Tumor Treating Fields therapy with standard systemic therapy versus standard systemic therapy alone in metastatic non-small-cell lung cancer following progression on or after platinum-based therapy (LUNAR): a randomised, open-label, pivotal phase 3 study

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Summary

Background Tumor Treating Fields (TTFields) are electric fields that disrupt processes critical for cancer cell survival, leading to immunogenic cell death and enhanced antitumour immune response. In preclinical models of non-small-cell lung cancer, TTFields amplified the effects of chemotherapy and immune checkpoint inhibitors. We report primary results from a pivotal study of TTFields therapy in metastatic non-small-cell lung cancer.

Methods This randomised, open-label, pivotal phase 3 study recruited patients at 130 sites in 19 countries. Participants were aged 22 years or older with metastatic non-small-cell lung cancer progressing on or after platinum-based therapy, with squamous or non-squamous histology and ECOG performance status of 2 or less. Previous platinum-based therapy was required, but no restriction was placed on the number or type of previous lines of systemic therapy. Participants were randomly assigned (1:1) to TTFields therapy and standard systemic therapy (investigator's choice of immune checkpoint inhibitor [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) or standard therapy alone. Randomisation was performed centrally using variable blocked randomisation and an interactive voice–web response system, and was stratified by tumour histology, treatment, and region. Systemic therapies were dosed according to local practice guidelines. TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average of at least 18 h/day device usage. The primary endpoint was overall survival in the intention-to-treat population. The safety population included all patients who received any study therapy and were analysed according to the actual treatment received. The study is registered with ClinicalTrials.gov, NCT02973789.

Findings Between Feb 13, 2017, and Nov 19, 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139). The median age was 64 years (IQR 59–70), 178 (64%) were male and 98 (36%) were female, 156 (57%) had non-squamous non-small-cell lung cancer, and 87 (32%) had received a previous immune checkpoint inhibitor. Median follow-up was 10·6 months (IQR 6·1–33·7) for patients receiving TTFields therapy with standard therapy, and 9·5 months (0·1–32·1) for patients receiving standard therapy. Overall survival was significantly longer with TTFields therapy and standard therapy than with standard therapy alone (median 13·2 months [95% CI 10·3–15·5] vs 9·9 months [8·1–11·5]; hazard ratio [HR] 0·74 [95% CI 0·56–0·98]; p=0·035). In the safety population (n=267), serious adverse events of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone. The most frequent grade 3–4 adverse events were leukopenia (37 [14%] of 267), pneumonia (28 [10%]), and anaemia (21 [8%]). TTFields therapy-related adverse events were reported in 95 (71%) of 133 patients; these were mostly (81 [85%]) grade 1–2 skin and subcutaneous tissue disorders. There were three deaths related to standard therapy (two due to infections and one due to pulmonary haemorrhage) and no deaths related to TTFields therapy.

Interpretation TTFields therapy added to standard therapy significantly improved overall survival compared with standard therapy alone in metastatic non-small-cell lung cancer after progression on platinum-based therapy without exacerbating systemic toxicities. These data suggest that TTFields therapy is efficacious in metastatic non-small-cell lung cancer and should be considered as a treatment option to manage the disease in this setting.

Funding Novocure.

Research in context

Evidence before this study

A search of PubMed for ("tumor treating fields" OR TTFields OR (alternating electric fields AND therapy)) AND (non-small cell lung cancer) from Jan 1, 2003, to April 30, 2023, with no language restrictions, identified one pilot phase 1/2 study (EF-15; NCT00749346) of alternating electric fields delivered by a portable medical device (NovoTTF-100L, Novocure, Haifa, Israel) concomitant with pemetrexed. Patients recruited at institutes in Switzerland in 2008 and 2009 had advanced non-small-cell lung cancer progressing on previous therapy; 90% had received a platinum-based treatment. The study found that adding Tumor Treating Fields (TTFields) therapy to pemetrexed (a recommended second-line therapy when patients were enrolled) had preliminary signs of efficacy, including median progression-free survival of 22 weeks, median overall survival of 13·8 months, and a 1-year survival rate of 57%. Skin inflammation was the only common device-related adverse event, with mild (24% of patients) to moderate (2%) dermatitis beneath the arrays, which generally improved with the application of topical steroids, and no TTFields therapy-related serious adverse events were reported. Preclinical studies also suggested efficacy for TTFields in non-small-cell lung cancer; treatment reduced non-small-cell lung cancer cell line viability with maximum effect at a frequency of 150 kHz, and this effect was additive with several different systemic therapy agents. In addition, cell death induced by TTFields enhanced antitumour immune responses and the effect of immune checkpoint inhibitors in mouse lung cancer models. Clinical studies of TTFields therapy have also been conducted in six other oncology indications, including two randomised, pivotal phase 3 studies in glioblastoma. One of these (EF-14; NCT00916409) demonstrated significantly longer overall survival in patients receiving TTFields therapy with standard-of-care therapy, compared with standard-of-care therapy alone.

Added value of this study

To our knowledge, LUNAR is the first randomised, pivotal phase 3 study to examine TTFields therapy for non-small-cell lung cancer. Despite the advent of immune checkpoint inhibitors, an unmet need remains for new options that can extend survival without adding to disease or treatment burden in second-line therapy and beyond for patients with metastatic non-small-cell lung cancer. Before LUNAR, and since the OAK study of atezolizumab in 2017 (NCT02008227), no phase 3 study enrolling patients irrespective of tumour driver mutation status had shown a survival improvement after progression on platinum-based therapy.

Implications of all the available evidence

These data warrant consideration of TTFields therapy as an option for patients with metastatic non-small-cell lung cancer, as an innovative first-in-class treatment method that can be incorporated into daily life and added to existing therapies.

Introduction

Metastatic non-small-cell lung cancer remains incurable despite the introduction of many new and effective therapies, including immune checkpoint inhibitors as first-line therapy. Platinum agents are part of standard-of-care systemic therapy, either in combination with or after first line immune checkpoint inhibitor, or for patients who cannot tolerate immune checkpoint inhibitors.[1,2] However, once a patient's cancer has progressed on platinum-based therapy, treatment options to extend survival are limited. Current approaches include other chemotherapy regimens, mainly docetaxel with or without ramucirumab, or an immune checkpoint inhibitor.[1]

New treatments are needed to improve survival in non-small-cell lung cancer. Tumor Treating Fields (TTFields) are electric fields that disrupt multiple intracellular processes critical for cancer cell survival and proliferation. TTFields therapy is delivered locoregionally and non-invasively to the tumour site by a portable medical device that uses two pairs of arrays placed on the skin of the patient's thorax (appendix p 30). TTFields therapy has approval from the US Food and Drug Administration (FDA) and has the Conformité Européenne mark for glioblastoma on the basis of two randomised, pivotal, phase 3 studies,[3,4] as well as for unresectable pleural mesothelioma.[5] TTFields therapy is not associated with systemic toxicity; the most common device-related adverse event is manageable skin irritation that occurs due to skin contact with device components, not the electric fields themselves.[6,7] Additionally, patient-reported outcomes from a randomised clinical study of TTFields therapy in glioblastoma found no difference in health-related quality of life, with the exception of itchy skin, for patients using the device on the scalp with chemotherapy versus those receiving chemotherapy alone.[8]

Data from preclinical models of non-small-cell lung cancer have shown that the maximal anticancer effects of TTFields occur at 150 kHz (lower or higher frequencies are less effective)[9] and include disruption of mitosis with downstream induction of immunogenic cell death, leading to an enhanced antitumour immune response.[10,11] Additionally, TTFields treatment has been shown to amplify the effectiveness of immune checkpoint inhibitors or taxanes in preclinical models,[9–11] supporting the integration of these treatments. These data, as well as a pilot phase 1/2 study showing safety and feasibility in pretreated patients with advanced non-small-cell lung cancer receiving second-line treatment with pemetrexed,[12] provided the rationale for the pivotal phase 3 LUNAR study. Here we report the primary data from LUNAR, which compared the addition of TTFields therapy to standard systemic therapy (docetaxel or investigator's choice of immune checkpoint inhibitor) with standard

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See **Online** for appendix

systemic therapy alone in patients with metastatic non-small-cell lung cancer progressing on or after platinum-based therapy.

Methods

Study design and participants

LUNAR was a pivotal (the equivalent of phase 3 for medical device studies), randomised, open-label clinical study with 130 sites opened across 19 countries in North America, Europe, and Asia (appendix pp 3–9). The study design is shown in the appendix (p 31), and the full protocol and statistical analysis plan are available as supplementary material (appendix pp 37, 111).

