of 40% Docetaxel and 60% Immune checkpoint inhibitors
3. Of the patients receiving Immune checkpoint inhibitors, two thirds will receive Nivolumab, one sixth Pembrolizumab and one sixth Atezolizumab.

Based on these assumptions and the reported survival benefit of each of the standard of care agents defined in the protocol, the expected survival of the control arm (calculated based on the weighted average of reported median overall survival by the expected use of each drug in the studies described in Section 2.1 above) is as follows:

1. All control patients: Median survival = 10.78 months
2. Patients on Immune checkpoint inhibitors: Median Survival = 12.05 months
3. Patients on Docetaxel: Median Survival = 8.9 months

The following table elaborates on the rationale for the expected median overall survival (in months) of the control arm patients based on the literature:

Trial	Median Overall Survival (in Months)					
	Nivolumab vs. Docetaxel		Pembrolizumab vs. Docetaxel		Atezolizumab vs. docetaxel	
Histology	Nivolumab	Docetaxel	Pembrolizumab	Docetaxel	Atezolizumab	Docetaxel
Squamous	9.2	6	NA	NA	8.9	7.7
Non-Squamous	12.2	9.4	NA	NA	15.6	11.2
All	11.45	8.55	12.7	8.5	13.8	9.6

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).

In order to detect a Hazard ratio of <0.75 of NovoTTF-200T treated patients compared to the control group (corresponding to an increase in median OS from 10.8 months to 14.3 months respectively), the study was originally designed to accrue a sample size of 240 patients per arm (480 patients total) in order to achieve a power of 80% at a two sided alpha level of 0.05. To allow for 10% loss to follow up in the study, the total sample size was therefore designed to be 534 patients (267 in each arm). Sample size assessment was performed using the SAS 9.4 software package using a logrank test.

One interim analysis was planned to be performed on the OS data available after 432 patients out of 534 patients have been enrolled. The interim analysis was be performed by the DMC statistician and shared with the DMC members. The results of the analysis were not planned to be shared with the study investigators or the sponsor unless the DMC recommended stopping the study for futility or success at the interim analysis. In order to allow for two analyses (interim, and final) in the study, the alpha level used at each time point was calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function (approximately 0.00306 at the interim analysis and 0.04694 at the final analysis). If the primary endpoint met the predefined threshold of $p < 0.00306$ at the interim analysis, the study may have been stopped early for efficacy.

The sponsor was planned to use conditional power (CP) to assess the need for early termination for futility. This was planned to be calculated at the interim analysis using the logrank score statistic of the data collected until the interim point and the specific assumptions about the treatment effect estimated by the original sample size design. The futility index (one minus the conditional power) is the probability of accepting the null hypothesis under the alternative hypothesis given the interim data. A high futility index indicates a small probability of success (rejecting H_0). The study was to be stopped if the futility index is above 0.9.

The assumptions used in the sample size calculations were planned to be evaluated at the interim analysis. If it appeared that the event rate and/or the treatment effect may be smaller than expected, adaptation of the sample size would have been considered in order to allow for adequate study power. The DMC could recommend to the study sponsor to continue enrollment of the study in order to reach a larger sample size adequately powered to test the primary endpoint. The DMC were not allowed to recommend lowering the sample size, nor powering the study to achieve a hazard ratio >0.80.

A total of 210 sites will participate in this study in order to allow for the entire study to be accrued within 54 months. At least 30% of the sites will be in the United States.

On March 31st, 2021, the LUNAR Study independent DMC conducted their annual review of the study. In addition, the DMC conducted the prespecified Interim Analysis per the LUNAR study protocol. The interim analysis was performed by the DMC statistician and shared with the DMC members. Following the review of interim data analysis, the DMC concluded that continuing accrual up to 534 patients as originally planned is likely unnecessary and possibly unethical. The DMC recommended to accrue a total of approximately 276 patients with 12 months follow up, which would provide appropriate toxicity and efficacy data to evaluate the planned LUNAR study endpoints, while maintaining the statistical power of the study. The DMC recommended to make no further changes to the study protocol. The Study Sponsor as well as all study investigators remained blinded to all study data.

8.4 RANDOMIZATION AND STRATIFICATION

Patients will be stratified by tumor histology (non-squamous vs. squamous) and standard of care chosen (immune checkpoint inhibitors or Docetaxel). Patients are centrally randomized using an IxRS system at a 1:1 ratio to 2 treatment arms within 28 days of ICF signature, using variable blocked randomization:

1. Arm I: Patients receive TTFields using the NovoTTF-200T System together with Immune checkpoint inhibitors or Docetaxel.
2. Arm II: Patients receive Immune checkpoint inhibitors or Docetaxel.

8.5 DATA MONITORING COMMITTEE

An independent Data and Monitoring Committee (DMC), comprised of an oncologist, pulmonologist and statistician (independent from the study) will be formed to monitor the safety data from the study. Although there are no anticipated significant safety issues with the device, the adverse event data will be reviewed by the DMC to determine if there are any unexpected safety concerns with the device that warrant study termination or if the study should be stopped for futility or efficacy purposes (futility and efficacy will be tested at the pre-specified interim analysis only).

Specifically, DMC safety reviews will be performed once after 20 patients on the study have received at least one month of treatment with TTFields concomitant to immune checkpoint inhibitors and then again after 40 patients on the study have received at least one month of treatment with TTFields concomitant to immune checkpoint inhibitors. The DMC will also perform a safety review after the first 20 patients treated with TTFields have a minimum follow up of 100 days after the last treatment day with TTFields. 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:

- All adverse events, including serious adverse events and device or drug related AEs
- Overall survival of patients enrolled in the study

9 DATA MANAGEMENT

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 designee. 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 designee. 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.

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. The site will not destroy such records without giving the Sponsor prior written notice and the opportunity to further store such records, at the

Sponsor's cost and expense. CRFs will be retained for a minimal period of 10 years after completion of the study. Clinical records kept by the Sponsor will be held in locked cabinet.

10 AMENDMENTS TO THE PROTOCOL

All protocol amendments will be submitted to the 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 protocols 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 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. Such deviations shall be documented and reported to the Sponsor and the IRBs/ECs as soon as possible, but in no event later than 5 working days after the emergency occurred.

Protocol deviations are to be reported in the deviation/violation log provided with the investigator site file and the CRF. Serious protocol deviations are to be reported in writing with the corresponding log to Sponsor and to IRBs/ ECs within 24 hours. Investigators will be retrained by the Sponsor or its representative. Investigators not complying with the protocol might be at the discretion of the Sponsor disqualified to the participation in the clinical study.

12 DEVICE ACCOUNTABILITY

Device accountability is ensured by Novocure through the following procedures:

- Shipping of clinical devices: SOP-USOC-003 Final release
- Use of clinical devices : SAP ERP
- Return of clinical devices : SOP-USOC-006 : Technical support-RMA Process

When a new patient enrolls to the device arm of the study, the equipment and arrays are provided by Novocure to the patient. At this time all ongoing corresponding inventory movement transactions are completed within the ERP to show that the specific serial numbers and lot numbers have been allocated to this specific patient number (patients are identified by number only).

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

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, personnel of the relevant participating Center must try to obtain acknowledgment before the patient participates in this study. The Center'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.

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 patient privacy concerning research specific information. In addition to signing the IRB/EC Informed Consent, all patients must sign the Research Authorization component of the informed consent form where applicable. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents. All patients 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 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.

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes

listed above. Serious may also include any other event that the investigator or company judges to be serious. In addition, sites are responsible for reporting serious adverse events to their local IRB/EC according to their institutional requirements.

A planned hospitalization for pre-existing condition, or a procedure required by the clinical investigation plan, without a serious deterioration in health, is not considered to be a serious adverse event.

Hospitalization duration of less than 24 hours is not considered to be a seriousness criterion.

Disease Progression per se is not considered as an adverse event unless it meets the above mentioned criteria/outcomes, then it has to be reported as serious adverse event.

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 the applicable national regulations in all participating countries. Novocure will be responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation.

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

1. Review the investigator's assessment of all **serious adverse events** and determine and document in writing their relationship to the investigational device;
2. Review all DDs and determine and document in writing whether they could have led to a serious adverse device effect.
3. Report or ensure the reporting to the IRB/EC by the Principal Investigator(s), of all **serious adverse events, UADEs/USADEs** and **device deficiencies** that could have led to a serious adverse device effect, if required by national regulations or by the IRB/EC.
4. Report to regulatory authorities, within the required time period, all **serious adverse events**, **UADEs/USADEs**, and **device deficiencies** that could have led to a serious adverse device effect, if required by national regulations.

