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CLINICAL INVESTIGATION

Tumor Treating Fields Therapy After Stereotactic Radiosurgery for Brain Metastases From Non-Small Cell Lung Cancer: Final Results of the Phase 3 METIS Study

Minesh P. Mehta, MD,[a,b] Vinai Gondi, MD,[c] Manmeet Singh Ahluwalia, MD,[a] David Roberge, MD,[d] Terence Tai Weng Sio, MD, MS,[e] Daniel M. Trifiletti, MD,[f] Thierry Muanza, MD,[g] Ana Misir Krpan, MD, PhD,[h] Zhengfei Zhu, MD,[i] Naren R. Ramakrishna, MD, PhD,[j] John B. Fiveash, MD,[k] Philippe Metellus, MD, PhD,[l] Jinming Yu, MD,[m] Chiachien Jake Wang, MD,[n] Julian Jacob, MD, PhD,[o] Christian F. Freyschlag, MD,[p] Tibor Csőszi, MD,[q] Andrea Salmaggi, MD,[r] Alisa Taliansky, MD,[s] Ana Lucas, MD,[t] Jürgen Debus, MD, PhD,[u] Paul D. Brown, MD,[v] and Maciej Harat, MD[w,x] on behalf of the METIS study investigators

[a]Miami Cancer Institute, Baptist Health, Florida International University, Miami, Florida; [b]Herbert Wertheim College of Medicine, Florida International University, Miami, Florida; [c]Northwestern University Feinberg School of Medicine, Chicago, Illinois; [d]Centre Hospitalier de l'Université de Montréal, Montréal, Quebec, Canada; [e]Department of Radiation Oncology, Mayo Clinic, Phoenix, Arizona; [f]Mayo Clinic, Jacksonville, Florida; [g]Departments of Neurology & Neurosurgery, Experimental Medicine, McGill University, Montréal, Quebec, Canada; [h]Specialty Hospital Radiochirurgia Zagreb, Sveta Nedelja, Croatia; [i]Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China; [j]Department of Radiation Oncology, Orlando Health Cancer Institute, Orlando, Florida; [k]Birmingham School of Medicine, University of Alabama, Birmingham, Alabama; [l]Department of Neurosurgery, Private Hospital Clairval, Marseille, France; [m]Shandong Cancer Hospital, Huaiyin District, Jinan City, People's Republic of China; [n]Willis-Knighton Cancer Center, Shreveport, Louisiana; [o]Department of Radiation Oncology, University Hospitals Pitié-Salpêtrière, Paris, France; [p]Department of Neurosurgery, Medical University Innsbruck, Innsbruck, Austria; [q]Semmelweis University, Pankreász Betegségek Intézete, Budapest, Hungary; [r]Alessandro Manzoni Hospital, Lecco, Italy; [s]The Neuro-Oncology Service, Sheba Medical Center, Ramat Gan, Israel; [t]Catalan Institute of Oncology, Barcelona, Spain; [u]Department of Radiation Oncology, Heidelberg University Medical Center, Heidelberg, Germany; [v]Mayo Clinic Cancer Center (MCCC), Rochester, Minnesota; [w]Department of Clinical Medicine, Faculty of Medicine, Bydgoszcz University of Science and Technology, Bydgoszcz, Poland; and [x]Department of Neurooncology and Radiosurgery, Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland

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Corresponding author: Minesh P. Mehta, MD; E-mail: mineshm@baptisthealth.net

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Purpose: Improved treatments for brain metastases from non-small cell lung cancer (NSCLC BM) are needed to prolong time to intracranial progression (TTIP) without increasing neurotoxicity. Tumor Treating Fields (TTFields), electric fields delivered via skin-based arrays that disrupt cancer cell division, have demonstrated efficacy and safety in glioblastoma, NSCLC, and pancreatic cancer.

Methods and Materials: In the phase 3 METIS trial (NCT02831959), adults with 1 to 10 newly diagnosed NSCLC BMs suitable for stereotactic radiosurgery (SRS) receiving optimal therapy for extracranial disease were randomized 1:1 to SRS followed by TTFields (150 kHz) or SRS alone. Radiologic progression was assessed by an independent radiology review committee. The primary endpoint was TTIP (Response Assessment in Neuro-Oncology Brain Metastases criteria). Secondary endpoints included overall survival, neurocognitive function, quality of life (QoL), and safety.

Results: Patients (N = 298) were followed for a median of 8.6 (0.07-85.2) months. TTFields significantly delayed TTIP (hazard ratio [HR], 0.72 [95% CI, 0.53-0.98]; Fine-Gray $P = .044$). Intracranial progression rates at months 2, 6, 12, and 24 were 13.6% versus 22.1% ($P = .034$), 33.7% versus 46.4% ($P = .018$), 46.9% versus 59.4% ($P = .023$), and 53.6% versus 65.2% ($P = .031$; post hoc). Time to distant intracranial progression favored TTFields therapy, although not statistically significantly (HR, 0.76 [95% CI, 0.51-1.12]; log-rank $P = .165$; post hoc). In patients receiving immune checkpoint inhibitors (n = 118), the delays in both TTIP (HR, 0.63 [95% CI, 0.39-1.0]; Cox $P = .049$; Fine-Gray $P = .055$) and time to distant intracranial progression (HR, 0.41 [95% CI, 0.21-0.81]; log-rank $P = .0087$, post hoc) were more pronounced. Device-related adverse events were mainly grade ≤2 skin events. TTFields did not cause QoL deterioration, and improvements in deterioration-free survival and time to deterioration of the global health status, physical functioning and fatigue domains were observed (post hoc).

Conclusions: By significantly prolonging TTIP, without worsening QoL or cognitive function, TTFields after SRS is a new treatment option for patients with NSCLC BMs, including those receiving immune checkpoint inhibitor. © 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Approximately 10% of patients with advanced non-small cell lung cancer (NSCLC) have brain metastases (BMs) at diagnosis; 40% will develop BMs during the course of the disease.[1,2] Overall survival (OS) and quality of life (QoL) of patients with BMs are poor, even with treatment[3]: patients typically have 1 or more neurologic symptoms, including headaches and seizures, and many lose autonomy because of neurocognitive and functional deficits.[4]

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BM management in patients with NSCLC relies primarily on resection or stereotactic radiosurgery (SRS).[5,6] SRS is recommended for patients with 1 to 4 small (diameter <4 cm) BMs,[7] may be used for patients with 5 to 10 BMs[7]; and is increasingly used for >10 BMs.[8-10] However, the increasing efficacy of systemic therapies for extracranial disease has improved prognosis for some patients with BMs, which has prolonged the time during which intracranial progression can occur following SRS. The increased risk of intracranial progression following upfront SRS alone is due to the high probability of micrometastatic seeding of the brain parenchyma.[11] Whole brain radiation therapy (WBRT) improves distant (and local) intracranial disease control, but not OS rates, even in combination with SRS, and is associated with increased rates of neurocognitive decline.[7] The potential requirement for repeated use of salvage therapies to manage recurrent BMs, whether SRS or WBRT, may lead to worsening neurocognitive decline (WBRT) or potential radionecrosis (WBRT and SRS).[12-14] This scenario creates a substantial unmet need for brain-penetrant therapies that improve initial intracranial control, increase duration of effect, and preserve QoL and neurocognition.

Tumor Treating Fields (TTFields) are electric fields that exert physical forces to disrupt cellular processes critical for cancer cell viability and tumor progression.[15-17] They inhibit cancer cell growth in preclinical models of multiple tumor types through antimitotic effects and effects on DNA repair, antitumor immunity, cell membrane permeability, and autophagy.[18] TTFields therapy is delivered to the tumor site using a portable medical device comprising a field generator and arrays that are placed on the skin.[19] In clinical studies, TTFields therapy combined with systemic therapy has improved OS or progression-free survival (PFS) in phase 3 trials in metastatic NSCLC,[20] newly diagnosed glioblastoma,[21-23] and locally advanced pancreatic cancer.[24] In patients with metastatic NSCLC, TTFields with an immune checkpoint inhibitor or docetaxel significantly improved median OS compared with systemic therapy alone.[20] In patients with newly diagnosed glioblastoma, TTFields therapy with maintenance temozolomide significantly improved median PFS and median OS versus temozolomide alone.[21] The benefit in these studies led to the approval of TTFields therapy for use in glioblastoma and metastatic NSCLC.[19,25]

Based on the proven efficacy of TTFields in patients with NSCLC and patients with intracranial tumors, the pivotal phase 3 METIS trial (NCT02831959) was designed to evaluate the efficacy, safety, neurocognitive, and QoL outcomes of TTFields therapy in patients with BMs associated with advanced NSCLC without known actionable mutations and treated with SRS.