An independent Data Monitoring Committee (comprising an oncologist, pulmonologist, and statistician) monitored data, assessed overall survival and safety results at an interim analysis, and provided recommendations to the sponsor. The protocol and all amendments were approved by the relevant ethics committee and competent authority at each participating site. This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was conducted in compliance with good clinical practice guidelines (EN ISO 14155:2011) and all relevant national and regional regulations.

Eligible participants were adults (aged ≥22 years, to meet the FDA definition of an adult patient according to device regulations) with a histological or cytological diagnosis of metastatic non-small-cell lung cancer (squamous or non-squamous) whose tumours had shown radiological progression at any site during or after platinum-based systemic therapy. No eligibility restriction or requirement was placed on the biomarker status of a patient or tumour, or on previous treatments, with the exception that all patients had received previous platinum-based therapy. Patients who had progression to metastatic disease within 6 months of completing platinum-based therapy in the adjuvant setting were also eligible. Eligibility stipulated an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and a life expectancy of at least 3 months. Patients were also ineligible if they had clinically significant (as determined by the investigator) haematological, hepatic, or renal dysfunction (defined as neutrophil count $<1\cdot5\times10^9$ cells per L and platelet count $<100\times10^9$ per L, bilirubin $>1\cdot5$ times the upper limit of normal [ULN], aspartate aminotransferase or alanine aminotransferase [or both] $>2\cdot5$ times ULN [or >5 times ULN if the patient had documented liver metastases], and serum creatinine $>1\cdot5$ times ULN).

A protocol amendment on April 7, 2020, allowed inclusion of neurologically stable patients with treated central nervous system metastases. Key exclusion criteria were severe comorbidities (eg, clinically significant haematological, hepatic, renal, or cardiac dysfunction), cerebrovascular accident within 6 months of randomisation, or an unrelated malignancy within 3 years of entering the study (excluding stage 1 prostate cancer, non-melanoma skin cancer, and in-situ cervical cancer or breast cancer). All patients provided written informed consent. Full eligibility criteria are listed in the appendix (pp 10–11).

Randomisation

Patients were enrolled by the investigator. Within 28 days of providing informed consent, the investigator assigned eligible patients to a standard systemic therapy (an immune checkpoint inhibitor [nivolumab, pembrolizumab, or atezolizumab] or docetaxel) on the basis of the investigator's best clinical judgement, existing guidelines, availability, and according to standard practice. Patients were randomly assigned (1:1) to receive TTFields therapy to the thorax concomitant with standard therapy or to receive standard therapy alone. The choice of standard therapy was made before randomisation. Randomisation was determined centrally using variable blocked randomisation and an interactive voice–web response system and stratified by tumour histology (squamous or non-squamous), treatment (docetaxel or an immune checkpoint inhibitor), and region (North America, western Europe and Israel, and eastern Europe). The allocation sequence was generated by the sponsor. LUNAR was an open-label study and treatment allocation was not masked.

Procedures

Standard therapies were dosed according to local practice guidelines and instructions provided with each drug over the period patients received treatment in LUNAR (2017–22). The standard for docetaxel was intravenous (75 mg/m²) administration over 1 h every 3 weeks. Nivolumab was administered intravenously at 240 mg every 2 weeks, 480 mg every 4 weeks, or as a bodyweight-based dose. Pembrolizumab was administered as an intravenous dose infusion at 200 mg every 3 weeks, 400 mg every 6 weeks (over 30 min), or as a bodyweight-based dose. Atezolizumab was administered as an intravenous infusion (840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks) over 1 h. All standard systemic therapies were administered until disease progression or unacceptable toxicity. Assessment of tumour PD-L1 status was not mandated; however, investigators reported PD-L1 expression test results in case report forms if available.

TTFields therapy (150 kHz) was delivered continuously to the thoracic region with the recommendation to achieve an average usage of at least 75% of each day (18 h/day) with the NovoTTF device system (device manufactured by Novocure, Root, Switzerland; appendix p 30); this usage threshold was associated with positive clinical benefit in glioblastoma.[13] Array layouts were determined by the investigator based on sex, disease burden, and patient body size (appendix p 32) and were modified as needed throughout the treatment period.

Patients who initiated the study using the NovoTTF-100L system were offered the option (by a protocol amendment on Oct 5, 2020) to have therapy delivered with the identical treatment parameters from the smaller and lighter (1·2 kg vs 2·7 kg) next-generation NovoTTF-200T system (appendix p 30). Patients and caregivers were trained to use the device by the investigator, other health-care provider, or a device support specialist (sponsor-provided). Arrays were replaced (and shifted back and forth approximately 2 cm from the original position to minimise the potential for skin irritation) every 3–4 days. TTFields therapy usage time (device-captured data) was reported monthly to investigators, presented as an average of monthly use during the period.

Follow-up visits were conducted every 6 weeks (±1 week) for radiological assessment of disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for patients receiving docetaxel, or immune-related RECIST for patients receiving an immune checkpoint inhibitor.[14,15] A review of performance status, a physical examination (including of vital signs), complete blood count, and serum chemistry panel (including blood urea nitrogen or urea, creatinine, sodium, potassium, glucose, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin) were performed, and quality-of-life questionnaires were administered. The full schedule of visits and follow-up is described in the appendix (p 2).

Study therapy was continued until radiological progression per RECIST or immune-related RECIST as assessed by the investigator, intolerable toxicity, or patient request (for any reason). Treatment breaks of up to 3 weeks were allowed for TTFields therapy-related adverse events. After progression, patients were offered the investigator's choice of salvage therapy. Patients could continue to receive TTFields therapy with the next line of salvage therapy if they discontinued study systemic therapy due to progression outside of the field (and had in-field disease control), or if the patient had intolerable toxicity to systemic therapy.

Safety was assessed at each follow-up visit (from the time of randomisation until 100 days after terminating study treatment), with adverse events reported according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[16] A modified grading system used to characterise TTFields therapy-related skin adverse events is shown in the appendix (p 12). Because TTFields therapy is used almost continuously (the device is portable to allow use inside and outside the home), the potential impact on quality of life is particularly relevant. As such, patient-reported outcomes were included in the LUNAR clinical study. Global health status was measured at baseline and every 6 weeks using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, an established and validated instrument for collecting patient reported outcomes in oncology studies.[17] A paper copy of the questionnaire was completed according to EORTC guidelines by the patient at follow-up visits. Patient sex, race, and ethnicity were defined by the investigator and source-verified by the sponsor against medical records.

Outcomes

The primary endpoint was overall survival in patients receiving TTFields therapy with standard therapy compared with standard therapy alone. Key secondary endpoints were overall survival in subgroups receiving either docetaxel or an immune checkpoint inhibitor. Other secondary endpoints (reported here) were progression-free survival and overall response rate (both per radiological assessment); overall survival by squamous and non-squamous histology; measurement of patient-reported, health-related quality-of-life scores; and adverse events. Secondary endpoints of overall survival and progression-free survival in TTFields therapy-treated subgroups with average monthly device usage of more than 75% and 75% or less; progression-free survival by squamous and non-squamous histology; overall survival and progression-free survival in subgroups who received nivolumab, pembrolizumab, or atezolizumab; and overall survival of patients who received TTFields therapy with docetaxel compared with patients treated with an immune checkpoint inhibitor alone will be reported elsewhere as part of more extensive analyses.

Overall survival was defined as the time from randomisation to the date of death from any cause or censoring at the last follow-up date. Progression-free survival was defined as the time from date of randomisation until date of disease progression, or death by any cause. Deaths occurring after a patient missed two or more consecutive follow-up visits were censored at the last date of tumour assessment. Patients whose cancer had not progressed or who had not died at the time of analysis were censored at the date of the most recent evaluable tumour assessment. Patients with no post-baseline follow-up radiological tumour assessment were censored at the date of randomisation. Overall radiological response rate was defined as a complete or partial response, and best response (complete response, partial response, stable disease, progressive disease, or not evaluable) was calculated for each treatment group. The change in EORTC QLQ-C30 global health score from baseline is reported here; additional patient-reported outcomes collected in the study will be reported as a separate publication.

Statistical analysis

The study was designed to detect a hazard ratio (HR) of death of less than 0·75 in patients receiving TTFields therapy with standard therapy versus standard therapy alone using two-sided proportional hazards testing, a two-sided α of 0·05, and 80% power. This required a

sample size of 534 patients, after allowing for 10% patient loss during follow-up, with an 18-month study follow-up period. The key secondary endpoints of overall survival in the docetaxel and immune checkpoint inhibitor subgroups were to be tested hierarchically if the primary endpoint was met (to preserve type I error) at the 0·05 (two-sided) level.