5. Report all relevant safety information to the DMC, according to written procedures.
   Ensure that the IRB/EC and the regulatory authorities are informed of significant new information about the clinical investigation.
6. In case of **serious adverse device effects**, **UADEs/USADEs,** and **device deficiencies** that could have led to serious adverse device effects, determine whether risk analysis needs to be updated and assess whether corrective or preventive action is required.

Reportable events will be reported by the Sponsor's safety officer (Sharon Perez, Novocure Inc., 195 Commerce Way, Portsmouth, NH 03801, United States, email: DeviceSafety@novocure.com, Phone: +1 603 319 1907 or designee.).

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. If the toxicity is not characterized adequately by the NCI toxicity scale, the investigator will use the adjectives MILD, MODERATE, SEVERE, POTENTIALLY LIFE-THREATENING and DEATH 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 prolongation of hospitalization indicated; disabling; limiting self care ADL
POTENTIALLY LIFE-THREATENING	Grade 4	Life-threatening consequences; urgent intervention indicated.
DEATH	Grade 5	Death related to AE.

Modified Grading for TTFields-Related Skin Adverse Events:

Grade 1 – Asymptomatic or mild symptoms AND 1. No intervention required OR only topical treatment intervention indicated 2. Treatment interruption of less than 3 days may be required.
Grade 2 – Moderate symptoms AND Systemic therapy required OR event is requiring interruption of TTFields for more than 3 days.
Grade 3 – Severe or medically significant but not immediately life threatening AND hospitalization OR prolongation of existing hospitalization indicated
Grade 4 –

Life threatening consequences AND urgent intervention indicated

15.4 DETERMINATION OF CAUSALITY OF ADVERSE EVENTS

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

None:	The event is clearly related to an event that may be due to environmental or accidental occurrence or other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Unlikely	The event is most likely produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and** does not follow a known response pattern to the study drug or device.
Possible	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and/or** follows a known response pattern to the study drug or device, **but** could have been produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Probable	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Definite	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and either** occurs immediately following study drug administration or use of device **or** improves on stopping the study drug or device, **or** reappears on repeat exposure.

15.5 ELICITING ADVERSE EVENT INFORMATION

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study patient using concise medical terminology. In addition, each study patient will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be, "Since your last clinic visit have you had any health problems?"

15.6 ADVERSE EVENT REPORTING PERIOD

The adverse event reporting period will begin immediately following randomization. Adverse events will be collected for 100 days 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, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the adverse event reporting period that the investigator assesses as possibly, probably or definitely related to the investigational device should also be reported as an adverse event.

15.7 FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS

All adverse events should be followed until they are resolved or the investigator assesses them as chronic or stable or the patient's participation in the study ends.

In addition, all serious adverse events and those non-serious events assessed by the investigator as possibly, probably or definitely related to the investigational device should continue to be followed even after the patient's participation in the study is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

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

Reportable events will be reported by Sharon Perez, Novocure Inc., 195 Commerce Way, Portsmouth, NH 03801, United States, email: DeviceSafety@novocure.com , Phone: +1 603 319 1907 or designee.

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 the National Competent Authorities where the clinical investigation has commenced, if required by national regulations:

- for all reportable events as described in section 15.8.1 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it: immediately, but not later than 2 calendar days after awareness by Novocure of a new reportable event or of new information in relation with an already reported event.

- any other reportable events as described in section 15.8.1 or a new finding/update to it: immediately, but not later than 7 calendar days following the date of awareness by Novocure of the new reportable event or of new information in relation with an already reported event.

The Investigator should submit to the Medical Monitor a report of any UADE occurring during the study immediately but not later than 1 business day and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. The Medical Monitor will investigate if the event is UADE and, if so, report it to Novocure, as soon as possible but no later than 3 days after learning of the event. Expedited report to health authorities and to all reviewing IRBs/ECs and participating Investigators will follow within 10 working days after first learning of the event by the Medical Monitor.

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. The Investigator will follow-up with the subject periodically during the pregnancy and document its outcome. If the pregnancy or outcome of the pregnancy is associated with an SAE, that SAE should be reported. SAEs will include any report of congenital anomaly/birth defect, elective termination for medical reasons, or spontaneous miscarriage.

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 monitoring or auditing identifies serious or repeated deviations on the part of an investigator. If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and Novocure shall keep each other informed of any communication received from either the EC or the regulatory authority.

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,

- Novocure shall remain responsible for providing resources to fulfill the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical investigation, and
- the Principal Investigator or authorized designee shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

When Novocure concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions and decides to lift the temporary suspension, Novocure shall inform the Principal Investigators, the ECs, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the IRBs/ECs and, where appropriate, regulatory authorities before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee shall inform them of the reasons for resumption.

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

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.

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

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

	SCREENING / BASELINE		RANDOMIZATION	FOLLOW UP	POST PD IN THE THORAX AND/OR LIVER	SURVIVAL FOLLOW UP
	T=(-28)-0 days (baseline evaluation)	T=(-14)-0 days (baseline evaluation)	T=Day 0	T= q6 weeks from randomization until PD in the thorax and/or liver (day 42, 84, … ± 7 days)	T=30 ± 7; 60 ± 7; 100-107 days after PD in the thorax and/or liver	T= q4 weeks after last visit (day 28, 56, … post last visit +/- 7 days)
Coagulation tests		+		#	#	
Quality of life questionnaire		+		+		
Randomization			+			
Adverse Events and device deficiency				+	+	
Review of treatment usage time				+		
Radiological Assessment per irRECIST/RECIST				+		
Telephone Follow up for survival						+

+ : Item should be performed during the designated visit

: Item should be performed during the designated visit only if clinically relevant/applicable

- PD-L1 expression and genetic test results will be collected if applicable and available
- Physical examination includes head and neck, cardiac, pulmonary, abdominal, skin, extremities, neurological examinations and vital signs (weight at screening/baseline, temperature, respiratory rate, blood pressure, heart rate).
- Serum Chemistry includes: BUN/Urea, creatinine, sodium, potassium, glucose, ALT, AST, ALP, bilirubin
- Coagulation tests include: PT/INR, aPTT/PTT
- MRI (and not CT) scan of the brain must be performed at baseline
- The EORTC QLQ C30 with LC13 addendum will be used as the quality of life questionnaire
- Radiological assessment: RECIST Criteria for all patients, irRECIST for patients treated with immune checkpoint inhibitors After 1 year of follow-up in the absence of PD, imaging examinations may be performed every 12 weeks

- Post PD follow up is not required if a study follow up visit took place more than 100 days after last study treatment

APPENDIX C IMMUNE-RELATED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Nishino M et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013

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

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Statistical Analysis Plan

Novocure GmbH

EF-24

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

Covance Study ID: 13092

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Clinical Development Commercialization Services

Table of Contents

Reviewers 4
Glossary of Abbreviations 5
1. Source Documents 6
2. Protocol Details 6
2.1. Study Objectives 6
2.1.1. Primary Objectives 6
2.1.2. Secondary Objectives 6
2.2. Overall Study Design 7
2.3. Sample Size and Power 9
3. Efficacy and Safety Variables 10
3.1. Primary Efficacy Endpoint 10
3.2. Secondary Efficacy Endpoints 10
3.2.1. Key Secondary Efficacy Endpoints 10
3.2.2. Additional Secondary Efficacy Endpoints 10
3.3. Safety Variables 13
3.3.1. Extend of Exposure and Device compliance 13
3.3.2. Adverse Events (AEs) 13
3.3.3. Laboratory Evaluations 14
3.3.4. Vital Signs 14
3.3.5. Physical Examination 15
4. Pharmacokinetic/Pharmacodynamic variables 15
5. Analysis populations 15
5.1. Intent-to-treat Population 15
5.2. Safety Population 15
6. DATA Handling 15
6.1. Time points and Visit Windows 15
6.2. Handling of Dropouts, Missing Data, and Outliers 16
7. Statistical Methods 16
7.1. General Principles 16
7.2. Subject Disposition and Data Sets Analyzed 18