Materials and Methods

Trial design

METIS was a prospective, open-label, randomized, international phase 3 trial. The protocol was approved by relevant ethics committees and institutional review boards at each participating site. The study was conducted according to the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before enrollment. The study was designed by the sponsor (Novocure GmbH) and the investigators. Data were collected by the investigators and analyzed by sponsor-employed or -funded statisticians. All authors contributed to data interpretation and vouch for the completeness, accuracy, and fidelity of the study to the protocol.

Patients

Eligible patients were aged ≥18 years with a life expectancy of ≥3 months, Karnofsky performance status ≥70, and newly diagnosed BMs from a histologically or cytologically confirmed primary or metastatic NSCLC tumor within 5 years before the study. Patients with 1 inoperable BM or 2 to 10 brain lesions confirmed using contrast magnetic resonance imaging (MRI) scan and suitable for SRS (<10 cm^3, longest tumor diameter <3 cm, and cumulative volume of all tumors ≤15 cm^3) were eligible. Exclusion criteria included known somatic tumor mutations (*ALK*, *EGFR*, *ROS-1*, and *B-RAF*), presence of a single operable BM, significant edema (midline shift >10 mm), leptomeningeal metastases, and significant comorbidities. Full inclusion and exclusion criteria are provided (Appendix E1).

Randomization and treatment

Patients were centrally randomized 1:1 using an Interactive Web Response System to receive either SRS followed by TTFields therapy or SRS alone (Fig. E1). Patients were stratified by prior systemic therapy (previously treated vs previously untreated), tumor histology (nonsquamous vs squamous), and number of BMs (1-4 vs 5-10 BMs, based on study baseline MRI scan). Follow-up was for 12 months following randomization of the last patient.

Patients underwent single-fraction or hypofractionated SRS within 21 days of randomization (see Appendix E2 for details). TTFields therapy (150 kHz) using the NovoTTF-200M device (Novocure GmbH) was initiated within 7 days of completing SRS. Treatment planning to target known BMs was determined using NovoTAL software (Novocure GmbH),[26] with an array layout selected to maximize TTFields therapy intensity in the area of maximal disease burden based on the baseline MRI scan. Patients receiving initial treatment with the NovoTTF-100M device could switch to the lighter next-generation NovoTTF-200M system following a protocol amendment. For a detailed description of the device, its setup, and features, see Appendix E2 and Figure E2. Patients received TTFields therapy until second progression in the brain, death, or unacceptable side effects. Patients in the SRS-only arm who experienced a second intracranial progression event could cross over to

receive TTFields therapy until the second subsequent intracranial progression event.

Supportive care included symptomatic treatment as determined by the treating physician, including antiepileptic drugs, anticoagulants, pain control medications, and nausea control medications. All patients were expected to receive optimal systemic therapy for extracranial disease according to local practice.

Objectives

The primary objective was time to intracranial progression, a composite endpoint comprising the cumulative probability of local progression, clinical worsening, and neurologic death (defined as death resulting from BMs based on investigator clinical assessment); and the proportion of patients free from distant progression (new lesions), measured from the date of initial SRS treatment to either intracranial progression as assessed by an independent radiologic review committee (IRRC), blinded to treatment allocation, using Response Assessment in Neuro-Oncology Brain Metastases criteria[27] (see Appendix E2), or neurologic death, whichever occurred first.

Secondary endpoints included time to neurocognitive failure following initial SRS, measured as the first decline on one of the following: the Hopkins Verbal Learning Test—revised free recall, delayed recall, and delayed recognition; the Controlled Oral Word Association Test; and Trial Making Test Parts A and B, analyzed by a central review team blinded to treatment allocation. Additional secondary endpoints were OS, measured from initial SRS treatment to either death or censoring at the last follow-up visit, and radiologic response of brain lesions using Response Assessment in Neuro-Oncology Brain Metastases and modified Response Evaluation Criteria in Solid Tumors version 1.1, as assessed by an IRRC.[28]

Exploratory secondary endpoints were the rate of intracranial progression at 2, 4, 6, 8, 10, and 12 months post-SRS therapy and health-related QoL (HRQoL) using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ C-30) questionnaire with the Brain Neoplasms 20-item addendum.

Safety was assessed based on the frequency and severity of investigator-recorded treatment-emergent adverse events (TEAEs) using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.[29]

Time to distant intracranial progression was assessed based on site evaluation and post hoc by the IRRC for consistency. Additional post hoc analyses included time to intracranial progression in defined subgroups, as well as the effect on distant intracranial progression, assessed by independent central review, of treatment with immune checkpoint inhibitors (ICIs) during the study before first progression. Deterioration-free survival (DFS) rates and time to deterioration (TTD, not including death as an event) in QoL using 5-point (little change) and 10-point (moderate change) minimally important differences (MIDs), and European Quality of Life 5 Dimensions 3 Level Version (EQ-5D 3L) DFS, determined by mapping the EORTC QLQ C-30 HRQoL measure onto the EQ-5D 3L, were also assessed post hoc.[30]

Statistical analysis

A sample size of 240 patients was required to detect an increase in median time to intracranial progression, hypothesized to be 7.7 months for the SRS-only arm, to a target of 13.4 months in the SRS followed by TTFields arm, based on a 36-month study duration (24 months for accrual and 12 months for follow-up). The sample size was initially 270 patients (135 patients in each arm) to account for a 12.5% loss to follow-up. Following an Independent Data Monitoring Committee recommendation on July 6, 2022, the sample size was increased to 298 patients because of an increased number of subjects dropping out during the study. Patients who were randomized to treatment comprised the intention-to-treat analysis population, used for all efficacy assessments. For data analysis, the patients' treatment group was based on the treatment they were randomized to receive. The safety analysis population comprised all patients who received SRS as a minimum treatment (Fig. 1).

The primary endpoint was summarized using a cumulative incidence approach that estimated the probability of the event over time. The treatment difference was tested using a Fine-Gray test with 2-sided $\alpha = 0.05$. The hazard ratio (HR) with 95% CI and P value were estimated using cumulative incidence competing risk, with 2-sided $\alpha = 0.05$. Both Fine-Gray (subdistribution) and Cox proportional (cause-specific) hazards models were used, and P-values from both models are presented. Death from all other causes apart from neurologic death because of BMs occurring before evidence of intracranial progression or second intracranial progression was considered as a competing risk, and patients were censored at that point. Censoring of patients for the primary endpoint also occurred for the following: discontinuation or loss to follow-up before intracranial progression (censored at last MRI date); absence of a postbaseline MRI scan (censored at date of SRS treatment); failure to undergo SRS treatment (censored at date of randomization). The cumulative incidence competing risk regression model was used to adjust for the baseline stratification factors (number of metastases, prior systemic therapy, and tumor histology). Testing of the secondary endpoints, time to neurocognitive failure, OS, and radiologic response rate; the exploratory secondary endpoints; and post hoc analyses is detailed in the Appendix E3.