Overall survival and progression-free survival were evaluated with two-sided log rank tests, at an α level of 0·05, stratified by treatment (immune checkpoint inhibitor or docetaxel) and tumour histology. A protocol amendment (on May 21, 2021) removed site as a stratification factor before analyses were performed. Medians, CIs, and rates were estimated using the Kaplan-Meier method. HRs with 95% CIs and p values were estimated using a stratified Cox proportional hazards model, with stratification variables introduced as covariates. The significance threshold for analyses was set at p values of less than 0·05. The time-to-event analysis included censoring of subjects who had not experienced an event. The majority of censoring related to patients who had not experienced an event by the data cutoff date. Other censoring was mostly informative and due to patient withdrawal or physician decision. The proportional hazards assumption was not violated, as assessed by visual inspection of log of the negative log of estimated survivor functions. Landmark survival rates at 1 year, 2 years, and 3 years were analysed post hoc. A multivariable analysis using a Cox proportional hazards regression model was performed post hoc to statistically test the effect of parameters (treatment group, type of standard treatment, histology, geographical region, age, sex, performance status, tumour PD-L1 biomarker status, and smoking history) on overall survival in the intention-to-treat population. For overall response rates, the 95% CI was calculated based on the exact binomial distribution (Clopper-Pearson).

Efficacy endpoints were analysed in all randomly assigned patients (intention-to-treat population). Progression-free survival in patients receiving an immune checkpoint inhibitor or docetaxel was a post-hoc analysis. For overall response rate and best response, patients lacking evaluable data were analysed as non-responders. Safety and treatment data were compiled from all patients who received any study therapy and were analysed according to the actual treatment received. For patient-reported outcomes, it was hypothesised that administration of TTFields therapy with standard therapy would not cause a greater decline in mean quality-of-life scores than standard therapy alone. The mean change from baseline in EORTC QLQ-C30 global health scores was calculated for each timepoint and, as previously validated, a change from baseline of ten points or more was considered to represent a clinically significant change.[18] Analyses were performed using SAS software, version 9.4. There was no imputation of missing data. Full details are provided in the statistical analysis plan (appendix p 111).

At the request of the Data Monitoring Committee due to ethical concerns of prolonged accrual, an interim analysis took place on March 31, 2021, after 48 months of active accrual (the expected entire study period, and with 28% of the expected overall survival events having occurred). This replaced the prespecified interim analysis planned for when 432 patients (of the original 534 sample) had been enrolled, and for which the Lan-DeMets method using the O'Brien and Fleming spending function had calculated an α level of approximately 0·00306, with α=0·04694 remaining for the final analysis. The alternative interim analysis was performed by the Data Monitoring Committee statistician and shared with the committee members. Based on these results, the Data Monitoring Committee concluded that continuing accrual to the planned 534 patients was likely to be unnecessary and possibly unethical. The Data Monitoring Committee recommended that accrual of approximately 276 patients, with a 12-month study follow-up period, would be sufficient to provide toxicity and efficacy data to evaluate the planned endpoints, while maintaining statistical power. The Data Monitoring Committee statistician indicated that the interim analysis had an efficacy boundary of 0·0038 and calculated a
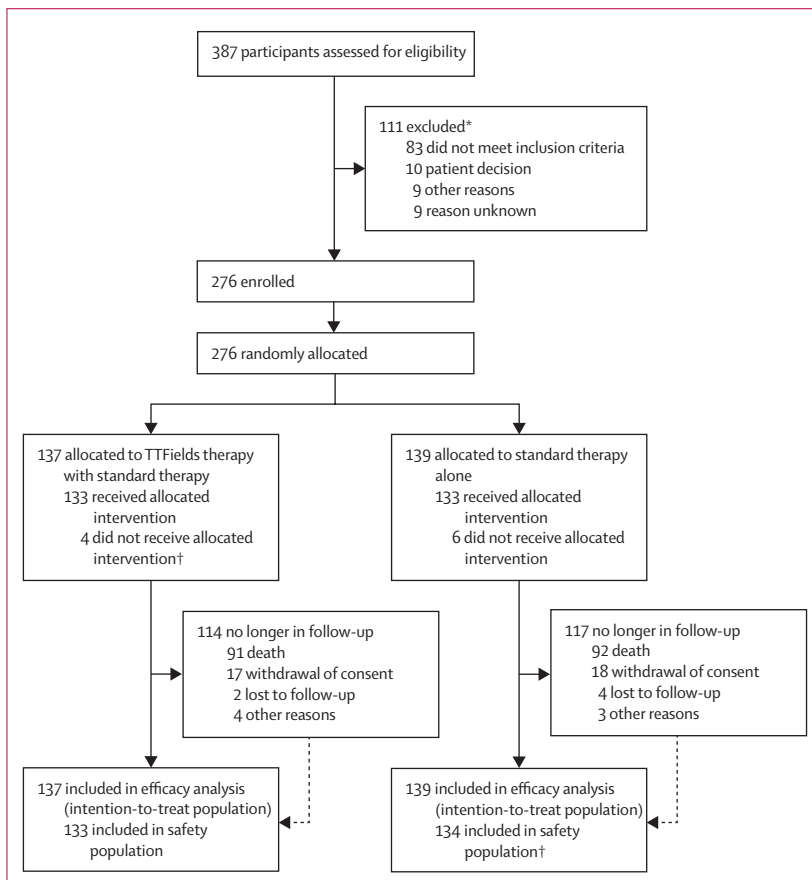

Figure 1: Trial profile
TTFields=Tumor Treating Fields. *One patient who failed screening was randomised. †One patient randomly assigned to TTFields therapy with standard therapy instead received standard therapy alone.

revised two-sided α of 0·0462 for the full analysis with the new target accrual. The sponsor and all investigators remained masked to all study data. The Data Monitoring Committee recommended no further changes to the study protocol. This study is registered with ClinicalTrials.gov, NCT02973789.

Role of the funding source

Novocure designed the study, collated data, conducted data analysis, contributed to data interpretation, funded editorial support, and reviewed the manuscript. The study was designed by the sponsor (Novocure) and the investigators. Data were collected by the investigators and analysed by sponsor-employed or sponsor-funded statisticians.

Results

Between Feb 13, 2017, and Nov 19, 2021, 276 patients were enrolled and randomly assigned to receive TTFields therapy with standard therapy (n=137) or standard therapy alone (n=139; figure 1). All eligible participants were

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)	TTFields therapy with immune checkpoint inhibitor subgroup (n=66)	Immune checkpoint inhibitor subgroup (n=68)	TTFields therapy with docetaxel subgroup (n=71)	Docetaxel subgroup (n=71)
Age, years	63 (36–85)	65 (22–86)	64 (36–85)	65 (23–86)	63 (43–81)	65 (22–81)
Sex						
Female	46 (34%)	52 (37%)	22 (33%)	23 (34%)	24 (34%)	29 (41%)
Male	91 (66%)	87 (63%)	44 (67%)	45 (66%)	47 (66%)	42 (59%)
Race						
American Indian or Alaska Native	0	2 (1%)	0	1 (1%)	0	1 (1%)
Asian	16 (12%)	12 (9%)	7 (11%)	5 (7%)	9 (13%)	7 (10%)
Black or African American	3 (2%)	3 (2%)	1 (2%)	2 (3%)	2 (3%)	1 (1%)
Pacific Islander	1 (1%)	0	1 (2%)	0	0	0
White	111 (81%)	111 (80%)	54 (82%)	53 (78%)	57 (80%)	58 (82%)
Other or missing	6 (4%)	11 (8%)	3 (5%)	7 (10%)	3 (4%)	4 (6%)
Region						
North America	41 (30%)	43 (31%)	14 (21%)	17 (25%)	27 (38%)	26 (37%)
Western Europe and Israel	42 (31%)	41 (29%)	25 (38%)	24 (35%)	17 (24%)	17 (24%)
Eastern Europe	41 (30%)	43 (31%)	21 (32%)	22 (32%)	20 (28%)	21 (30%)
East Asia	13 (9%)	12 (9%)	6 (9%)	5 (7%)	7 (10%)	7 (10%)
ECOG performance status						
0	38 (28%)*	40 (29%)	20 (30%)*	22 (32%)	18 (25%)	18 (25%)
1	93 (68%)*	95 (68%)	44 (67%)*	46 (68%)	49 (69%)	49 (69%)
2	6 (4%)	4 (3%)	2 (3%)	0	4 (6%)	4 (6%)
Smoking history						
Never smoked	20 (15%)	23 (17%)	10 (15%)	12 (18%)	10 (14%)	11 (15%)
Current smoker	35 (26%)	29 (21%)	19 (29%)	17 (25%)	16 (23%)	12 (17%)
Former smoker	81 (59%)	87 (63%)	37 (56%)	39 (57%)	44 (62%)	48 (68%)
Unknown	1 (1%)	0	0	0	1 (1%)	0
Months since initial diagnosis	10·3 (2·7–127·2)	9·9 (2·5–164·6)	10·1 (2·8–98·4)	8·5 (2·7–164·6)	10·4 (2·7–127·2)	11·1 (2·5–68·9)
Previous therapy	137 (100%)	139 (100%)	66 (100%)	68 (100%)	71 (100%)	71 (100%)
Best response to previous therapy						
Complete response	8 (6%)	5 (4%)	4 (6%)	3 (4%)	4 (6%)	2 (3%)
Partial response	32 (23%)	36 (26%)	19 (29%)	13 (19%)	13 (18%)	23 (32%)
Stable disease	47 (34%)	44 (32%)	25 (38%)	21 (31%)	22 (31%)	23 (32%)
Progressive disease	29 (21%)	36 (26%)	10 (15%)	20 (29%)	19 (27%)	16 (23%)
Unknown	21 (15%)	17 (12%)	8 (12%)	10 (15%)	13 (18%)	7 (10%)
Missing	0	1 (1%)	0	1 (1%)	0	0
Previous lines of systemic therapy						
One	119 (87%)	121 (87%)	64 (97%)	63 (93%)	55 (77%)	58 (82%)
Two	9 (7%)	10 (7%)	2 (3%)	3 (4%)	7 (10%)	7 (10%)
Three or more	6 (4%)	2 (1%)	0	0	6 (8%)	2 (3%)
Missing	3 (2%)	6 (4%)	0	2 (3%)	3 (4%)	4 (6%)
						(Table 1 continues on next page)