7.3. Protocol Deviations 18
7.4. Demographics and Other Baseline Characteristics 19
7.5. Medical History 20
7.6. Previous and Concomitant Medications 20
7.7. Efficacy 21
7.7.1. Primary Efficacy Analysis 21
7.7.2. Secondary Efficacy Analysis 21
7.7.3. Exploratory Secondary Efficacy Analysis 23
7.7.4. Sensitivity Analysis 28
7.7.5. Subgroup Analysis 28
7.8. Safety 29
7.8.1. Extent of Exposure and device compliance 29
7.8.2. Adverse Events 30
7.8.3. Adverse Device Effect (ADE) and Serious Adverse Device Effect (SADE) .... **Error! Bookmark not defined.**
7.8.4. Unanticipated Adverse Device Effect (UADE) and Unanticipated Serious Adverse Device Effect (USADE) ..... **Error! Bookmark not defined.**
7.8.5. Device Deficiency ..... **Error! Bookmark not defined.**
7.8.6. Laboratory Evaluations 31
7.8.7. Vital Signs 32
7.8.8. Physical Examination 32
7.9. Interim Analysis 32
8. Changes in Planned Analysis 33
9. References 34
10. Appendices 35
10.1. EF-24 Study Calendar 35
10.2. Scoring algorithm for the EORTC-QLQC30 37
10.3. Scoring algorithm for the LC13 39

Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
ADE	Adverse Device Effect
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence Interval
Cm	Centimeter
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DD	Device Deficiency
DMC	Data and Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	Food and Drug Administration
irRECIST	Immune-Related Response Evaluation Criteria In Solid Tumors
ITT	Intent to Treat
MRI	Magnetic Resonance Imaging
MST:	Mean Survival Time
NSCLC	Non-Small-Cell Lung Cancer
OS	Overall Survival
PD-L1	Programmed Death Ligand 1
PFS	Progression Free Survival
PT	Prothrombin time
PTT	Partial Thromboplastin Time
QLQ C-30	EORTC's Quality of life Questionnaire
QLQ- LC13	EORTC's Cancer Quality of life Questionnaire Lung Cancer Module
RECIST:	Response Evaluation Criteria In Solid Tumors
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAF	Safety Population
SOC	Standard of Care
TTFields	Tumor Treatment Fields
UADE	Unanticipated adverse device effect
ULN	Upper Limit Normal
USADE	Unanticipated Serious Adverse Device Effect

1. SOURCE DOCUMENTS

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	Last approval date-31MAY2021	6
eCRF	10JUN2021	

2. PROTOCOL DETAILS

2.1. Study Objectives

2.1.1. Primary Objectives

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.

2.1.2. 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.
3. 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.
4. 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.
5. 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.

6. 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.
7. To analyze the effects of NovoTTF-100L with each type of immune checkpoint inhibitor on OS and PFS.
8. To analyze the effects of NovoTTF-100L on OS and PFS within each histological subgroup (squamous and non-squamous).
9. To analyze whether average monthly usage of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.
10. To assess adverse events, severity and frequency, associated with treating patients with docetaxel or immune checkpoint inhibitors concomitant with TTFields using the NovoTTF-100L System.

2.2. Overall Study Design

This is a pivotal prospective, randomized, open-label multicenter study. This randomized study is designed to test the efficacy and safety of TTFields, using the NovoTTF-100L System, concurrent with standard therapies for stage 4 non-small cell lung cancer (NSCLC) patients, following progression while on or after platinum based treatment. The study population are the patients with histology based diagnosis of stage 4 NSCLC, above 22 years of age, following disease progression on or after receiving platinum based chemotherapy. Patients will be stratified as below:

- Standard of care therapy:
  - Immune checkpoint inhibitor
  - Docetaxel
- Histology:
  - Squamous
  - Non-Squamous
- Region:
  - North America
  - Western Europe and Israel
  - Eastern Europe

A total of 534 patients with NSCLC will be centrally randomized using an IxRS system at a 1:1 ratio to 2 treatment arms (267 per treatment arm) within 28 days of signing the informed consent form:

- Arm I: Patients who receive docetaxel or immune checkpoint inhibitor concomitant with TTFields using the NovoTTF-100L System set to an output frequency of 150kHz.
- Arm II: Patients who receive docetaxel or immune checkpoint inhibitors without TTFields.

As described in Section 2.3 the sample size was reduced from 534 to 276 patients, equally distributed to treatment arms I and II.

On both arms, patients receiving docetaxel whose lung cancer progresses based on RECIST criteria, or perceiving immune checkpoint inhibitors whose lung cancer progresses based on irRECIST criteria, will switch to a next line of treatment according to local practice.

Patients on arm I will initiate NovoTTF-100M by the investigator within 7 days of randomization, preferably concomitant to the administration of docetaxel / immune checkpoint inhibitors, and in any case between +/- 3 days of administering the systemic treatment. NovoTTF-100L treatment delivers TTFields to the thorax and liver. Therefore patients receiving NovoTTF-100L 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). Patients must use the device for at least 18 hours a day on average. The maximum duration of treatment break allowed for AEs related to TTFields is 3 weeks.

For standard of care agents, Docetaxel is administered at 75 mg/m^2 IV over 1 hour every 3 weeks. Three drugs as immune checkpoint inhibitors will be used in this study, Nivolumab, Pembrolizumab, and Atezolizumab. Nivolumab is administered at a dose of 240 mg every 2 weeks, pembrolizumab is administered in a dose of 200 mg every 3 weeks, and Atezolizumab is administered in a dose of 1200 mg as an intravenous infusion over 60 minutes every 3 weeks. Patients will remain on standard of care treatment until disease progression or unacceptable toxicity. Dose modification may be used in the Docetaxel, but not in all immune checkpoint inhibitors.

Patients on both arms should also receive the best supportive care available at each site. Following progression patients may be offered standard NSCLC-directed therapy and salvage therapy based on local practice at each site. Surgery and radiation therapy are allowed prior to disease progression.

The overall schedule of the study is as follows:

1. Screening period. Baseline evaluation will be performed within 14 days of randomization.
2. Randomization will be performed within 28 days of signing the informed consent form.
3. NovoTTF-100M will be initiated within 7 days after randomization. Treatment will be continuing until progression (PD) in the liver or thorax according to RECIST or irRECIST (based on their standard treatment). During treatment period, follow-up visit will be performed once every 6 week (±1 week). After 1 year of follow-up in the absence of PD, imaging examination may be performed every 12 weeks.
4. Post progression follow up will be performed for all patients 30 days (±1 week), 60 days (±1 week), and 100 days (±1 week) after disease progression (PD) in the liver or thorax.
5. Survival follow-up will be performed every 4 weeks (±1 week) for survival following post progression visits.

Detail schedule of events are included in the appendix 10.1.

2.3. Sample Size and Power

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

1. 25% of patients will have squamous histology and 75% non-squamous histology
2. Standard of care treatments in both arms will consist of 40% Docetaxel and 60% Immune checkpoint inhibitors
3. Of the patients receiving Immune checkpoint inhibitors, two thirds will receive Nivolumab, one sixth Pembrolizumab and one sixth Atezolizumab.

Based on these assumptions and the reported survival benefit of each of the standard of care agents defined in the protocol, the expected survival of the control arm is as follows:

- All control patients: Median survival = 10.78 months
- Patients on Immune checkpoint inhibitors: Median Survival = 12.05 months
- Patients on Docetaxel: Median Survival = 8.9 months

Patient accrual will last 30 months and follow up for an additional 18 months (48 months total study duration).

In order to detect a Hazard ratio of <0.75 of NovoTTF-100L treated patients compared to the control group (corresponding to an increase in median OS from 10.8 months to 14.3 months respectively), a sample size of 240 patients per arm (480

patients total) is required to achieve a power of 80% at a two sided alpha level of 0.05. To allow for 10% loss to follow up in the study, the total sample size will be 534 patients (267 in each arm). Sample size assessment was performed using the SAS 9.4 software package.

On March 31st, 2021, an interim analysis was performed by the DMC statistician and shared with the DMC members. Following the review of interim data analysis, the DMC concluded that continuing accrual up to 534 patients as originally planned is likely unnecessary and possibly unethical. The DMC recommended to accrue a total of approximately 276 patients with 12 months follow up, which would provide appropriate toxicity and efficacy data to evaluate the planned LUNAR study endpoints, while maintaining the statistical power of the study.

3. EFFICACY AND SAFETY VARIABLES

3.1. Primary Efficacy Endpoint

Overall survival (OS) 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 as time from randomization to date-of-death of any cause or censored at the last follow up date. OS (months) will be calculated as:

Overall Survival (months) = (Date of death of any cause/censor – Date of randomization +1)/30.4375.

3.2. Secondary Efficacy Endpoints

3.2.1. Key Secondary Efficacy Endpoints

1. Overall survival of patients treated with docetaxel + TTFields compared to overall survival of patients treated with docetaxel alone (superiority). Overall survival will be determined the same as primary endpoint.