To evaluate changes in HRQoL over time and evaluate the longitudinal course of patients' experience of disease and treatment, a linear mixed-model repeated-measures (MMRM) analysis was used to estimate treatment effect over time by comparing mean changes from baseline in

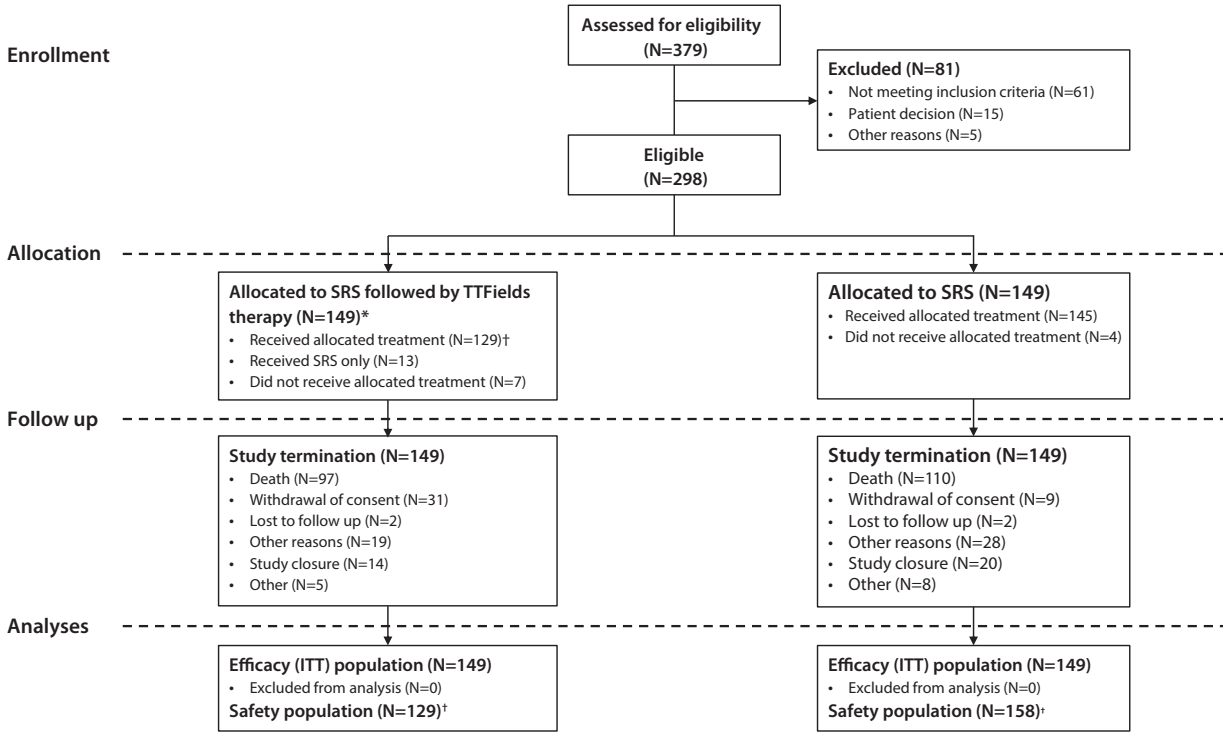

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram. *Abbreviations:* ITT = intention-to-treat; SRS = stereotactic radiosurgery; TTFields = Tumor Treating Fields. *Seventeen patients crossed over from the control arm to receive TTFields after the second intracranial progression. †Seven patients randomized to the experimental arm did not undergo SRS or TTFields therapy; an additional 13 subjects underwent SRS without TTFields.

items on the EORTC QLQ with the Brain Neoplasms 20-item questionnaire. In addition, a sensitivity analysis was performed using a predictive mean matching regression model for imputation of missing data by replacing missing values with an observed value from a patient with a similar value predicted by regression analysis. Several complete plausible data sets were generated using this method, analyzed separately using linear MMRM analysis, and subsequently pooled to present final estimates.

Adverse event (AE) data are summarized as overall incidence, severity, and relatedness to therapy. AEs that occurred after patients treated with SRS alone crossed over to TTFields therapy are summarized separately.

Results

Patients and treatment

Between October 2016 and March 2, 2023, 379 patients were screened, and 298 were enrolled at 78 sites in 13 countries and subsequently randomized (149 per arm, intention-to-treat population; Fig. 1). The safety analysis population comprised 287 patients, 129 who received TTFields therapy following SRS and 158 SRS only (Fig. 1). Numbers of patients who completed neurocognitive function and HRQoL assessments are shown in Table E1.

Baseline characteristics and disease history were balanced (Table 1). Most patients (78.2%) had 1 to 4 BMs. Median time from initial diagnosis of NSCLC to randomization was 1.8 (0.1-61.2) months, median time from BM diagnosis to randomization was 0.6 (0-6.4) months, and 48% of patients had received systemic therapy for NSCLC before the study. The median follow-up duration was 8.6 (0.07-85.2) months.

Of the 149 patients randomized to TTFields therapy following SRS, 129 received TTFields therapy, 13 received SRS only, and 7 received no treatment. In the SRS-only arm, 145 patients received SRS, and 4 received no treatment; 17 of these patients subsequently crossed over to receive TTFields therapy following a second intracranial progression. The duration of SRS treatment and treated lesion volumes were similar between treatment arms (Table 1). Please refer to the Appendix E2 for further details regarding SRS doses.

The median duration of TTFields therapy was 15.7 (0.1-193.1) weeks, with a median monthly device usage (the percentage of the time that the device is used over 1 month) of 67.1% (0.8%-96.7%). In the 17 patients in the SRS-only arm who crossed over to receive TTFields therapy, the median duration of TTFields therapy was 7.4 (0.9-161.7) weeks with median monthly usage of 63.0% (20.9%-84.0%). Ninety-one patients started treatment with the

Table 1 Patient baseline and disease characteristics

Characteristic	SRS → TTFields (N = 149)	SRS only (N = 149)	Overall (N = 298)
Age (y)			
Mean (± SD)	63.5 (9.34)	62.6 (8.16)	63.1 (8.76)
Median (range)	63.0 (37-84)	64.0 (39-78)	63.5 (37-84)
Gender, n (%)			
Male	88 (59.1)	98 (65.8)	186 (62.4)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.7)	1 (0.3)
Asian	35 (23.5)	23 (15.4)	58 (19.5)
Black or African American	9 (6.0)	8 (5.4)	17 (15.7)
Native Hawaiian or Other Pacific Islander	0	1 (0.7)	1 (0.3)
White	99 (66.4)	110 (73.8)	209 (70.1)
Other	3 (2.0)	5 (3.4)	8 (2.7)
Not Reported	3 (2.0)	1 (0.7)	4 (1.3)
BMI (kg/m^2)			
n	144	145	289
Mean (range)	24.1 (16, 39)	25.1 (15, 45)	24.6 (15, 45)
Karnofsky performance status, n (%)			
70	28 (18.8)	27 (18.1)	55 (18.5)
80	50 (33.6)	47 (31.5)	97 (32.6)
90	53 (35.6)	62 (41.6)	115 (38.6)
100	18 (12.1)	13 (8.7)	31 (10.4)
No. of BMs, n (%)			
1-4	117 (78.5)	116 (77.8)	233 (78.2)
5-10	32 (21.5)	33 (22.2)	65 (21.8)
Time since initial NSCLC diagnosis (mo)			
n	149	149	298
Mean (± SD)	7.29 (11.54)	8.76 (12.49)	8.02 (12.03)
Median (range)	1.51 (0.2-55.7)	2.20 (0.1-61.2)	1.82 (0.1-61.2)
Time since BM diagnosis (mo)			
n	149	149	298
Mean (± SD)	0.72 (0.61)	0.77 (0.69)	0.75 (0.65)
Median (range)	0.62 (0.0-6.4)	0.62 (0.0-4.9)	0.62 (0.0-6.4)
Pathological diagnosis for NSCLC, n (%)			
Adenocarcinoma	112 (75.2)	117 (78.5)	229 (76.8)
Squamous cell carcinoma	23 (15.4)	23 (15.4)	46 (15.4)
Other	11 (7.4)	8 (5.4)	19 (6.4)
Large cell carcinoma	3 (2.0)	1 (0.7)	4 (1.3)
Received prior systemic therapy for NSCLC, n (%)			
No	78 (52.3)	77 (51.7)	155 (52.0)
Yes	71 (47.7)	72 (48.3)	143 (48.0)

(*Continued*)

Table 1 (*Continued*)

Characteristic	SRS → TTFields (N = 149)	SRS only (N = 149)	Overall (N = 298)
Received any other interventions for NSCLC diagnosis, n (%)			
No	102 (68.5)	99 (66.4)	201 (67.4)
Yes	47 (31.5)	49 (32.9)	96 (32.2)
Unknown	0	1 (0.7)	1 (0.3)
SRS treatment	N = 129	N = 158	N = 287
Treated, n (%)	129 (100)	158 (100)	297 (100)
Median (range) duration of SRS treatment, d	1.0 (1.0-15.0)	1.0 (1.0-29.0)	-
Single-fraction/multifraction SRS, n (%)			
Single-fraction	82 (63.6)	114 (72.2)	-
Multifraction	47 (36.4)	44 (27.8)	-
Median (range) sum of treated lesion volumes, cm^3	3.05 (0.03-41.6)	3.1 (0.1-23.0)	-

Abbreviations: BM = bone metastasis; BMI = body mass index; NSCLC = non-small cell lung cancer; SRS = stereotactic radiosurgery; TTFields = Tumor Treating Fields.