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)	TTFields therapy with immune checkpoint inhibitor subgroup (n=66)	Immune checkpoint inhibitor subgroup (n=68)	TTFields therapy with docetaxel subgroup (n=71)	Docetaxel subgroup (n=71)
(Continued from previous page)						
Previous immune checkpoint inhibitor						
Yes	43 (31%)	44 (32%)	1 (2%)	2 (3%)	42 (59%)	42 (59%)
No	94 (69%)	95 (68%)	65 (98%)	66 (97%)	29 (41%)	29 (41%)
Histological type						
Non-squamous	79 (58%)	77 (55%)	37 (56%)	37 (54%)	42 (59%)	40 (56%)
Squamous	58 (42%)	62 (45%)	29 (44%)	31 (46%)	29 (41%)	31 (44%)
PD-L1 tumour proportion score						
<1%	23 (17%)	23 (17%)	12 (18%)	16 (24%)	11 (15%)	7 (10%)
1–49%	37 (27%)	40 (29%)	17 (26%)	18 (26%)	20 (28%)	22 (31%)
≥50%	10 (7%)	18 (13%)	5 (8%)	8 (12%)	5 (7%)	10 (14%)
Unknown	67 (49%)	58 (42%)	32 (48%)	26 (38%)	35 (49%)	32 (45%)
Liver metastasis	21 (15%)	22 (16%)	9 (14%)	8 (12%)	12 (17%)	14 (20%)‡
Brain metastasis†	0	2 (1%)	0	0	0	2 (3%)‡

Data are median (range) or n (%). Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer. *Baseline performance status was unavailable for two patients, who were instead assessed at the first follow-up visit. †Patients with brain metastases were excluded under the original study design, which was later amended to allow enrolment of patients with stable brain metastases. ‡One patient had both liver and brain metastasis.

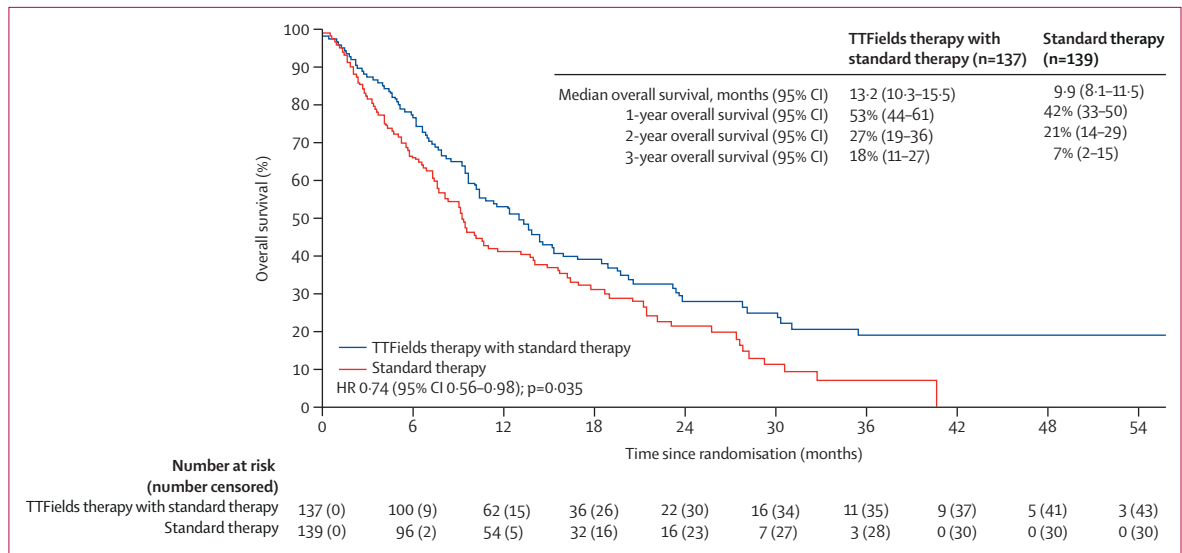*Table 1:* Baseline characteristics of the intention-to-treat population

Figure 2: Overall survival in the intention-to-treat population
Kaplan-Meier estimate of overall survival. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. HR=hazard ratio. TTFields=Tumor Treating Fields.

assigned to therapy (n=276). Their median age was 64 years (IQR 59–70), 178 (64%) were male and 98 (36%) were female, and 232 (84%) were current or former smokers. At baseline, the majority (156 [57%]) had non-squamous histology, 43 (16%) had liver metastasis, and ten (4%) had an ECOG performance score of 2. Other baseline demographics and characteristics were also similar across groups (table 1). Most participants (240 [87%]) had received only one previous line of systemic therapy; more patients in the docetaxel subgroup had received previous treatment

with an immune checkpoint inhibitor than had those in the immune checkpoint inhibitor subgroup (84 [59%] of 142 patients *vs* three [2%] of 134 patients; table 1).

At data cutoff, median follow-up was 10·6 months (IQR 6·1–33·7) for patients assigned to TTFields therapy with standard therapy and 9·5 months (0·1–32·1) for patients assigned to standard therapy alone. Patients who received standard therapy (266 [97%]) were administered systemic therapy for a median of 12·5 weeks (IQR 5·1–25·1). The median duration of TTFields therapy

was 14·6 weeks (IQR 5·3–41·1) with an immune checkpoint inhibitor and 12·7 weeks (3·9–22·0) with docetaxel. 270 (98%) of 276 patients discontinued the study, mostly due to progression or death (167 [61%] of 276; appendix p 13). For patients with device usage data, TTFields therapy was delivered over the first 3 months with an immune checkpoint inhibitor for a median of 56% of each day (IQR 37–70), and with docetaxel for a median of 57% of each day (36–76). Over the entire course of the study, a monthly average device usage of at least 18 h/day (75% of each day) was reached by 13 (19%) of 67 patients in the immune checkpoint inhibitor subgroup and 17 (26%) of 66 patients in the docetaxel subgroup.

Of the 276 patients assigned to study therapy, 77 (28%) received salvage systemic therapy after discontinuing

study therapy due to disease progression; the most frequent agents used were docetaxel (24 [31%] of 77 patients) and gemcitabine (21 [27%]; appendix p 14). 42 (32%) of the 133 patients who received TTFields therapy continued device use beyond disease progression after suspension of standard therapy; 22 in the immune checkpoint inhibitor subgroup (n=67) continued for a median of 34 days (IQR 17–57) after discontinuation, and 20 in the docetaxel subgroup (n=66) continued for a median of 18 days (5–43). Disease progression and occurrence of adverse events were the most common reasons for discontinuation of post-study TTFields therapy.