2. Overall survival of patients treated with Immune checkpoint inhibitors + TTFields compared to overall survival of patients treated with Immune checkpoint inhibitors alone (superiority). Overall survival will be determined the same as primary endpoint.

3.2.2. Additional Secondary Efficacy 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 determined the same as primary endpoint.

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.

   Progression-free survival is defined as the time from the date of randomization until the date of disease progression in the liver or thorax according to RECIST or irRECIST (depending if the patient is receiving docetaxel or immune checkpoint inhibitor, respectively) or death (by any cause in the absence of progression). Deaths occurred after last tumor assessment without progression are considered event if it occurs within 6 weeks after the last tumor assessment, otherwise it will be censored at the last tumor assessment date.

   Patients who have not progressed or died at time of analysis will be censored at the time of the last date of assessment from their last evaluable RECIST or irRECIST assessment. Patients who have no post baseline tumor assessment will be censored at their randomization date. PFS (months) will be calculated as:

   Progression-free survival (months) = (Date of PFS event/censor – Date of randomization +1)/30.4375.

3. Overall radiological response rate of patients treated with docetaxel or Immune checkpoint inhibitors + TTFields compared with that of patients treated with docetaxel or Immune checkpoint inhibitors alone.

   Radiological response is defined as patients with best overall response (BOR) of partial response (PR) or complete response (CR) based on RECIST criteria for patients received docetaxel or irRECIST criteria for patients received immune checkpoint inhibitor, as recorded by investigator on the eCRF.

   Overall radiological response rate (RRR) is defined as proportion of randomized patients with radiological response following study treatments.

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.

   Quality of life questionnaire include EORTC QLQ C30 (question 1 to 30) with LC13 addendum (question 31-43).

The EORTC QLQ-C30 is a questionnaire developed to assess cancer patients' measurement of global aspects of health-related quality of life (HRQoL). The QLQ-C30 is a 30-item self-administered questionnaire, with items grouped into five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea/vomiting), and a 2-item global health related quality-of-life scale (global health status/QoL).

Five single-item symptom measures are also included providing measurements on additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, diarrhea) and 1 item on the financial impact of the disease. See scoring algorithm for the EORTC-QLQ-C30 in Appendix 10.2.

Higher scores on the global health status/QoL and functioning scales indicate better health status/function, but higher scores on symptom scales/items represent a higher level of symptoms.

EORTC QLQ-LC13 is cancer quality of life questionnaire lung cancer module. It is a supplementary lung cancer-specific questionnaire to be used in conjunction with the QLQ-C30. The lung cancer questionnaire module comprises both multi-item and single-item measuring 13-item on lung cancer symptoms (cough, hemoptysis, dyspnea, site-specific pain) and its treatment-related side-effects (sore mouth, dysphagia, peripheral neuropathy, alopecia). The QLQ-LC13 was scored in a manner analogous to the QLQ-C30; higher scores indicated a greater degree of symptom. For the question "Did the pain medication help if taken", high score represents the helpfulness of the medication. See scoring algorithm for the EORTC-QLQ-LC13 in Appendix 10.2.

5. Analyses of the effects of NovoTTF-100L with each type of immune checkpoint inhibitor (Nivolumab, Pembrolizumab or Atezolizumab) on OS and PFS will be performed.

6. Analysis of the effects of NovoTTF-100L on OS and PFS will be tested within each histological subgroup (squamous and non-squamous).

7. The effect of treatment usage with NovoTTF-100L (as calculated from the device log file) will be tested to determine whether average monthly usage of over 75% of the time leads to better OS and PFS outcomes, as seen in glioblastoma patients treated with TTFields.

   Average monthly usage will be calculated as: {sum [usage*(Last date of the current analysis-first date of the current analysis+1)]/total duration of NovoTTF-100L treatment} * 30.4375.

The OS and PFS outcomes will be compared between the usage >75% group vs <=75% group.

3.3. Safety Variables

3.3.1. Extend of Exposure and Device compliance

3.3.1.1. Extend exposure to NovoTTF-100M

Extend of exposure to NovoTTF-100M will be summarized descriptively for the patients who randomized to the NovoTTF-100M arm as:

- Duration of exposure(days) is calculated as:
  - Last date of NovoTTF-100M treatment - first date of NovoTTF-100M treatment + 1
- Any treatment interruptions for greater than 3 days (yes, No) and reasons.
- Discontinue NovoTTF-100M (yes, no), and reasons.
- Average monthly usage (%)

Average monthly usage will be calculated as: {sum [usage*(last date of the current analysis-first date of the current analysis+1)]/total duration of NovoTTF-100L treatment} * 30.4375.

3.3.1.2. Exposure to Standard of Care

Standard of care in this study contains four drugs: Docetaxel, Pembrolizumab, Nivolumab, and Atezolizumab. For each drug, the following variables will be determined:

- Number of cycles received
  - A cycle is counted if the patient receives any treatment even if the full dose is not delivered.
- Total dose administered
- Duration of exposure in week
  - (last dose date – first dose date + 1)/7
- Dose modification, dose delayed, and drug discontinuation

3.3.2. Adverse Events (AEs)

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary [Version 23.0]. The adverse event reporting period will begin immediately following randomization. Adverse events will be collected until last study follow up visit and for 100 days following treatment termination

Treatment-emergence adverse events (TEAEs) are events with start date on or after the first date of any study treatment (including SOC or TTFields), or events with start date prior to the date of first treatment whose severity worsens on or after the date first treatment.

Assessment of AE severity will be based on the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 4.03.

The relationship between an AE and study device is assessed as definite, probable, possible, unlikely, or none. A device-related AE is an AE considered by the investigator as definitely, possibly, or probably related to study device. If the relationship is unknown or missing, it is also considered as related to study device.

3.3.3. Laboratory Evaluations

The following hematology, serum chemistry, and coagulation analytes recorded in the eCRF will be analyzed in this study. Absolute values will be compared to the local laboratory reference range and classified as low (below range), normal (within range or on limits of range) and high (above range). All values classified as high or low will be flagged on the listings. The baseline value will be defined as last scheduled or unscheduled value prior to start of treatment. For post-baseline, only data from scheduled visits will be included in the summary tables.

Hematology	Serum Chemistry	Coagulation
Red Blood Cell Count Hematocrit Hemoglobin White Blood Cell Count Mean Corpuscular Volume (MCV) Eosinophils Basophils Lymphocytes Neutrophils Monocytes Platelets	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline Phosphatase Total Bilirubin Creatinine Blood Urea Nitrogen (BUN) Potassium Sodium Glucose	Prothrombin Time (PT) Partial Thromboplastin Time (PTT) **For Women Only** serum pregnancy test

3.3.4. Vital Signs

The following vital signs will be evaluated at the time points specified in study calendar.

- systolic and diastolic blood pressure (mmHg);
- heart rate (bpm);
- respiratory rate (breaths/min);
- body temperature (°C).

- weight (kg)

the baseline value will be defined as last scheduled or unscheduled value collected prior to start of treatment. For post-baseline, only data from scheduled visits will be included in the summary tables.

3.3.5. Physical Examination

Physical examination assessments including abdomen, Cardiac, head and neck, extremities, skin, pulmonary, and neurological will be performed according to the study schedule. Any clinically significant abnormal result after baseline should be recorded as an AE.

4. PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES

Not applicable.

5. ANALYSIS POPULATIONS

5.1. Intent-to-treat Population

The Intent-to-treat (ITT) will consist of all randomized subjects regardless of treatment receipt. ITT subjects are analyzed according to the randomized treatment.

5.2. Safety Population

The safety analysis (SAF) dataset will include all patients who received any amount of TTFields or standard of care in the study. Safety subjects are analyzed according to the actual treatment received.

6. DATA HANDLING

6.1. Time points and Visit Windows

Day 1 is defined as the first dose day of standard of care of Docetaxel or immune checkpoint inhibitor treatment, or initial day of receiving TTFields after randomization, whichever occurs first. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

All data will be analyzed using nominal study visits as defined in the Study Schedule of Assessment and eCRF. Data collected at unscheduled visits will be listed only, except for the following:

- Data from unscheduled visits will be included in the calculation of baseline laboratory values.

- Data from unscheduled visits will be included in the calculation of the worst CTCAE grade or abnormality used in the laboratory shift tables.

6.2. Handling of Dropouts, Missing Data, and Outliers

No imputation method for missing values will be used unless otherwise specified. The subject data listings will present the observed data without any imputation.