There is no statistically significant difference between the treatment arms in any of the demographic/baseline characteristics or prior NSCLC and brain metastasis history parameters.

NovoTTF-100M device, 55 with the NovoTTF-200M device, and 8 switched from the NovoTTF-100M device to the NovoTTF-200M device.

Overall, 70.5% (210/298) of patients received systemic anticancer therapy for a median duration of 2.1 (0.0-53.5) months when on study; there were no statistically significant differences in the type of systemic anticancer therapy used between treatment arms (Table E2). Salvage therapies, including WBRT, SRS, and surgery, were used in 42 patients in the TTFields therapy arm and 53 patients in the SRS-only arm, most commonly SRS (TTFields therapy following SRS, 30/42; SRS only, 43/53).

Efficacy

The primary endpoint of time to intracranial progression was significantly improved in patients who received TTFields following SRS versus SRS only (Fine-Gray test $P = .044$). The risk of intracranial progression was reduced by approximately 28% (HR, 0.72 [95% CI, 0.53-0.98]; Fine-Gray $P = .044$; Cox $P = .039$) (Fig. 2). The individual component endpoint data from this composite endpoint are also shown in Figure E3A-D. Improvement in time to intracranial progression was not driven by neurologic death, which occurred at a similarly low incidence with both TTFields following SRS and SRS only

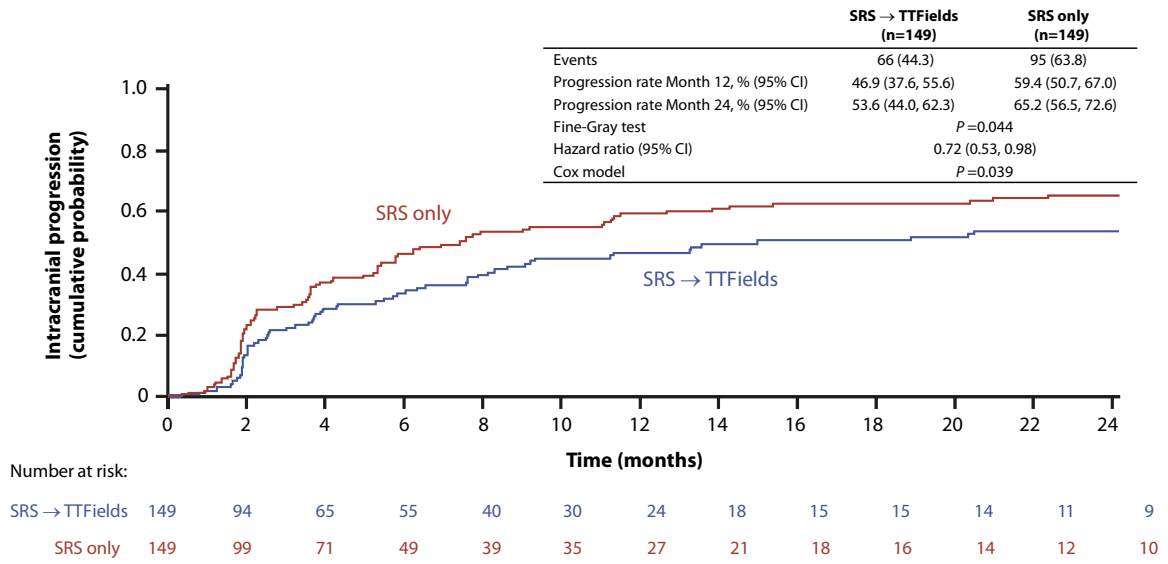

Fig. 2. Cumulative probability of intracranial progression over a 24-month follow-up period. *Abbreviations:* SRS = stereotactic radiosurgery; TTFields = Tumor Treating Fields.

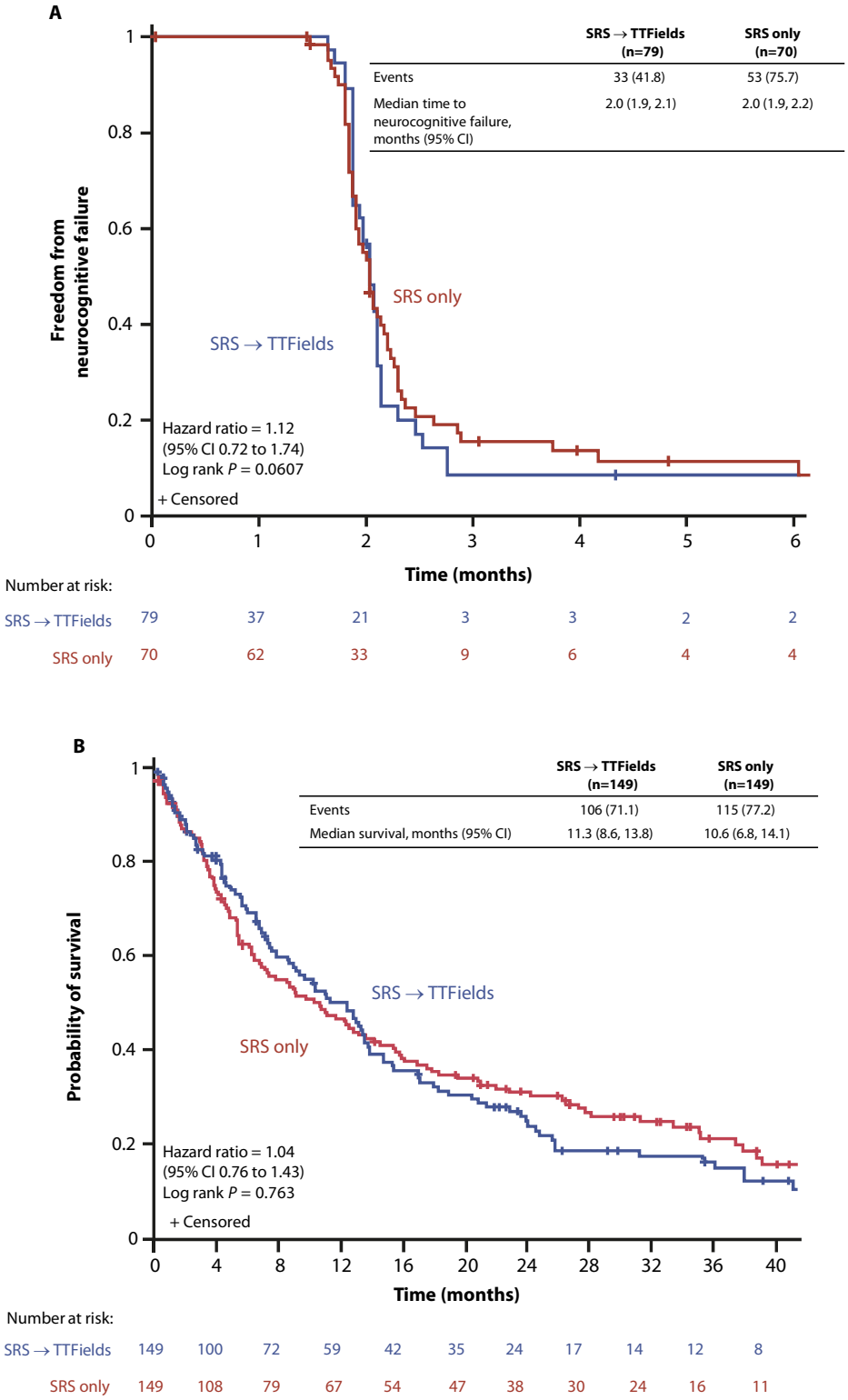

Fig. 3. Probability of neurocognitive failure (A) and overall survival (B) during follow-up. *Abbreviations:* SRS = stereotactic radiosurgery; TTFields = Tumor Treating Fields.