At data cutoff, 92 deaths had occurred in the group of 137 patients assigned to TTFields therapy and standard
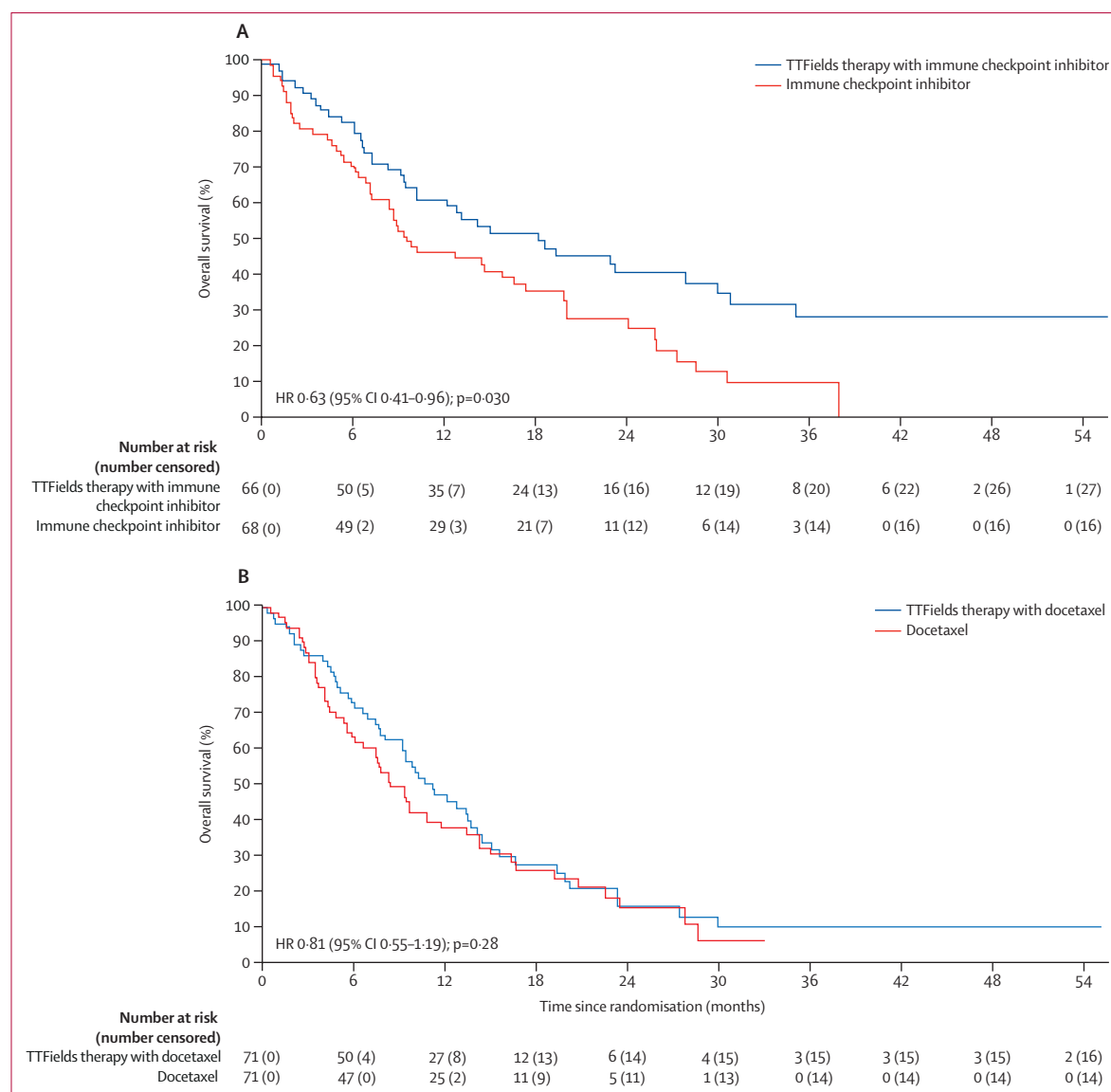

Figure 3: Overall survival in the immune checkpoint inhibitor subgroup (A) and docetaxel subgroup (B) of the intention-to-treat population
Kaplan-Meier estimates of overall survival. TTFields=Tumor Treating Fields.

therapy, and 109 deaths had occurred in the 139 patients assigned to standard therapy alone. Overall survival was significantly longer with TTFields therapy and standard therapy versus standard therapy alone (figure 2). Median overall survival was 13·2 months (95% CI 10·3–15·5) with TTFields therapy and standard therapy compared with 9·9 months (8·1–11·5) with standard therapy alone, yielding an HR of 0·74 (95% CI 0·56–0·98; p=0·035) in favour of TTFields therapy. The 1-year overall survival rate was 53% (95% CI 44–61) with TTFields therapy and standard therapy, and 42% (33–50) with standard therapy alone.

In the immune checkpoint inhibitor subgroup, 38 deaths occurred in the 66 patients assigned to receive TTFields therapy, and 52 deaths occurred in the 68 patients assigned to immune checkpoint inhibitor alone. The addition of TTFields therapy significantly improved overall survival compared with an immune checkpoint inhibitor alone, with respective median overall survival of 18·5 months (95% CI 10·6–30·3) and 10·8 months (8·2–18·4) and an HR of 0·63 (95% CI

0·41–0·96; p=0·030; figure 3A). The 1-year overall survival rate was 60% (95% CI 47–71) with TTFields therapy and an immune checkpoint inhibitor and 46% (33–57) with an immune checkpoint inhibitor alone.

In the subgroup receiving docetaxel, 54 deaths occurred in the 71 patients assigned to receive TTFields therapy, and 57 deaths occurred in the 71 patients assigned to docetaxel alone. Median overall survival was 11·1 months (95% CI 8·2–14·1) with TTFields therapy and docetaxel and 8·7 months (6·3–11·3) with docetaxel alone, with an HR of 0·81 (95% CI 0·55–1·19; p=0·28; figure 3B). The 1-year overall survival rate was 46% (95% CI 33–57) with TTFields therapy and docetaxel and 38% (27–49) with docetaxel alone.

Multivariable analysis using a Cox proportional hazards regression model identified a significant effect for TTFields therapy with standard therapy versus standard therapy, and for immune checkpoint inhibitor versus docetaxel as standard therapy, whereas other factors, including age, sex, ECOG performance status, PD-L1 status, smoking history, and histology did not significantly affect overall survival (appendix p 15). For overall survival results by histology, patients with non-squamous non-small-cell lung cancer assigned to TTFields therapy with standard therapy (n=79) had 50 deaths and median overall survival of 12·6 months (95% CI 8·8–19·8), and those assigned to standard therapy alone (n=77) had 58 deaths and median overall survival of 9·9 months (6·9–16·4; HR 0·80, 95% CI 0·54–1·16; p=0·28). Patients with squamous non-small-cell lung cancer assigned to TTFields therapy with standard therapy (n=58) had 42 deaths and median overall survival of 13·9 months (95% CI 9·7–17·1), and those assigned to standard therapy alone (n=62) had 51 deaths and median overall survival of 10·1 months (8·3–14·3; HR 0·67, 95% CI 0·44–1·01; p=0·050; appendix p 33).

104 progression events occurred in the group assigned to TTFields therapy and standard therapy and 118 progression events occurred in the group assigned to standard therapy alone; median progression-free survival was 4·8 months (95% CI 4·1–5·7) and 4·1 months (3·1–4·6), respectively (HR 0·85, 95% CI 0·67–1·11; p=0·23; figure 4). Progression-free survival in subgroups receiving an immune checkpoint inhibitor or docetaxel is shown in the appendix (p 34).

The overall response rate with TTFields therapy and standard therapy was 20·4% (95% CI 14·0–28·2) versus 17·3% (11·4–24·6) with standard therapy alone (two-sided p=0·50; table 2). All complete responses (n=5) occurred in patients receiving an immune checkpoint inhibitor (four with TTFields therapy, one with immune checkpoint inhibitor alone).

In the safety population of patients who received standard therapy, 16 (12%) of 133 in the group receiving TTFields with standard therapy and 19 (14%) of 134 in the group receiving standard therapy alone required dose reductions to the standard therapy regimen.
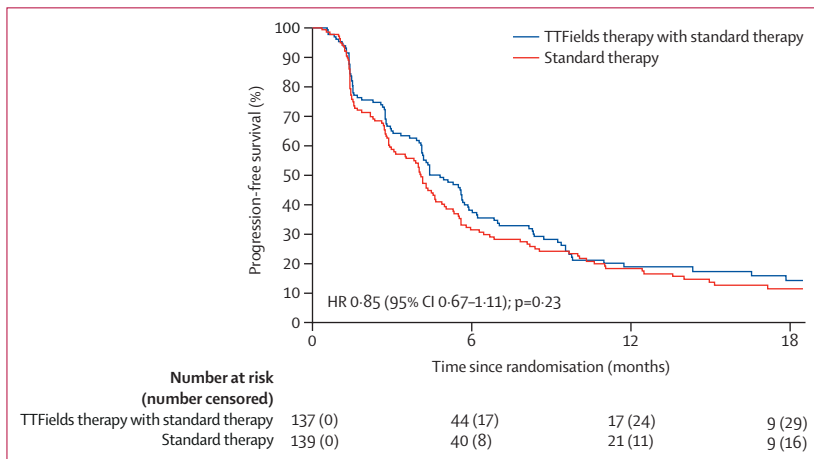

Figure 4: Progression-free survival in the intention-to-treat population
Kaplan-Meier estimates of progression-free survival. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields.