Incomplete dates (partial or missing dates) for start date of AEs will be imputed and used to determine treatment-emergent AEs as follows:

- If year, month, and day for an AE start date are all missing, the first study treatment date (Day 1) will be used for the imputation.
- If month and day for an AE start date are missing, the first study treatment date (Day 1) will be used for the imputation given the year of the AE start date is the same as the year of the first study treatment date. Otherwise, impute the missing month and day with 01JAN.
- If only day for an AE start date is missing, the first study treatment date (Day 1) will be used for the imputation given the year and the month of the AE start date are the same as the year and the month of first study treatment date (Day 1). Otherwise, impute the missing day with the 1st day of the month.

If an imputed AE start date is later than the corresponding AE end date, the imputed AE start date will be replaced with the AE end date.

7. STATISTICAL METHODS

7.1. General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

Efficacy data will be summarized and analyzed on the ITT analysis set. Safety and treatment compliance data will be summarized based on the Safety Population. Demography and other baseline characteristics data will be summarized based on the ITT analysis set.

Baseline is defined as last evaluation performed prior to receive study treatment. Measurements that are obtained after the first date of study treatment will be considered post-baseline values. Change from baseline is defined as (post-baseline value – baseline value).

Time-to-event endpoints will be summarized using Kaplan-Meier (KM) method to estimate the median, and the 25th and 75th percentiles.

The following principles will be applied to all TFLs unless otherwise stated:

Table 1 Statistical Analysis General Principles

Principle	Value
Treatment group labels and order presented	1. SOC + TTFields • Docetaxel + TTFields • Immune Checkpoint Inhibitors + TTFields 2. SOC Alone • Docetaxel • Immune Checkpoint Inhibitors
Tables	Data in summary tables for safety will be presented by treatment group, and overall, and visit (where applicable). Data in summary tables for efficacy will be presented by treatment group.
Listings	All data collected presented by treatment group, subject, and visit date (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of subjects (N), mean, standard deviation, median, quartiles, minimum, maximum
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)]
Denominator for percentages	By-visit summaries: number of subjects with no-missing data at the visit assessed in the analysis population of each treatment group; Other summaries: Number of subjects in the analysis population of each treatment group, unless specified otherwise.
Include "Missing" as category	Yes, included for demographics and other baseline characteristics when the number of missing is greater than zero for at least one treatment group. Missing post-baseline values will not be summarized, unless otherwise specified.
Display for percentage	One decimal place, except for 100%
Display for 0 percentages	0
Display to one more decimal place than collected value	Mean, Median, quartiles
Display to two more decimal places than collected value	Standard Deviation Confidence interval
Display to p-value	P-values will be rounded to 3 decimal places. P-values less than 0.0005 (e.g. 0.0002) will not be rounded to 3 decimal places (e.g. 0.000) but instead be displayed as <0.001. P-values output as

Principle	Value
	<0.0001 by statistical software will not be rounded and displayed in the same way ('<0.0001').
Date Format	DDMMMYYYY

7.2. Subject Disposition and Data Sets Analyzed

Subject disposition will include all subjects and will be listed and summarized by treatment group and overall and will include the number and percentage of subjects:

- Screened;
- Randomized;
- Randomized and not treated;
- Treated;
- Included in each study population (ITT Population, Safety Population)
- Subject discontinued active participation
- Reason for discontinuation of active participation:
    - Patient request (excluding intolerable toxicity)
    - Lack of compliance
    - Intolerable toxicity
    - irPD/PD in thorax or liver
    - Death
    - Withdrawal of consent
    - Adverse event
    - Other
- Subject who removal from survival follow-up, including the reason:
    - Death
    - Lost to Follow-Up
    - Withdrawal of Consent
    - Other

Subjects who are screen failure and the reason for screen failure will be listed.

7.3. Protocol Deviations

All protocol deviations will be listed. Important protocol deviations will be summarized by treatment group for the ITT population.

7.4. Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for ITT populations.

Standard descriptive statistics will be presented for the continuous variable of:

- Age (years);
- Weight (kg);
- Height (cm);
- Average number of cigarettes smoked per day;
- Number of years smoked cigarettes;
- Time since initial NSCLC diagnosis (years) that calculated as:
    - (Date of randomization -Date of NSCLC primary diagnosis+1)/365.25
- Time since radiological progression (years) according to RECIST Criteria v1.1 that calculated as:
    - (Date of randomization - Date of radiological progression while on or after first platinum based systemic therapy+1)/365.25

The total counts and percentages of subjects will be presented for the categorical variables of:

- Gender (Female, Male)
    - Childbearing potential (Yes, No), if female
    - If no, reason (Surgically sterile, Post-menopausal, Other)
- Race (American Indian Or Alaska Native, Asian, Black or African American, Native Hawaiian Or Other Pacific Islander, White, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown)
- Cigarette smoking status (Never, Current, Former)
- ECOG Performance status (0, 1, 2)
- Standard of care treatment from (Immune checkpoint inhibitor, Docetaxel)
- Tumor histology from CRF (Non-squamous, Squamous)
- Region (North America, Western Europe and Israel, Eastern Europe, East Asia)
- T stage per AJCC 7th ED. (T1, T2, T3, T4, Unknown)
- N stage per AJCC 7th ED. (N0, N1, N2, N3, Unknown)
- M stage per AJCC 7th ED. (M0, M1, Unknown)
- Treatment received for NSCLC diagnosis (Yes, No)

- Received any procedures for NSCLC (Yes, No)

7.5. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.0]. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for safety population by system organ class (SOC) and preferred term (PT) for each treatment group and overall. Subjects with more than one medical history within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one medical history within a particular PT are counted only once for that PT. Tables will be sorted in descending overall frequency by SOC, and then in descending overall frequency by PT within SOC, and then alphabetically.

7.6. Previous and Concomitant Medications

A listing of prior NSCLC therapies and procedures will be presented.

Medications received prior to or concomitantly with treatment will be coded using WHODrug Dictionary enhanced [March 2016], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken and discontinued prior to the first date of study treatment.
- Concomitant medications are those with a start date on or after the first date of study treatment, or those with a start date before the first date of study treatment and a stop date on or after the first date of study treatment or ongoing end of study.

If a medication cannot be classified as "prior" or "concomitant" because of missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed together and summarized separately for ITT populations for each treatment group and overall.

The number and percentage of patients using each medication will be displayed together with the number and percentage of patients using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term. Tables will be sorted in descending overall frequency by ATC-Level 2, ATC-Level 4, and generic term, and then alphabetically.

7.7. Efficacy

7.7.1. Primary Efficacy Analysis

The primary endpoint is to compare overall survival (OS) of patients treated with TTFields concomitant with standard of care of docetaxel or immune checkpoint inhibitor (SOC) versus patients treated with SOC alone (superiority).

The primary endpoint will be summarized using Kaplan-Meier (KM) estimate. The treatment difference will be tested using a stratified two-sided log rank test with an alpha of 0.0462 in ITT population. The hazard rate for standard of care of Docetaxel or immune checkpoint inhibitor (SOC) is represented by hSOC and the hazard for TTFields with SOC is represented by hSOC+TTF. with the null hypothesis being H_0=0.75 and the alternate hypothesis being
$H_A \neq 0.75$. The comparison itself is defined between h_{SOC} and $h_{SOC+TTF}$, as follows:
H_0: Hazard Ratio = $h_{SOC+TTF} / h_{SOC} = 0.75$
H_A: Hazard Ratio = $h_{SOC+TTF} / h_{SOC} \neq 0.75$

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

Hazard ratio with 95% CI and p-value will be estimated using stratified Cox proportional hazards model with the stratification variables as covariates.

The stratified variables will be based on two stratification factors according to data from the IVRS: standard of care therapy and tumor histology. If any strata has less than 10 patients, that stratification factor will be removed from the analysis.

The overall survival will be summarized using Kaplan-Meier (KM) estimate. The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the KM method for the two treatment groups. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group. Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each treatment group in the summary table. The KM plot of OS will be displayed for each treatment group with tick marks to identify censored observations.

OS data will also be listed.

7.7.2. Secondary Efficacy Analysis

The key secondary endpoints will be tested hierarchically only if the primary endpoint is met (hierarchical testing) in order to avoid multiplicity in type I error.