(Fig. E3B and Table E3), was evident at month 2, and was sustained: the rate of intracranial progression was significantly better with TTFields therapy following SRS than SRS only at 2, 6, 8, and 12 months (Table E4), as well as at 24 months ($P = .031$, post hoc). There was no significant difference in the secondary endpoints of time to neurocognitive failure (Fig. 3A), OS (Fig. 3B), and radiologic response rate (Table E5).

Time to distant intracranial progression assessed by the sites did not differ significantly; however, post hoc analysis, based on IRRC analysis to align with the primary endpoint,

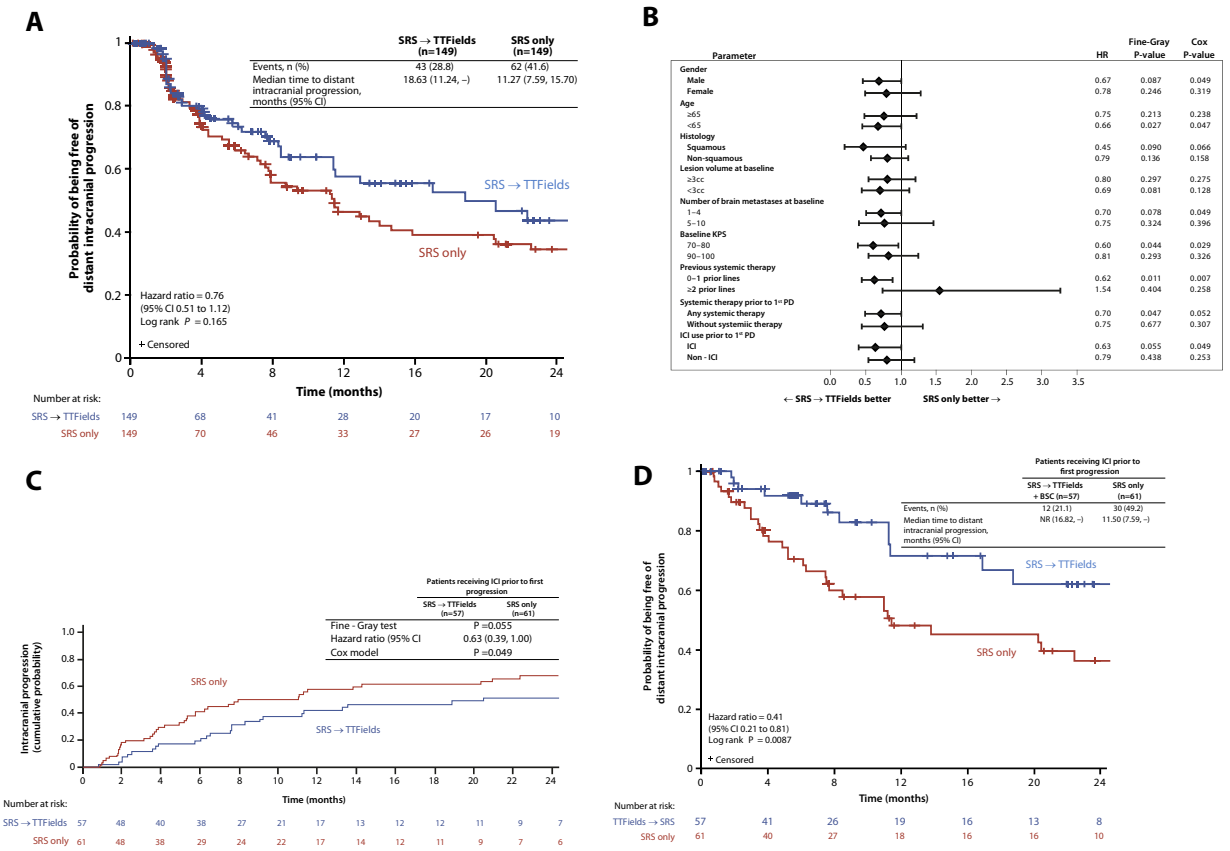

Fig. 4. Post hoc analysis of time to distant intracranial progression assessed by independent central radiographic review (A); time to intracranial progression by RANO-BM in defined subgroups (B); cumulative probability of intracranial progression in patients who received ICIs during the study before first progression (C); and time to distant progression assessed by independent central radiologic review in patients who received ICIs during the study before first progression (D). *Abbreviations:* HR = hazard ratio; ICI = immune checkpoint inhibitor; KPS = Karnofsky performance score; PD = disease progression; RANO-BM = Response Assessment in Neuro-Oncology for Brain Metastases; SRS = stereotactic radiosurgery; TTFields = Tumor Treating Fields.

favored TTFields therapy following SRS, with a 24% reduction in the risk of distant intracranial progression, while not reaching statistical significance (Fig. 4A; HR, 0.76, [95% CI, 0.51-1.12], log-rank P = .165). Subgroup analysis of time to intracranial progression performed post hoc showed an overall trend favoring TTFields therapy in all subgroups (Fig. 4B), with a significant improvement in patients previously treated with 0 to 1 lines of prior systemic therapy (HR, 0.62 [95% CI, 0.43-0.87]; Fine-Gray P = .011; Cox P = .007). Time to intracranial progression was also significantly improved with TTFields therapy following SRS in the subgroup of patients who received ICIs on study before first progression (HR, 0.63 [95% CI, 0.39-1.0]; Fine-Gray P = .055; Cox P =.049; Fig. 4B, C and Fig. E4A), as was time to distant intracranial progression, based on IRRC analysis (HR, 0.41 [95% CI, 0.21-0.81]; log-rank P = .0087; Fig. 4D and Fig. E4B).

Safety

Most patients (266/287 [92.7%]) had at least 1 AE (Table 2). The most frequently reported were associated with systemic therapy or the disease itself and were reported with similar frequency in both arms, eg, anemia (TTFields therapy following SRS 27.9% vs SRS only 25.3%), fatigue (26.4% vs 25.3%), malignant neoplasm progression (27.9% vs 23.4%), musculoskeletal pain (24.0% vs 25.3%), and headache (23.3% vs 20.3%) (Table 2). There were 115 (40.1%) grade 5 AEs reported overall (n = 46 TTFields following SRS; n = 69 SRS only; Table 2), not including fatalities caused by intracranial progression. The most frequently reported grade 5 AE was malignant neoplasm progression (31/46 [67.4%] vs 34/69 [49.3%]), as reported by the investigator. Serious AEs (SAEs; AEs resulting in death, or being life-threatening, requiring hospitalization or prolonging existing hospitalization, or causing a persistent or significant disability or incapacity, cancer, or a congenital anomaly or birth defect) were reported in 190/287 (66.2%) patients and were similar in both treatment arms (Table E6).