	TTFields therapy with standard therapy group (n=137)	Standard therapy group (n=139)
Patients with at least one post-baseline scan, n	122	127
Overall response, n (%; 95% CI)	28 (20·4%; 14·0–28·2)	24 (17·3%; 11·4–24·6)
Best overall response, n (%)		
Complete response	4 (3%)	1 (1%)
Partial response	24 (18%)	23 (17%)
Stable disease	67 (49%)	65 (47%)
Progressive disease	24 (18%)	36 (26%)
Not evaluable	3 (2%)	2 (1%)

Response rates were calculated from the intention-to-treat population. Standard therapy refers to an immune checkpoint inhibitor or docetaxel. TTFields=Tumor Treating Fields.

Table 2: Response rates

	TTFields therapy with an immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	29 (43%)	29 (43%)	3 (4%)	5 (7%)	28 (42%)	20 (30%)	6 (9%)	6 (9%)	22 (33%)	22 (33%)	11 (17%)	8 (12%)	18 (26%)	23 (34%)	16 (24%)	4 (6%)
Blood and lymphatic system disorders																
Anaemia	12 (18%)	4 (6%)	1 (1%)	0	7 (11%)	2 (3%)	0	0	9 (14%)	5 (8%)	0	0	11 (16%)	9 (13%)	0	0
Leukopenia	1 (1%)	1 (1%)	1 (1%)	0	2 (3%)	0	2 (3%)	0	3 (5%)	6 (9%)	10 (15%)	0	3 (4%)	3 (4%)	14 (21%)	0
Thrombocytopenia	1 (1%)	1 (1%)	0	0	0	0	0	0	4 (6%)	2 (3%)	0	0	2 (3%)	0	1 (1%)	0
Febrile neutropenia	0	0	0	0	0	0	0	0	0	6 (9%)	0	0	0	3 (4%)	0	0
Lymphopenia	0	2 (3%)	0	0	0	0	0	0	2 (3%)	1 (2%)	0	0	1 (1%)	0	0	0
Cardiac disorders																
Myocardial infarction	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	1 (1%)	1 (1%)	0	0
Pericardial effusion	0	1 (1%)	0	0	0	0	0	0	1 (2%)	0	1 (2%)	0	0	0	0	0
Cardiac failure	0	0	0	0	0	0	0	0	0	1 (2%)	1 (2%)	0	0	0	0	0
Coronary artery disease	0	0	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	0	0
Gastrointestinal disorders																
Diarrhoea	11 (16%)	1 (1%)	0	0	13 (20%)	0	0	0	12 (18%)	1 (2%)	0	0	12 (18%)	0	0	0
Nausea	8 (12%)	0	0	0	10 (15%)	1 (2%)	0	0	17 (26%)	0	0	0	10 (15%)	0	0	0
Constipation	4 (6%)	0	0	0	5 (8%)	0	0	0	11 (17%)	0	0	0	10 (15%)	0	0	0
Vomiting	6 (9%)	0	0	0	6 (9%)	1 (2%)	0	0	7 (11%)	1 (2%)	0	0	7 (10%)	0	0	0
Abdominal pain	2 (3%)	0	0	0	5 (8%)	0	0	0	7 (11%)	0	0	0	3 (4%)	0	0	0
Dysphagia	4 (6%)	0	0	0	1 (2%)	0	1 (2%)	0	9 (14%)	0	0	0	1 (1%)	0	0	0
Mouth ulceration	1 (1%)	0	0	0	4 (6%)	0	0	0	3 (5%)	2 (3%)	0	0	6 (9%)	0	0	0
Ileus	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	0	1 (1%)	0	0
Intestinal perforation	0	0	0	1 (1%)	0	0	0	0	0	0	1 (2%)	0	0	0	0	0
General disorders and administration site conditions																
Fatigue	14 (21%)	2 (3%)	0	0	20 (30%)	2 (3%)	0	0	18 (27%)	3 (5%)	0	0	20 (29%)	8 (12%)	0	0
Localised oedema	6 (9%)	0	0	0	8 (12%)	0	0	0	13 (20%)	1 (2%)	0	0	11 (16%)	2 (3%)	0	0
Pain	8 (12%)	1 (1%)	0	0	3 (5%)	0	0	0	8 (12%)	1 (2%)	0	0	13 (19%)	1 (1%)	0	0
Pyrexia	5 (7%)	0	0	0	9 (14%)	0	0	0	3 (5%)	1 (2%)	0	0	9 (13%)	0	0	0
General physical health deterioration	1 (1%)	1 (1%)	1 (1%)	0	2 (3%)	1 (2%)	1 (2%)	0	0	4 (6%)	0	0	0	0	0	0
Euthanasia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (1%)
Immune system disorders																
Drug hypersensitivity	0	0	0	0	0	1 (2%)	0	0	0	0	0	0	1 (1%)	1 (1%)	0	0
Infections and infestations																
Pneumonia	4 (6%)	4 (6%)	0	0	4 (6%)	3 (5%)	2 (3%)	2 (3%)	1 (2%)	9 (14%)	2 (3%)	0	4 (6%)	7 (10%)	1 (1%)	0
Respiratory tract infection	11 (16%)	2 (3%)	0	0	15 (23%)	0	0	0	5 (8%)	1 (2%)	0	1 (2%)	5 (7%)	0	0	0
Infection	5 (7%)	0	0	0	1 (2%)	0	0	0	3 (5%)	2 (3%)	0	1 (2%)	5 (7%)	0	0	0
Urinary tract infection	2 (3%)	1 (1%)	0	0	5 (8%)	1 (2%)	1 (2%)	0	2 (3%)	2 (3%)	0	0	4 (6%)	0	0	0
Sepsis	0	0	0	0	0	1 (2%)	1 (2%)	1 (2%)	0	0	3 (5%)	0	0	1 (1%)	1 (1%)	0
Gastroenteritis	0	0	0	0	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	1 (1%)	1 (1%)	0	0

(Table 3 continues on next page)