The study is powered to detect an alternative hypothesis of HR = 0.75. Let Δ be the HR then we can describe the three-sided hypothesis as

H_N : $0.75 \leq \Delta \leq 1.33$
H_+ : $\Delta < 0.75$
H_- : $\Delta > 1.33$

The principle of partitioning indicates that since these three hypotheses are distinct and can each be tested at 0.05. H_N is two-sided; H_+ and H_- are each one-sided. The first objective is to determine if S0C+TTF is superior to SOC alone which is accomplished by rejecting H_N and H_- at the one-sided 0.025 level. This is a gatekeeper for the key secondary hypotheses examining components of SOC compared to those components plus TTF. These subgroups will only be tested if SOC+TTF is found to be superior. The components of SOC will be combined by therapeutic class so there are only 2 subgroups (Immune checkpoint inhibitors or Docetaxel), each tested at the 0.025 (one-sided) level:

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 $H_A < 0.75$.
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 $h_{TTF+immune}$. 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_{immune} and $h_{TTF+immune}$, as following:

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

The analysis of OS for each of the secondary endpoints uses same methodology as described for the primary endpoint. The treatment difference will be tested using a stratified two-sided log rank test with an alpha of 0.05 stratified by standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis. The overall survival will be summarized using Kaplan-Meier (KM) estimate. The median, 25th and 75th

percentiles of OS with 95% CIs will be estimated using the KM method for the two treatment groups. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group. Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each treatment group in the summary table. The KM plot of OS will be displayed for each treatment group with tick marks to identify censored observations.

Hazard ratio with 95% CI and p-value will be estimated using stratified Cox proportional hazards model with the stratification variables as covariates.

7.7.3. Exploratory Secondary Efficacy Analysis

7.7.3.1. Overall Survival in Docetaxel+TTFields vs Immune Checkpoint Inhibitor Alone

Analysis of OS will be performed to test whether TTFields with docetaxel is non-inferior to immune checkpoint inhibitors alone. The non-inferiority will be tested using a stratified Cox Proportional Hazard model with the stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis. Hazard ratio and the corresponding 95% CI will be presented. Immune checkpoint inhibitors have been shown to extend survival with a hazard ratio of 0.67 compared to Docetaxel; a non-inferiority margin of 50% is equal to an upper bound of the hazard ratio Confidence interval of 1.25. If the upper limit of the 95% confidence interval excludes 1.25 then we can generate the hypothesis that TTFields with SOC of Docetaxel are non-inferior to SOC of Immune checkpoint inhibitors.

The treatment difference will also be tested using a stratified two-sided log rank test with an alpha of 0.05 stratified by standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the KM method for the two treatment groups. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group. Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each treatment group in the summary table.

7.7.3.2. Progression-free Survival (PFS)

The effect of TTF+SOC over SOC alone for PFS will be estimated using A two-sided stratified log rank test at an alpha level of 0.05. The stratification factors are standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of progression-free survival with 95% CIs will be estimated using the Kaplan-Meier method for the two treatment groups. The number and proportion of patients progression free at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group.

Summaries of the number and percentage of subjects having events, and the number and percentage of subjects censored at the last known evaluable RECIST or irRECIST assessment or last follow-up date will also be provided.

7.7.3.3. Overall Radiological Response Rate

Overall radiological response rate (RRR) and its two-sided 95% confidence interval, which is based on the exact binomial distribution (Clopper-Pearson), will be presented.

The difference of RRR between the patients treated with TTFields concomitant with SOC and the patients treated with SOC alone, as well as the associated 2-sided 95% CI will be calculated using a chi square test at the significance level of 0.05 (two-sided).

In addition, the number and percentage of each response (CR, PR, SD, PD, and NE) for best overall response will be summarized by each treatment.

Assessment of target lesions, non-target lesions, new lesions and overall response will be listed by treatment for each visit.

7.7.3.4. Quality of Life Questionnaire Scores

Scores from 0-100 will be derived for all multi-item or single item scales of the EORTC QLQ-C30 and QLQ-LC13.

For EORTC QLQ-C30, there are a total of 15 scales/scores:

- 5 functional scales in EORTC QLQ-C30: physical, role, cognitive, emotional, and social
- 3 multi-item symptom scales in EORTC QLQ-C30: fatigue, pain, and nausea/vomiting;

- 6 single item symptom scales in EORTC QLQ-C30: dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties
- Global health status/QoL scale in EORTC QLQ-30.

For EORTC QLQ-LC13, there are a total of 9 scales/scores:

- 1 multi-item symptom scales in EORTC QLQ-LC13: dyspnea;
- 5 single item lung cancer associated symptom scales in EORTC QLQ-LC13: cough, hemoptysis, pain in chest, pain in arm or shoulder and pain in other parts;
- 4 treatment-related side-effects scales in EORTC QLQ-LC13: sore mouth, dysphagia, neuropathy, alopecia;

In addition, there is a question about pain medication: did subject take any pain medication (Yes or No) and how useful is the medication.

The scores for each symptom and side-effect scale will be summarized using descriptive statistics by treatment and visit. The score of change from baseline for each scale will also be summarized descriptively for all post-baseline visits. For the pain medication, the score of the usefulness of the medication will be summarize the same way as other scales for patient who takes pain medication.

7.7.3.5. Effects of NovoTTF-100L with Each Type of Immune Checkpoint Inhibitors on OS and PFS

Analysis of the effects of NovoTTF-100L with each type of immune checkpoint inhibitors will be performed in these treatment groups:

- Nivolumab +TTFields vs Nivolumab alone
- Pembrolizumab +TTFields vs Pembrolizumab alone
- Atezolizumab +TTFields vs Atezolizumab alone

7.7.3.5.1. Overall Survival

The treatment difference in OS will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group.

Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each treatment group in the summary table.

7.7.3.5.2. Progression-free Survival

The treatment difference in PFS will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group. The number and proportion of patients progression free at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group.

Summaries of the number and percentage of subjects having events, and the number and percentage of subjects censored at the last known evaluable RECIST or irRECIST assessment or last follow-up date will also be provided.

7.7.3.6. Effects of NovoTTF-100L on OS and PFS Within Each Histological Subgroup

Analysis of the effects of NovoTTF-100L on OS and PFS will be performed in each histological subgroup:

- Squamous: SOC + TTFields vs SOC alone
- Non-squamous: SOC + TTFields vs SOC alone

7.7.3.6.1. Overall Survival

The treatment difference in OS in each subgroup will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group in each subgroup. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group in each subgroup.

Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each treatment group in each subgroup in the summary table.

7.7.3.6.2. Progression-free Survival

The treatment difference in PFS in each subgroup will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each treatment group in each subgroup. The number and proportion of patients progression free at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by treatment group in each subgroup.

Summaries of the number and percentage of subjects having events, and the number and percentage of subjects censored at the last known evaluable RECIST or irRECIST assessment or last follow-up date will also be provided.

7.7.3.7. Effect of Treatment Compliance with NovoTTF-100L

To test whether average monthly compliance of NovoTTF-100L over 75% of the time leads to better OS and PFS outcomes, the analysis of the effect of treatment compliance with NovoTTF-100L will be performed in SOC + TTFields treatment group as:

Average monthly usage > 75% vs <= 75%

7.7.3.7.1. Overall Survival

The difference in OS between >75% and <=75% groups will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of OS with 95% CIs will be estimated using the Kaplan-Meier method for each compliance group. The number and proportion of patients alive at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by compliance group.

Summaries of the number and percentage of subjects who have died, those censored, will also be provided for each compliance group in the summary table.

7.7.3.7.2. Progression-free Survival

The difference in PFS between >75% and <=75% groups will be performed using a stratified log rank test at alpha level of 0.05 with stratification factors of standard of

care therapy and tumor histology. If any strata have less than 10 patients, that stratification factor will be removed from the analysis.

The median, 25th and 75th percentiles of PFS with 95% CIs will be estimated using the Kaplan-Meier method for each compliance group. The number and proportion of patients progression free at 3 monthly intervals from randomization (3, 6, 9, 12 etc.) will be summarized (using the KM analysis) and presented by compliance group.

Summaries of the number and percentage of subjects having events, and the number and percentage of subjects censored at the last known evaluable RECIST or irRECIST assessment or last follow-up date will also be provided.

7.7.3.8. Salvage Therapy

The number and percentage of subjects who have reporting of taking salvage systemic therapy will be summarized by agent and treatment group.

All salvage treatment data will be listed.

7.7.4. Sensitivity Analysis

Sensitivity analysis will be performed if deemed appropriate.

7.7.5. Subgroup Analysis

Related subgroup analyses are included as secondary analysis based on protocol.

7.7.6. Multi-center Studies

In addition to the two stratification factors that will be used for the primary and key secondary endpoints the randomization has been stratified by geographic region to verify that any potential differences in treatment patterns across geographic regions are equally distributed between the treatment arms. We will evaluate the homogeneity of treatment effect by country, geographic region (Chinese patients vs. rest of the world) and protocol version.