Device-related AEs were experienced by 65 of the 129 patients who were treated with TTFields therapy (Table E7). The majority of these were skin and subcutaneous tissue disorders (Table E8), all of which were grade 1 or 2. In addition, 16 patients had TTFields therapy-related nervous

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Table 2 Adverse events experienced by ≥10% of patients overall or with grade 5 severity according to treatment arm, SOC and PT and by maximum severity—safety analysis population

AE experienced	SRS → TTFields (N = 129)					SRS only (N =158)					Overall (N = 287)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Any AE, n (%)	10 (7.8)	27 (20.9)	34 (26.4)	8 (6.2)	46 (35.7)	5 (3.2)	21 (13.3)	38 (24.1)	8 (5.1)	69 (43.7)	15 (5.2)	48 (16.7)	72 (25.1)	16 (5.6)	115 (40.1)
Blood and lymphatic system disorders, n (%)	16 (12.4)	17 (13.2)	14 (10.9)	4 (3.1)	0	15 (9.5)	13 (8.2)	22 (13.9)	8 (5.1)	0	31 (10.8)	30 (10.5)	36 (12.5)	12 (4.2)	0
Anemia, n (%)	15 (11.6)	12 (9.3)	9 (7.0)	0	0	17 (10.8)	7 (4.4)	13 (8.2)	3 (1.9)	0	32 (11.1)	19 (6.6)	22 (7.7)	3 (1.0)	0
Leukopenia, n (%)	11 (8.5)	4 (3.1)	4 (3.1)	1 (0.8)	0	8 (5.1)	5 (3.2)	6 (3.8)	0	0	19 (6.6)	9 (3.1)	10 (3.5)	1 (0.3)	0
Thrombocytopenia, n (%)	6 (4.7)	3 (2.3)	5 (3.9)	1 (0.8)	0	7 (4.4)	8 (5.1)	6 (3.8)	1 (0.6)	0	13 (4.5)	11 (3.8)	11 (3.8)	2 (0.7)	0
Cardiac disorders, n (%)	3 (2.3)	4 (3.1)	4 (3.1)	1 (0.8)	1 (0.8)	8 (5.1)	6 (3.8)	4 (2.5)	0	3 (1.9)	11 (3.8)	10 (3.5)	8 (2.8)	1 (0.3)	4 (1.4)
Cardiac failure, n (%)	0	0	0	0	1 (0.8)	0	1 (0.6)	0	0	3 (1.9)	0	1 (0.3)	0	0	4 (1.4)
Ear and labyrinth disorders, n (%)	8 (6.2)	0	1 (0.8)	0	0	4 (2.5)	3 (1.9)	2 (1.3)	0	0	12 (4.2)	3 (1.0)	3 (1.0)	0	0
Eye disorders, n (%)	8 (6.2)	1 (0.8)	0	1 (0.8)	0	10 (6.3)	5 (3.2)	1 (0.6)	0	0	18 (6.3)	6 (2.1)	1 (0.3)	1 (0.3)	0
Gastrointestinal disorders, n (%)	25 (19.4)	27 (20.9)	7 (5.4)	0	0	22 (13.9)	24 (15.2)	16 (10.1)	1 (0.6)	2 (1.3)	47 (16.4)	51 (17.8)	23 (8.0)	1 (0.3)	2 (0.7)
Constipation, n (%)	10 (7.8)	10 (7.8)	1 (0.8)	0	0	17 (10.8)	7 (4.4)	1 (0.6)	0	0	27 (9.4)	17 (5.9)	2 (0.7)	0	0
Intestinal perforation, n (%)	0	0	0	0	0	0	0	0	0	2 (1.3)	0	0	0	0	2 (0.7)
Nausea, n (%)	17 (13.2)	6 (4.7)	2 (1.6)	0	0	10 (6.3)	14 (8.9)	5 (3.2)	0	0	27 (9.4)	20 (7.0)	7 (2.4)	0	0
Vomiting, n (%)	7 (5.4)	2 (1.6)	1 (0.8)	0	0	5 (3.2)	9 (5.7)	3 (1.9)	0	0	12 (4.2)	11 (3.8)	4 (1.4)	0	0
General disorders and administration site conditions, n (%)	33 (25.6)	29 (22.5)	9 (7.0)	0	4 (3.1)	33 (20.9)	30 (19.0)	11 (7.0)	0	9 (5.7)	66 (23.0)	59 (20.6)	20 (7.0)	0	13 (4.5)
Death, n (%)	0	0	0	0	3 (2.3)	0	0	0	0	5 (3.2)	0	0	0	0	8 (2.8)
Fatigue, n (%)	16 (12.4)	12 (9.3)	6 (4.7)	0	0	21 (13.3)	12 (7.6)	7 (4.4)	0	0	37 (12.9)	24 (8.4)	13 (4.5)	0	0
General physical health deterioration, n (%)	0	1 (0.8)	0	0	1 (0.8)	0	0	0	0	1 (0.6)	0	1 (0.3)	0	0	2 (0.7)
Edema peripheral, n (%)	17 (13.2)	12 (9.3)	1 (0.8)	0	0	12 (7.6)	11 (7.0)	1 (0.6)	0	0	29 (10.1)	23 (8.0)	2 (0.7)	0	0
Organ failure, n (%)	0	0	0	0	0	0	0	0	0	1 (0.6)	0	0	0	0	1 (0.3)
Pain, n (%)	10 (7.8)	4 (3.1)	0	0	0	10 (6.3)	7 (4.4)	3 (1.9)	0	0	20 (7.0)	11 (3.8)	3 (1.0)	0	0

(*Continued*)

Table 2 (*Continued*)

AE experienced	SRS → TTFields (N = 129)					SRS only (N =158)					Overall (N = 287)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pyrexia, n (%)	13 (10.1)	2 (1.6)	0	0	0	9 (5.7)	5 (3.2)	0	0	0	22 (7.7)	7 (2.4)	0	0	0
Sudden death, n (%)	0	0	0	0	0	0	0	0	0	2 (1.3)	0	0	0	0	2 (0.7)
Hepatobiliary disorders, n (%)	8 (6.2)	1 (0.8)	4 (3.1)	0	0	4 (2.5)	4 (2.5)	0	0	0	12 (4.2)	5 (1.7)	4 (1.4)	0	0
Immune system disorders	1 (0.8)	0	0	0	0	3 (1.9)	2 (1.3)	0	0	0	4 (1.4)	2 (0.7)	0	0	0
Infections and infestations, n (%)	7 (5.4)	26 (20.2)	18 (14.0)	3 (2.3)	5 (3.9)	15 (9.5)	24 (15.2)	26 (16.5)	6 (3.8)	6 (3.8)	22 (7.7)	50 (17.4)	44 (15.3)	9 (3.1)	11 (3.8)
COVID-19, n (%)	4 (3.1)	3 (2.3)	2 (1.6)	0	2 (1.6)	8 (5.1)	6 (3.8)	3 (1.9)	2 (1.3)	1 (0.6)	12 (4.2)	9 (3.1)	5 (1.7)	2 (0.7)	3 (1.0)
Herpes simplex meningoencephalitis, n (%)	0	0	0	0	0	0	0	0	0	1 (0.6)	0	0	0	0	1 (0.3)
Infection, n (%)	3 (2.3)	7 (5.4)	2 (1.6)	0	0	8 (5.1)	14 (8.9)	5 (3.2)	0	0	11 (3.8)	21 (7.3)	7 (2.4)	0	0
Pneumonia, n (%)	0	6 (4.7)	9 (7.0)	2 (1.6)	1 (0.8)	2 (1.3)	4 (2.5)	14 (8.9)	1 (0.6)	1 (0.6)	2 (0.7)	10 (3.5)	23 (8.0)	3 (1.0)	2 (0.7)
Respiratory tract infection, n (%)	4 (3.1)	7 (5.4)	2 (1.6)	0	0	6 (3.8)	9 (5.7)	1 (0.6)	0	1 (0.6)	10 (3.5)	16 (5.6)	3 (1.0)	0	1 (0.3)
Sepsis, n (%)	0	0	0	1 (0.8)	2 (1.6)	0	0	3 (1.9)	1 (0.6)	2 (1.3)	0	0	3 (1.0)	2 (0.7)	4 (1.4)
Injury, poisoning and procedural complications, n (%)	10 (7.8)	6 (4.7)	3 (2.3)	0	0	8 (5.1)	13 (8.2)	4 (2.5)	1 (0.6)	0	18 (6.3)	19 (6.6)	7 (2.4)	1 (0.3)	0
Investigations, n (%)	19 (14.7)	14 (10.9)	2 (1.6)	2 (1.6)	0	17 (10.8)	11 (7.0)	5 (3.2)	1 (0.6)	0	36 (12.5)	25 (8.7)	7 (2.4)	3 (1.0)	0
Hepatic enzyme increased, n (%)	7 (5.4)	6 (4.7)	1 (0.8)	1 (0.8)	0	11 (7.0)	2 (1.3)	2 (1.3)	0	0	18 (6.3)	8 (2.8)	3 (1.0)	1 (0.3)	0
Metabolism and nutrition disorders, n (%)	18 (14.0)	16 (12.4)	13 (10.1)	1 (0.8)	0	27 (17.1)	13 (8.2)	10 (6.3)	4 (2.5)	0	45 (15.7)	29 (10.1)	23 (8.0)	5 (1.7)	0
Anorexia, n (%)	11 (8.5)	9 (7.0)	1 (0.8)	0	0	10 (6.3)	6 (3.8)	3 (1.9)	0	0	21 (7.3)	15 (5.2)	4 (1.4)	0	0
Hypokalemia, n (%)	8 (6.2)	3 (2.3)	3 (2.3)	0	0	10 (6.3)	2 (1.3)	2 (1.3)	0	0	18 (6.3)	5 (1.7)	5 (1.7)	0	0
Musculoskeletal and connective tissue disorders, n (%)	14 (10.9)	27 (20.9)	6 (4.7)	0	0	16 (10.1)	30 (19.0)	11 (7.0)	0	0	30 (10.5)	57 (19.9)	17 (5.9)	0	0
Muscular weakness, n (%)	9 (7.0)	7 (5.4)	5 (3.9)	0	0	4 (2.5)	9 (5.7)	1 (0.6)	0	0	13 (4.5)	16 (5.6)	6 (2.1)	0	0
Musculoskeletal pain, n (%)	9 (7.0)	21 (16.3)	1 (0.8)	0	0	11 (7.0)	19 (12.0)	10 (6.3)	0	0	20 (7.0)	40 (13.9)	11 (3.8)	0	0