	TTFields therapy with an immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Injury, poisoning, and procedural complications																
Fracture	1 (1%)	1 (1%)	0	0	1 (2%)	0	0	0	2 (3%)	0	1 (2%)	0	2 (3%)	0	0	0
Investigations																
Hepatic enzyme increased	9 (13%)	0	0	0	7 (11%)	3 (5%)	0	0	4 (6%)	0	0	0	5 (7%)	1 (1%)	0	0
Weight decreased	2 (3%)	1 (1%)	0	0	5 (8%)	0	0	0	5 (8%)	1 (2%)	0	0	4 (6%)	0	0	0
Metabolism and nutrition disorders																
Anorexia	11 (16%)	0	0	0	8 (12%)	0	0	0	10 (15%)	1 (2%)	0	0	11 (16%)	0	0	0
Hypokalaemia	3 (4%)	1 (1%)	0	0	4 (6%)	0	0	0	7 (11%)	2 (3%)	0	0	8 (12%)	0	0	0
Hypoalbuminaemia	3 (4%)	0	0	0	9 (14%)	0	0	0	6 (9%)	1 (2%)	0	0	7 (10%)	1 (1%)	0	0
Hyponatraemia	4 (6%)	0	1 (1%)	0	6 (9%)	3 (5%)	0	0	5 (8%)	2 (3%)	0	0	3 (4%)	2 (3%)	0	0
Hypercalcaemia	1 (1%)	1 (1%)	0	0	2 (3%)	1 (2%)	0	0	5 (8%)	1 (2%)	0	0	6 (9%)	0	0	0
Hyperglycaemia	2 (3%)	2 (3%)	0	0	1 (2%)	1 (2%)	0	0	4 (6%)	0	0	0	2 (3%)	1 (1%)	0	0
Dehydration	3 (4%)	0	0	0	1 (2%)	0	0	0	4 (6%)	1 (2%)	0	0	1 (1%)	1 (1%)	0	0
Musculoskeletal and connective tissue disorders																
Musculoskeletal pain	22 (33%)	1 (1%)	0	0	12 (18%)	3 (5%)	0	0	22 (33%)	3 (5%)	0	0	19 (28%)	2 (3%)	0	0
Muscular weakness	3 (4%)	0	0	0	1 (2%)	0	0	0	3 (5%)	1 (2%)	0	0	2 (3%)	1 (1%)	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)																
Tumour pain	1 (1%)	0	0	0	0	1 (2%)	0	0	0	2 (3%)	0	0	0	1 (1%)	0	0
Metastases to central nervous system	0	0	0	0	0	0	0	0	0	3 (5%)	0	0	0	2 (3%)	0	0
Metastases to bone	0	1 (1%)	0	0	0	0	0	0	0	1 (2%)	0	0	0	0	0	0
Nervous system disorders																
Neuropathy peripheral	1 (1%)	1 (1%)	0	0	4 (6%)	1 (2%)	0	0	8 (12%)	1 (2%)	0	0	7 (10%)	3 (4%)	0	0
Headache	8 (12%)	0	0	0	5 (8%)	0	0	0	4 (6%)	0	0	0	6 (9%)	0	0	0
Syncope	0	0	0	0	0	0	0	0	0	1 (2%)	0	0	1 (1%)	2 (3%)	0	0
Dysarthria	0	1 (1%)	0	0	0	0	0	0	0	1 (2%)	0	0	0	0	0	0
Paresis	0	0	1 (1%)	0	0	0	1 (2%)	2 (3%)	0	0	0	0	0	1 (1%)	0	0
Psychiatric disorders																
Sleep disorder	3 (4%)	0	0	0	1 (2%)	0	0	0	5 (8%)	0	0	0	8 (12%)	0	0	0
Confusional state	2 (3%)	0	0	0	0	0	0	0	2 (3%)	1 (2%)	0	0	1 (1%)	0	1 (1%)	0
Respiratory, thoracic, and mediastinal disorders																
Dyspnoea	9 (13%)	2 (3%)	0	0	13 (20%)	1 (2%)	0	0	8 (12%)	7 (11%)	0	0	17 (25%)	2 (3%)	1 (1%)	0
Cough	11 (16%)	0	0	0	13 (20%)	1 (2%)	0	0	13 (20%)	0	0	0	12 (18%)	0	0	0
Pulmonary haemorrhage	0	2 (3%)	0	2 (3%)	6 (9%)	0	0	0	3 (5%)	0	0	3 (5%)	5 (7%)	1 (1%)	0	0
Pleural effusion	3 (4%)	1 (1%)	0	0	0	2 (3%)	0	0	1 (2%)	2 (3%)	0	0	3 (4%)	5 (7%)	0	0
Respiratory failure	1 (1%)	0	0	1 (1%)	0	0	1 (2%)	2 (3%)	0	2 (3%)	0	2 (3%)	0	0	0	3 (4%)
Pneumonitis	2 (3%)	1 (1%)	0	0	2 (3%)	2 (3%)	0	0	0	0	1 (2%)	0	1 (1%)	1 (1%)	0	0
Pulmonary embolism	0	1 (1%)	0	1 (1%)	0	2 (3%)	1 (2%)	0	1 (2%)	3 (5%)	0	0	0	1 (1%)	0	0
Chronic obstructive pulmonary disease	1 (1%)	1 (1%)	0	0	1 (2%)	1 (2%)	0	1 (2%)	0	1 (2%)	0	0	0	1 (1%)	0	0
Hypoxia	0	0	0	0	0	0	0	0	1 (2%)	1 (2%)	0	0	1 (1%)	2 (3%)	0	0

(Table 3 continues on next page)

Overall, 30 (11%) of 267 patients discontinued standard therapy due to toxicity related to the standard therapy. Of the 133 patients who received TTFields therapy, 18 (14%) discontinued due to toxicity related to device usage.

Almost all (251 [94%] of 267 patients) reported at least one adverse event of any cause. Adverse events of any cause were observed in 129 (97%) of the 133 patients receiving TTFields therapy with standard therapy and 122 (91%) of 134 patients receiving standard therapy alone (table 3); grade 3–5 adverse events were observed in 78 (59%) patients receiving TTFields therapy with standard therapy and 75 (56%) patients receiving standard therapy alone (appendix pp 16–22). With the exception of dermatitis (60 [22%] of 267 patients), the most frequently reported adverse events were associated with the systemic therapies or the underlying cancer: fatigue (87 patients; 33%), musculoskeletal pain (84; 32%), anaemia (60; 23%), dyspnoea (60; 23%), diarrhoea (50; 19%), leukopenia (46; 17%), cough (50; 19%), and nausea (46; 17%). Serious adverse events of any cause were reported in 70 (53%) of 133 patients receiving TTFields therapy plus standard therapy and 51 (38%) of 134 patients receiving standard therapy alone; there was no specific event or class of events that appeared to occur more frequently in either group (appendix pp 23–26). Adverse events of any cause leading to treatment discontinuation were reported in 48 (36%) of 133 patients receiving TTFields therapy plus standard therapy and 27 (20%) of 134 patients receiving standard therapy alone. Adverse events leading to death occurred in 13 (10%) and ten (8%), respectively.

Serious adverse events related to standard therapy were reported in 25 (19%) of 133 patients also receiving TTFields therapy, and 20 (15%) of 134 receiving only standard therapy. Serious adverse events related to TTFields therapy were reported in four (3%) of the patients receiving TTFields therapy (appendix pp 27–29). 95 (71%) patients receiving TTFields therapy had at least one device-related adverse event; eight (6%) were grade 3. There were no grade 4 toxicities attributable to TTFields therapy (appendix p 29). The most frequent TTFields therapy-related adverse events were grade 1 to 2 skin adverse events: dermatitis (52 patients [39%]), pruritus (16 [12%]), rash (12 [9%]), and skin ulcer (11 [8%]). The incidence of TTFields therapy-related adverse events was generally similar between treatment subgroups: 49 (73%) patients receiving an immune checkpoint inhibitor and 46 (70%) patients receiving docetaxel. The frequency of cardiac events was similar between patients receiving TTFields therapy with standard therapy or standard therapy alone (19 [14%] patients and 18 [13%] patients, respectively), and TTFields therapy did not appear to change the rate or severity of pneumonitis (three [5%] patients with TTFields therapy and immune checkpoint inhibitor; four [6%] patients with immune checkpoint inhibitor alone). There were three deaths related to

	TTFields therapy with immune checkpoint inhibitor subgroup (n=67)				Immune checkpoint inhibitor subgroup (n=66)				TTFields therapy with docetaxel subgroup (n=66)				Docetaxel subgroup (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Atelectasis	0	1 (1%)	0	0	0	0	0	0	0	0	0	0	1 (1%)	2 (3%)	0	0
Bronchial obstruction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (3%)	0
Skin and subcutaneous tissue disorders																
Dermatitis	31 (46%)	1 (1%)	0	0	1 (2%)	0	0	0	23 (35%)	2 (3%)	0	0	2 (3%)	0	0	0
Alopecia	0	0	0	0	1 (2%)	0	0	0	13 (20%)	0	0	0	21 (31%)	1 (1%)	0	0
Pruritus	11 (16%)	0	0	0	7 (11%)	0	0	0	10 (15%)	1 (2%)	0	0	0	0	0	0
Rash	9 (13%)	1 (1%)	0	0	1 (2%)	0	0	0	7 (11%)	0	0	0	2 (3%)	0	0	0
Skin ulcer	8 (12%)	0	0	0	1 (2%)	0	0	0	7 (11%)	1 (2%)	0	0	3 (4%)	0	0	0
Rash maculo-papular	3 (4%)	0	0	0	4 (6%)	0	0	0	7 (11%)	1 (2%)	0	0	3 (4%)	0	0	0
Vascular disorders																
Hypertension	2 (3%)	0	0	0	1 (2%)	0	0	0	3 (5%)	3 (5%)	0	0	1 (1%)	0	0	0
Embolism	0	0	0	0	0	1 (2%)	0	0	1 (2%)	1 (2%)	0	0	0	0	0	0
Deep vein thrombosis	0	1 (1%)	0	0	0	1 (2%)	0	0	0	0	0	0	0	0	0	0

Data are n (%). Adverse events were compiled from the safety population. Adverse events are shown that occurred in ≥10% patients in any group or subgroup, or for which at least two grade ≥3 events were reported (all grade 3–5 events are provided in the appendix p 16), or for which a grade 5 event was reported. In the population assigned to receive TTFields with docetaxel, one patient received an immune checkpoint inhibitor, and one received an immune checkpoint inhibitor alone. In the population assigned to receive an immune checkpoint inhibitor, one patient received docetaxel. TTFields=Tumor Treating Fields.