Of the patients included in the final analysis, we will present descriptively the percentage and total number of patients enrolled and key study results (OS and PFS) by each site, country, geographic region and protocol version.

A test of homogeneity by site/country/region/protocol version will be performed to assess poolability. In case homogeneity will be proven for one of the specified parameters, it will enable to perform poolability of the study endpoint results across the study parameter (the site/ country / region/ protocol version) which has been

proven to show homogeneity. Doing so, will enable to perform an overall estimation of the study endpoints across the poolable parameter.

Only the large-enrolling site/country (at least five subjects) will be included in the poolability analysis to allow for a clinically meaningful analysis.

In case, the Log-Rank p-value for homogeneity will be less than 0.15, it will indicate no pooling of the data is appropriate.

7.8. Safety

7.8.1. Extent of Exposure and device compliance

7.8.1.1. Exposure to NovoTTF – 100L

Duration of exposure (weeks) and average monthly usage will be summarized descriptively for the patients who randomized to the NovoTTF arm. The total counts and percentages of subjects will be presented for the categorical variables of:

- Average compliance of >75% <=75% or of the time
- Any treatment interruptions for greater than 3 days (yes, no), and reason for treatment interruption for greater than 3 days:
    - Subject decision
    - Physician decision
    - Other
- Discontinue NovoTTF-100M (yes, no), and reason for discontinue NovoTTF-100M treatment:
    - Patient request (excluding intolerable toxicity)
    - Lack of compliance
    - Intolerable toxicity
    - irPD in thorax or liver
    - Death
    - Withdraw of consent
    - Adverse event
    - Other

All exposure to NOVOTTF-100M data will be listed.

7.8.1.2. Exposure to Standard of Care

Standard of care in this study contains four drugs: Docetaxel, Pembrolizumab, Nivolumab, and Atezolizumab. For each drug, number of cycles completed, total

dose administered, and duration of exposure will be summarized by each treatment group in safety population using continuous descriptive statistics.

In addition, the total counts and percentages of subjects will be summarized for the dose modification and drug discontinuation.

- Number of subjects with any dose modification (only for drug of Docetaxel)
- Number of subjects with any dose withheld
- Number of subjects with drug discontinuation, and the reason:
    - Disease Progression
    - Toxicity
    - Other

All exposure to SOC drug data will be listed.

7.8.2. Adverse Events

An overview table will summarize the number and percentage of subjects with at least one of the following AEs by treatment group and overall:

- any AE;
- any AE by maximum severity;
- study device-related AE;
- study device-related AE by maximum severity;
- systemic therapy -related AE;
- systemic therapy -related AE by maximum severity;
- AE leading to treatment discontinuation;
- SAE;
- any SAE by maximum severity;
- study device-related SAE;
- SAE leading to death;
- study device-related SAE leading to death;
- SAE leading to treatment discontinuation;

A similar overall table summarizing treatment emergent AE will also be created.

The number and percentage of subjects reporting each AE will be summarized by System Organ Class and Preferred Term (PT) for the Safety population. Tables will be sorted alphabetically by System Organ Class. PTs will be sorted by descending overall total. The following summaries will be produced:

- AEs, by System Organ Class and PT;
- AEs by PT;
- AEs related to study device, by System Organ Class and PT;
- AEs related to study device, by PT;
- AEs related to systemic therapy by System Organ Class and PT;
- AEs related to systemic therapy, by PT;
- AEs by maximum severity, by System Organ Class and PT;
- AEs related to study device by maximum severity, by System Organ Class and PT;
- AEs causing permanent discontinuation from treatment, by System Organ Class and PT;
- AEs related to study device causing permanent discontinuation from treatment, by System Organ Class and PT;
- SAEs, by System Organ Class and PT;
- SAEs related to study device, by System Organ Class and PT;
- AEs leading to death, by System Organ Class and PT.

In the above summaries, subjects with more than one AE within a particular System Organ Class are counted only once for that System Organ Class. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular System Organ Class or PT will be counted under the category of their most severe AE within that System Organ Class or PT.

No statistical comparisons of AEs between treatment groups will be performed.

All AE data will be listed by treatment group. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs leading to discontinuation of treatment, and AEs resulting in death will be produced.

7.8.3. Laboratory Evaluations

All laboratory data will be reported in International System of Units (SI) units. Reference range will be presented in the listing. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

Laboratory data will be summarized by treatment group, overall, and visit using standard descriptive statistics for the Safety population. Changes from baseline will also be summarized.

For hematology and serum chemistry, shift tables presenting from baseline to worst post baseline result will be provided for each treatment group.

For each laboratory analyte, only data from scheduled visits will be included in the summary tables. Unscheduled visit will be included in the listings.

7.8.4. Vital Signs

Vital signs data and changes from baseline in vital signs will be summarized by treatment group, overall, and visit using standard descriptive statistics for the Safety population.

7.8.5. Physical Examination

Physical examination data will be listed. For each physical examination body system, the number and percentage of patients with abnormalities at baseline and post-baseline will be summarized by treatment group in the Safety population.

7.9. Interim Analysis

One interim analysis will be performed on the OS data available after 27 months (when 432 patients out of 534 patients have been enrolled). The interim analysis will be performed by the DMC statistician and shared with the DMC members. The results of the analysis will not be shared with the study investigators or the sponsor unless the DMC recommends stopping the study for futility or success at the interim analysis. In order to allow for two analyses (interim, and final) in the study, the alpha level used at each time point was calculated according to the Lan-DeMets method using the O'Brien and Fleming spending function (approximately 0.00306 at the interim analysis and 0.04694 at the final analysis). If the primary endpoint meets the predefined threshold of $p < 0.00306$ at the interim analysis, the study may be stopped early for efficacy.

The sponsor will use conditional power (CP) to assess the need for early termination for futility. It will be calculated at the interim analysis using the log rank score statistic of the data collected until the interim point and the specific assumptions about the treatment effect estimated by the original sample size design. The futility index (one minus the conditional power) is the probability of accepting the null hypothesis under the alternative hypothesis given the interim data. A high futility index indicates a small probability of success (rejecting H_0). The study may be stopped if the futility index is above 0.9.

The assumptions used in the sample size calculations will be evaluated at the interim analysis.

The possible outcomes at the interim analysis as described by Liu and Xu (2021), assuming the above parameters, were divided to five zones:

1. α<0.003 stop the study due to efficacy "**efficacy zone**"
2. Conditional power (CP) > 80% but α>0.003 continue the study "**favorable zone**"
3. CP>50% but <80% corresponding to an interim hazard ratio from 0.75 to 0.79, consider increasing sample size to achieve 80% power "**promising zone**"
4. CP<50% but greater than 10% continue the study "**unfavorable zone**"
5. CP<10% stop the study due to futility "**futility zone**"

8. CHANGES IN PLANNED ANALYSIS

On March 17, 2021 the DMC statistician received the study data. Accrual had been active for 48 months – the equivalent of the expected entire study period including follow-up – with 211 patients randomized and a monthly accrual rate of 4.4 patients. The DMC requested to perform the interim analysis at this point due to ethical concerns of elongated accrual. At the time of the interim analysis there were 113 OS events, 28.3% of the expected 400 events.

The DMC recommended to accrue a total of approximately 276 patients with 12 months follow up, which would provide appropriate toxicity and efficacy data to evaluate the planned LUNAR study endpoints, while maintaining the statistical power of the study. This earlier than planned interim analysis, according to the DMC statistician, resulted in an efficacy boundary of 0.0038. The DMC statistician indicated that SAS SEQTEST was used to calculate the revised boundary. The two-sided alpha for full accrual would be 0.0462.

The Data Monitoring Committee (DMC) could have increased the sample size if interim hazard ratio was 0.75 to 0.79.

The "five zones" described above are related to alpha spending. Had the study been stopped for an α being in the "efficacy zone" or for a CP being in the "futility zone" then no further adjustment to the significance level would have been necessary. If the study was in the promising zone and the sample size increased, then we may assume that the hazard ratio was larger than 0.75, and the CP was probably >50% but less than 80%. We would have had those assumptions because of the maturity of the data and a hazard ratio within that range and the number of events then CP would have been larger than 50%. Given the elongated accrual period, the DMC may have decided that even if the study was in the promising zone, a sample size increase was unethical. The DMC recommended to decrease the sample size and neither to stop the study nor increase the sample size. It is therefore concluded that the study is either in the favorable or in the unfavorable zone.