(*Continued*)

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Table 2 (*Continued*)

AE experienced	SRS → TTFields (N = 129)					SRS only (N =158)					Overall (N = 287)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	0	3 (2.3)	6 (4.7)	0	31 (24.0)	2 (1.3)	4 (2.5)	3 (1.9)	0	34 (21.5)	2 (0.7)	7 (2.4)	9 (3.1)	0	65 (22.6)
Malignant neoplasm progression, n (%)	1 (0.8)	0	4 (3.1)	0	31 (24.0)	1 (0.6)	1 (0.6)	2 (1.3)	0	33 (20.9)	2 (0.7)	1 (0.3)	6 (2.1)	0	64 (22.3)
Tumor hemorrhage, n (%)	0	0	0	0	0	0	0	0	0	1 (0.6)	0	0	0	0	1 (0.3)
Nervous system disorders, n (%)	23 (17.8)	26 (20.2)	17 (13.2)	2 (1.6)	1 (0.8)	21 (13.3)	30 (19.0)	22 (13.9)	2 (1.3)	4 (2.5)	44 (15.3)	56 (19.5)	39 (13.6)	4 (1.4)	5 (1.7)
Brain edema, n (%)	0	1 (0.8)	0	0	0	1 (0.6)	3 (1.9)	5 (3.2)	0	1 (0.6)	1 (0.3)	6 (2.1)	11 (3.8)	1 (0.3)	1 (0.3)
Cerebrovascular accident, n (%)	0	0	0	0	0	1 (0.6)	0	0	0	1 (0.6)	1 (0.3)	0	0	0	1 (0.3)
Dizziness, n (%)	11 (8.5)	5 (3.9)	0	0	0	7 (4.4)	7 (4.4)	2 (1.3)	0	0	18 (6.3)	12 (4.2)	2 (0.7)	0	0
Headache, n (%)	17 (13.2)	12 (9.3)	1 (0.8)	0	0	15 (9.5)	13 (8.2)	4 (2.5)	0	0	32 (11.1)	25 (8.7)	5 (1.7)	0	0
Intracranial pressure increased, n (%)	0	0	0	0	0	0	2 (1.3)	1 (0.6)	0	1 (0.6)	0	2 (0.7)	1 (0.3)	0	1 (0.3)
Seizure, n (%)	1 (0.8)	3 (2.3)	6 (4.7)	1 (0.8)	1 (0.8)	3 (1.9)	7 (4.4)	3 (1.9)	1 (0.6)	1 (0.6)	4 (1.4)	10 (3.5)	9 (3.1)	2 (0.7)	2 (0.7)
Psychiatric disorders, n (%)	18 (14.0)	10 (7.8)	0	0	0	17 (10.8)	15 (9.5)	1 (0.6)	0	0	35 (12.2)	25 (8.7)	1 (0.3)	0	0
Sleep disorder, n (%)	9 (7.0)	4 (3.1)	0	0	0	11 (7.0)	7 (4.4)	1 (0.6)	0	0	20 (7.0)	11 (3.8)	1 (0.3)	0	0
Renal and urinary disorders, n (%)	5 (3.9)	8 (6.2)	2 (1.6)	0	1 (0.8)	5 (3.2)	5 (3.2)	4 (2.5)	1 (0.6)	1 (0.6)	10 (3.5)	13 (4.5)	6 (2.1)	1 (0.3)	2 (0.7)
Acute kidney injury, n (%)	1 (0.8)	0	1 (0.8)	0	0	0	2 (1.3)	3 (1.9)	1 (0.6)	1 (0.6)	1 (0.3)	2 (0.7)	4 (1.4)	1 (0.3)	1 (0.3)
Renal failure, n (%)	2 (1.6)	2 (1.6)	0	0	1 (0.8)	0	0	0	0	0	2 (0.7)	2 (0.7)	0	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders, n (%)	20 (15.5)	20 (15.5)	13 (10.1)	1 (0.8)	3 (2.3)	19 (12.0)	17 (10.8)	15 (9.5)	4 (2.5)	9 (5.7)	39 (13.6)	37 (12.9)	28 (9.8)	5 (1.7)	12 (4.2)
Chronic obstructive pulmonary disease, n (%)	0	1 (0.8)	0	0	0	0	0	2 (1.3)	1 (0.6)	1 (0.6)	0	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)
Cough, n (%)	12 (9.3)	9 (7.0)	0	0	0	9 (5.7)	9 (5.7)	2 (1.3)	0	0	21 (7.3)	18 (6.3)	2 (0.7)	0	0
Dyspnea, n (%)	6 (4.7)	9 (7.0)	2 (1.6)	0	0	12 (7.6)	4 (2.5)	4 (2.5)	1 (0.6)	0	18 (6.3)	13 (4.5)	6 (2.1)	1 (0.3)	0

(*Continued*)

Table 2 (*Continued*)

AE experienced	SRS → TTFields (N = 129)					SRS only (N = 158)					Overall (N = 287)				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pneumonitis, n (%)	0	0	2 (1.6)	0	0	0	1 (0.6)	0	0	1 (0.6)	0	1 (0.3)	2 (0.7)	0	1 (0.3)
Pulmonary hemorrhage, n (%)	4 (3.1)	2 (1.6)	2 (1.6)	0	0	0	1 (0.6)	2 (1.3)	0	1 (0.6)	4 (1.4)	3 (1.0)	4 (1.4)	0	1 (0.3)
Respiratory failure, n (%)	1 (0.8)	1 (0.8)	0	0	3 (2.3)	0	0	2 (1.3)	1 (0.6)	6 (3.8)	1 (0.3)	1 (0.3)	2 (0.7)	1 (0.3)	9 (3.1)
Skin and subcutaneous tissue disorders, n (%)	37 (28.7)	24 (18.6)	3 (2.3)	0	0	21 (13.3)	14 (8.9)	3 (1.9)	0	0	58 (20.2)	38 (13.2)	6 (2.1)	0	0
Rash, n (%)	13 (10.1)	5 (3.9)	1 (0.8)	0	0	5 (3.2)	3 (1.9)	1 (0.6)	0	0	18 (6.3)	8 (2.8)	2 (0.7)	0	0
Vascular disorders, n (%)	5 (3.9)	10 (7.8)	2 (1.6)	0	0	10 (6.3)	15 (9.5)	5 (3.2)	1 (0.6)	0	15 (5.2)	25 (8.7)	7 (2.4)	1 (0.3)	0

Abbreviations: AE = adverse event; PT = preferred term; SOC = system organ class; SRS = stereotactic radiosurgery; TTFields =Tumor Treating Fields.

system AEs, of which headache was the most common, occurring in 10.1% of patients (13/129), and there were 2 grade ≥3 device-related nervous system AEs (seizure n = 1; brain edema n = 1). Device-related AEs led to device discontinuation in 5.4% (7/129) of patients (skin-related AEs, n = 5; pain, n = 1; seizure, n = 1). Device-related AEs were reported in 29.4% (5/17) of patients who crossed over from SRS only to receive TTFields therapy; most were grade ≤2, although 1 patient reported a grade 3 headache.