Table 3: Summary of adverse events

standard therapy (two due to infections, and one due to pulmonary haemorrhage), and no deaths related to TTFields therapy.

Baseline patient-reported global health status, measured by EORTC QLQ-C30 questionnaire, was similar between patients assigned to TTFields therapy and standard therapy versus standard therapy alone. Global health status did not decline in either study group over 54 weeks of follow-up, and there was no difference between treatment groups that was considered clinically significant (appendix p 35).

Discussion

The randomised, pivotal phase 3 LUNAR study provides level 1 evidence that TTFields therapy, an innovative, locoregional treatment method, applied concomitantly with standard systemic therapy significantly improves overall survival in patients with metastatic non-small-cell lung cancer following progression on or after platinum-based therapy compared with standard systemic therapy alone. The overall survival benefit with TTFields therapy occurred without exacerbating the toxicities associated with systemic therapies; its safety profile was mostly limited to low-grade dermatological toxicity.

Docetaxel was established as second-line standard of care for metastatic non-small-cell lung cancer in 2000,[19,20] and remained standard until immune checkpoint inhibitor monotherapy showed a survival benefit after progression on platinum-based therapy 15 years later.[21–24] With immune checkpoint inhibitor therapy swiftly moving to the first-line setting, docetaxel regimens are again considered standard second-line therapy, providing a limited survival benefit with expected, but marked, toxicity.[25] Since the adoption of immune checkpoint inhibitors as first-line therapy, no additional phase 3 studies have shown a survival benefit after progression on platinum-based therapy. As such, a pressing need remains for additional, effective, and tolerable treatment options in the salvage setting.

Platinum-based therapy remains a standard of care in non-small-cell lung cancer, either in combination with immune checkpoint inhibitors (first-line therapy), or after disease progression on immune checkpoint inhibitor monotherapy (second-line therapy).[1] Optimising treatment after progression on platinum-based therapy remains an unmet need, particularly in the era of immune checkpoint inhibitors. In the LUNAR clinical study, overall survival was over 3 months longer with the addition of TTFields therapy, a clinically meaningful improvement that substantiates its use in this burdened patient population that has few other treatment options. A survival benefit of this magnitude is similar to the survival improvements observed in the landmark studies that established the role of immune checkpoint inhibitors as standard of care in second-line advanced non-small-cell lung cancer.[21–24] The survival benefit observed with the addition of TTFields therapy was also similar to that

reported in a randomised phase 2 study[26] that evaluated combination pembrolizumab and ramucirumab versus standard-of-care therapy (median overall survival 14·5 months [80% CI 13·9–16·1] vs 11·6 months [9·9–13·0]) in patients whose disease had previously progressed on combination immune checkpoint inhibitor and platinum-based therapy, although these specific phase 2 findings require confirmation in an appropriately powered phase 3 study before being considered a standard of care. Our finding that TTFields therapy improves survival without increasing the toxicity burden of systemic therapy suggests potential for TTFields therapy use with other second-line treatment options, including ramucirumab regimens.

TTFields therapy yielded an 8-month survival benefit in the subgroup receiving an immune checkpoint inhibitor. These results are underscored by findings in preclinical lung cancer models, in which immunogenic cell death induced by TTFields primed an anticancer immune response that could then be sustained via immune checkpoint inhibitor treatment, in turn leading to enhanced effectiveness when both treatments were used together.[10,11] Of note, patients in the docetaxel subgroup were more heavily pretreated than those in the immune checkpoint inhibitor subgroup. More than 50% of patients receiving docetaxel were previously treated with an immune checkpoint inhibitor in addition to platinum-based therapy. LUNAR was designed to detect the primary endpoint at 80% power in the intention-to-treat population only. Furthermore, the ability to detect changes in subgroups was affected by the reduced sample size recommended by the Data Monitoring Committee. As a result, the treatment subgroup analyses should be interpreted with caution and do not definitively show a differential treatment effect for TTFields therapy based on selected concomitant standard therapy. Additional studies are therefore warranted to validate the benefit of TTFields therapy with standard systemic therapies in non-small-cell lung cancer. LUNAR data also highlight that the benefit of TTFields therapy for non-small-cell lung cancer should be examined in other settings. The pilot phase 2 Keynote B36 clinical study (EF-36; NCT04892472) is evaluating TTFields therapy with an immune checkpoint inhibitor in patients with previously untreated advanced non-small-cell lung cancer. It would also be interesting to examine whether TTFields therapy can combat the major clinical problem of resistance to immune checkpoint inhibitor therapy that occurs in some patients.

The similar progression-free survival for patients receiving TTFields therapy with standard therapy versus standard therapy alone is consistent with results from several immunotherapy studies in advanced non-small-cell lung cancer,[21,23,24,26] in which it has been proposed that a delayed tumour response to therapy or longer post-progression survival (or both) relative to cytotoxic chemotherapy might be characteristic of

immunotherapies.[21,24] Additionally, because TTFields therapy is delivered locoregionally, future analyses are needed to understand patterns of progression, and how responses vary by the field dose experienced by the tumour, the nature of the systemic treatment, and daily device usage. Although confirmatory studies are needed, the overall survival advantage of TTFields therapy in LUNAR was observed despite few patients achieving the recommended daily device usage of 18 h or more that had been chosen based on studies in glioblastoma.[13] With increased clinical experience in non-small-cell lung cancer, usage rates might improve in the future; we also note that the patient-reported data from LUNAR suggest there was no quality of life burden associated with adding TTFields therapy to standard therapy.

The TTFields therapy safety profile in LUNAR was limited to mild-to-moderate local skin irritation underneath the arrays, with no evidence of internal or systemic safety concerns, including cardiac events. Although the frequencies of some adverse events of any cause were higher in the group receiving TTFields therapy, this group also showed longer follow-up and thus was expected to have concomitantly higher adverse event reporting given the inherent disease burden and age. These safety data are also consistent with previous clinical and real-world studies of TTFields therapy in other tumour types[4,5,27–31] in which, although multifactorial in nature, the skin adverse events related to TTFields therapy primarily arose from skin contact with the adhesive or hydrogel on the arrays, and not because of the electric fields treatment. In most cases, skin irritation was effectively controlled using prophylaxis and topical therapies. These include careful replacement of the arrays every 3–4 days, with new arrays shifted by approximately 2 cm from the previous layout, prophylactic use of topical steroids or cream calcineurin inhibitors, and simple skin care techniques; increased patient and caregiver education might reduce the risk of their development.[6,7] Although the full analysis of quality-of-life data from LUNAR is ongoing, patient-reported outcomes in newly diagnosed glioblastoma studies have shown that the device did not impair quality of life, consistent with global health status scores reported here, as measured by the validated EORTC QLQ-C30 questionnaire. In fact, TTFields therapy postponed the decline in quality of life compared with patients receiving standard systemic therapy alone.[8]

Study limitations include the open-label design. This design is considered standard and appropriate for a medical device clinical study based on the ethical concerns of exposing patients to a sham device that is expected to cause skin toxicities without the possibility of therapeutic efficacy. Although an open-label design might affect investigator-assessed secondary endpoints including progression, we considered it unlikely to alter the objective assessment of overall survival for the primary and key secondary endpoints. Concerns for open-label response bias regarding safety reporting are in part mitigated through the randomised design of this study. The study was run with protocol-required safety assessments and processes for evaluating, documenting, and reporting adverse events. An independent data safety monitoring board also provided a review of safety data during the study. Other limitations are that the study enrolled a low number of patients with brain metastases, potentially affecting the generalisability of these findings to that population, and patient accrual proceeded more slowly than planned in the original study design. LUNAR was also initiated before the advent of standard genetic profiling by next-generation sequencing in non-small-cell lung cancer, and thus little information about the relationship between TTFields therapy efficacy and tumour genetic subtype is available. Nevertheless, the study was open to a broad population with no restrictions on tumour biomarker or histological status, or type of previous therapy beyond disease progression on platinum-based therapy. Additionally, this was an international study, and the demographics of participants were largely reflective of the real-world patient population receiving second-line therapy.

Overall, the randomised, pivotal, phase 3 LUNAR study showed that TTFields therapy significantly improved overall survival when added to standard systemic therapies for patients with metastatic non-small-cell lung cancer with progression on or after platinum-based therapy, in both squamous and non-squamous disease. There were no new safety signals, and TTFields therapy did not appear to exacerbate the systemic toxicities of either immune checkpoint inhibitors or docetaxel. These pivotal efficacy and safety data suggest that TTFields therapy should be considered as a treatment option to manage the disease in this setting.

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