While the Sponsor is blinded to the data, power analyses of various alternative hypotheses indicate that **a minimum** of 190 OS events should be sufficient. Therefore, the final analysis will be performed after **a minimum** of 190 OS events

have been observed. Additionally, site as a stratification factor has been dropped since there is a smaller sample size and concerns about too many strata. Survival analysis with a stratified log-rank test will be performed using tumor histology (squamous cell vs. non-squamous cell) and standard of care treatment (docetaxel vs check-point inhibitors) as stratification factors. The two-sided significance level is 0.0462.

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10. APPENDICES

10.1. EF-24 Study Calendar

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

	SCREENING / BASELINE		RANDOMIZATION	FOLLOW UP	POST TREATMENT TERMINATION	SURVIVAL FOLLOW UP
	T=(-28)-0 days (baseline evaluation)	T=(-14)-0 days (baseline evaluation)	T=Day 0	T= q6 weeks from randomization until PD in the thorax and/or liver (day 42, 84, … ± 7 days)	T=30 ± 7; 60 ± 7; 100-107 days after discontinuing the last study treatment	T= q4 weeks after last visit (day 28, 56, … post last visit +/- 7 days)
Coagulation tests		+		#	+	
Quality of life questionnaire		+		+		
Randomization			+			
Adverse Events and device deficiency				+	+	
Review of treatment usage				+		
Radiological Assessment per irRECIST/RECIST				+		
Telephone Follow up for survival						+

+ : Item should be performed during the designated visit

: Item should be performed during the designated visit only if clinically relevant/applicable

- PD-L1 expression and genetic test results will be collected if applicable and available
- Physical examination includes head and neck, cardiac, pulmonary, abdominal, skin, extremities, neurological examinations and vital signs (weight at screening/baseline, temperature, respiratory rate, blood pressure, heart rate).
- Serum Chemistry includes: BUN, creatinine, sodium, potassium, glucose, ALT, AST, ALP, bilirubin
- Coagulation tests include: PT/INR, aPTT/PTT
- MRI (and not CT) scan of the brain must be performed at baseline
- The EORTC QLQ C30 with LC13 addendum will be used as the quality of life questionnaire
- Radiological assessment: RECIST Criteria for all patients, irRECIST for patients treated with immune checkpoint inhibitors

After 1 year of follow-up in the absence of PD, imaging examinations may be performed every 12 weeks.

10.2. Scoring algorithm for the EORTC-QLQC30

On the EORTC QLQ-C30 version 3 questionnaire, all items from 1 to 28 (table below) are four point scales with response categories 1 = "Not at all", 2 = "A little", 3 = "Quite a bit" and 4 = "Very much". Items 29 and 30 that constitute the rating of a patient's overall health status and quality of life are assessed on a 7-point Likert scale 1 – 7 with 1 = "Very poor" and 7 = "Excellent".

All of the scales and single-item measures will be transformed to range in score from 0 to 100 (Fayers et al 2001). A high scale score represents a higher response level, that is, a higher score represents a higher ("better") level of functioning, or a higher ("worse") level of symptoms. Thus;

- A high score for a functional scale represents a high / healthy level of functioning,
- A high score for the global health status / QoL represents a high QoL,
- A high score for a symptom scale / item represents a high level of symptomatology problems.

Table Scoring the QLQ-C30 version 3.0

Domain	Number of items	Item numbers
Global health status / QoL		
Global health status/QoL	2	29, 30
Functional scales		
Physical functioning	5	1, 2, 3, 4, 5
Role functioning	2	6, 7
Emotional functioning	4	21, 22, 23, 24
Cognitive functioning	2	20, 25
Social functioning	2	26, 27
Symptom scales / items		
Fatigue	3	10, 12, 18
Nausea and vomiting	2	14, 15
Pain	2	9, 19
Dyspnea	1	8
Insomnia	1	11
Appetite loss	1	13
Constipation	1	16
Diarrhea	1	17
Financial difficulties	1	28

The principle for scoring these scales is the same in all cases:

Step 1: Estimate the average of the items that contribute to the scale; this is the raw score. If items $Q_1, Q_2, \ldots, Q_n$ are included in a scale, then for that scale, the *RawScore, RS*, is derived as the mean of the component items;

$$RawScore = RS = \frac{(Q1 + Q2 + \ldots + Qn)}{n}$$

Step 2: Use a linear transformation to standardize the raw score, so that scores range from 0 to

100;

Then for Functional scales:

$$Score = \left\{1 - \frac{(RS-1)}{range}\right\} x\ 100$$

and for Symptom scales/items and Global health status / QoL:

$$Score = \left\{\frac{(RS-1)}{range}\right\} x\ 100$$

Note: *range* is the difference between the maximum possible value of the raw score *RS* and the minimum possible value. Therefore, the range of *RS* equals the range of the item values. For most items (1 to 28) scored 1 to 4, the *range* is 3 (=4-1). The exceptions are the items contributing to the global health status / QoL, which are 7-point questions with *range* = 6.

Example:

Emotional functioning which is derived from items Q_{21}, Q_{22}, Q_{23}, Q_{24},

$$RawScore = RS = \frac{(Q21 + Q22 + Q23 + Q24)}{4}$$

and then the Emotional functioning transformed score

$$Score = \left\{1 - \frac{(RS-1)}{3}\right\} x\ 100$$

Fatigue which is derived from items Q_{10}, Q_{12}, Q_{18},

$$RawScore = RS = \frac{(Q10 + Q12 + Q18)}{4}$$

and then the Fatigue functioning transformed score

$$Score = \left\{\frac{(RS-1)}{range}\right\} x\ 100$$

Missing data

Missing data may be classified as either missing items (one or more missing answers to questions within a questionnaire), or missing forms (the whole questionnaire is missing for a patient). Fayers and Machin (2000) (Fayers et al 2000) describe methods of analysis to use when data on response to items are

missing, including imputation techniques. This involves applying the equations already given under "Scoring procedures" for calculating the scale scores; the missing items in multi-item scales are simply ignored when making the calculations when less than half the items are completed.

The protocol for missing items then can be summarised as;

- Have at least half of the items from the multi-item scale been answered?

    o If Yes, use all the items that were completed, and apply the standard equations given on the previous pages for calculating the scale scores; ignore any items with missing values when making the calculations.

    o If No, set scale score to missing.

- For single-item measures, set score to missing

10.3. Scoring algorithm for the LC13

On the LC13 questionnaire, all symptom items from 31 to 42 are four point scales with response categories 1 = "Not at all", 2 = "A little", 3 = "Quite a bit" and 4 = "Very much". In addition to the four point symptom scales, the last questionnaire 43 "Did you take any medicine for pain" has two response categories - "yes" or "no". If the answer is "Yes", a follow-up question about the usefulness of the medication has response categories 1 = "Not at all", 2 = "A little", 3 = "Quite a bit" and 4 = "Very much".

All of the scales and single-item measures will be transformed to range in score from 0 to 100. A high scale score represents a higher response level, that is, a higher score represents a higher ("better") level of status, or a higher ("worse") level of symptoms. Thus a high score for a symptom scale / item represents a high level of symptomatology problems whereas high score for question 43 represent the usefulness of the medication.

Table Scoring the LC13

Domain	Number of items	Item numbers
Single item symptom scales		
Cough	1	31
Haemoptysis	1	32
Sore mouth or tongue	1	36
Dysphagia	1	37
Peripheral neuropathy	1	38
Alopecia	1	39
Pain in chest	1	40
Pain in arm or shoulder	1	41
Pain in other parts	1	42
Medicine for Pain	1	43
Did medication help with pain	1	43
Multi-item symptom scales		
Dyspnoea	3	33,34,35

The principle for scoring and missing value handle of these scales are the same as QLQ-C30.

Type of Approval (select one) : ☒ **SAP** ☒ **Initiation of Programming**

Sponsor Name:	**Novocure GmbH**		
Sponsor Protocol/CIP ID:	EF-24	**Covance Study ID:**	13092
SAP text filename:	Novocure_LUNAR_SAP_EF 24 Final 2.0 03JAN2022	**TFL shells filename:**	
Version:	Final 2.0	**Date:**	03JAN2022

Covance Approval(s):

Lead Statistician

Approval Signature Print Name: [redacted] Job Title: Principle Biostatistician Date	[redacted]

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Aanalysis datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature Print Name: [redacted] Job Title: Director, Biostatics and data management Date	[redacted]

Please scan/email completed form(s) to the Lead Statistician listed below:

Printed Name/Title:	[redacted]
Email:	[redacted]