One patient experienced a grade 5 SAE (seizure) reported by the investigator as possibly related to the device. However, a dedicated ad hoc Study Steering Committee unanimously agreed that the seizure episodes were related to underlying progressive disease and that the fatal SAE was "unlikely" to be related to the device (see safety narrative in Appendix E4).

HRQoL

HRQoL data were available for 39.6% and 19.5% of patients at 6 and 12 months, respectively, with overall assessment completion rates of 87.4% and 89.2% of available patients at each time point, with no differences in response rate between treatment arms (Table E1). Significant improvements in DFS for global health status, physical functioning, and fatigue were observed for patients receiving SRS followed by TTFields therapy using a 5-point MID, with an overall positive trend in most items, except for "itchy skin" (Fig. E5A). This overall observation remained evident when using the 10-point MID (Fig. E5B). Similarly, TTD analysis showed significant improvement in the physical functioning (5-point MID) and fatigue (5- and 10-point MID) items,[31,32] with significant worsening for the "itchy skin" item for patients receiving SRS followed by TTFields therapy (Fig. E5C, D).

Analysis of these data using MMRM showed significant improvement in global health status and physical functioning at month 2, while itchy skin was worse at months 2, 4, and 6 for patients receiving SRS followed by TTFields therapy (Table E9). When MMRM was performed with imputation for missing data, improved global health status at month 2 (LSMean difference, 6.5 [95% CI, 0.2-12.8]; P = .042) was seen for patients receiving SRS followed by TTFields therapy. There were no other significant differences in item scores between treatment arms. A post hoc analysis of HRQoL, mapping the EORTC QLQ C-30 onto the EQ-5D 3L, showed a significant DFS benefit (HR, 0.681 [95% CI, 0.468-0.991]; Fig. E6).

Discussion

Treatment of BMs from NSCLC using TTFields therapy following SRS provided a clinically meaningful 28% relative reduction in risk of intracranial progression, the primary study endpoint, compared with SRS only; a positive effect of

TTFields therapy was observed in all subgroups assessed. Analysis of the rate of intracranial progression provided further evidence of the benefit of TTFields therapy for intracranial progression, with a statistically significant improvement observed as early as 2 months following the start of treatment, with the difference between treatment arms maintained over the 24-month follow-up period (Fig. 2). The improvement in time to first intracranial progression was achieved with median monthly device usage of 67.1%, consistent with that seen in a similar population in the LUNAR study of TTFields therapy in NSCLC.[20] Treatment with TTFields therapy was also well tolerated without significant high-grade toxicity in this study population, with no new safety signals observed. TTFields therapy has also been applied concurrently with a wide array of systemic chemotherapy and immunotherapy treatments in other malignancies.[20-24]

No improvement in the secondary endpoints of OS, time to neurocognitive failure, and time to radiologic progression was observed with TTFields therapy following SRS versus SRS only. The lack of improvement in OS is not unexpected because similar studies investigating locoregional therapy for BMs have also failed to show an OS benefit.[33-35] Furthermore, a study designed to determine the correlation between outcome measures, including time to intracranial progression and OS in patients with BMs treated with SRS, showed no apparent correlation between OS and intracranial progression.[36] In the metastatic NSCLC setting, primary disease and its systemic management are believed to have the greatest impact on OS.

Although time to neurocognitive failure showed no improvement in patients receiving SRS followed by TTFields therapy, there was no apparent worsening in neurocognitive function in the TTFields therapy arm compared with SRS alone. Given the decline in neurocognitive function observed in studies of WBRT,[35,37,38] the absence of decline with TTFields therapy in the context of improved time to first intracranial progression suggests that TTFields therapy following SRS represents a potential alternative option to WBRT when managing BMs. However, approximately 50% of patients completed baseline tests, and fewer completed the follow-up tests because of the lack of availability of tests in local languages. Additionally, the study was not adequately powered to assess this issue, so the findings should be interpreted with caution.

No statistically significant effects on other secondary endpoints were observed. However, a 24% risk reduction in time to distant intracranial progression favored TTFields therapy after SRS. Array layouts were chosen to maximize TTFields therapy intensity in the area of maximal disease burden based on the baseline MRI scan and may not have optimally affected progression of pre-existing micrometastases beyond the targeted area (per protocol).

The LUNAR study showed a significant improvement in OS but not objective response rate or PFS.[20] Similar to our study, the subgroup of patients with NSCLC who received immunotherapy in LUNAR appeared to obtain greater benefit from TTFields therapy than those who did not. In preclinical studies in NSCLC models, TTFields produced an immunogenic cell death response that was sustained by ICI treatment.[39,40] In glioblastoma models, it has been shown that TTFields disrupt tumor cells, which results in the production of proinflammatory cytokines, type 1 interferons (T1IFNs), and T1IFN-responsive genes, inducing antitumor memory immunity.[41] In a phase 2 study in glioblastoma, TTFields and pembrolizumab showed synergy, with promotion of clonal T cell expansion via a T1IFN-driven trajectory by TTFields and adaptive replacement of these clones supported by pembrolizumab, leading to sustained T cell activation and memory formation.[42] Although TTFields therapy benefits patients irrespective of whether they have received prior systemic ICI therapy, it is possible that using TTFields therapy to treat BMs in patients receiving systemic ICIs has a more pronounced effect than when used in patients receiving other forms of systemic therapy.

HRQoL was not negatively impacted by TTFields therapy following SRS compared with SRS alone, and improvements in global health status, physical functioning, and fatigue DFS and TTD were observed. Patients receiving TTFields therapy experienced worsening itchy skin compared with SRS alone, probably due to the positioning of the transducer array on the skin of the scalp. In contrast, other locoregional therapies such as WBRT generally result in reduced HRQoL compared with SRS.[43] It is important to note that the ability to detect changes in HRQoL may have been influenced by the small number of patients who completed the questionnaire, although the compliance of the patients who were available to complete questionnaires was high, and data availability rapidly declined because of the poor health of the study population.

The duration of TTFields therapy was 15.7 weeks, similar to that in the LUNAR study.[20] The safety profile of TTFields therapy was consistent with that seen in other clinical trials of, and real-world evidence for, TTFields therapy and did not add to the burden of systemic TEAEs.[20,21,24] Device-related TEAEs were mainly grade 1/2 skin and subcutaneous tissue disorders, including skin irritation and pruritus, and nervous system disorders, specifically headache. Although 1 fatal seizure was initially attributed as device-related by the investigator, subsequent ad hoc steering committee review adjudged this unlikely to be related to TTFields therapy. No similar fatal TEAE related to TTFields therapy has been observed to date. Skin-related TEAEs primarily appear to be related to contact with the adhesive or hydrogel on the arrays. Such TEAEs can be managed by repositioning the arrays every few days and by using, for example, topical steroids or calcineurin inhibitors and appropriate skin care. Approximately 25% of study AE events were related to intracranial progression of disease, which in turn can independently and negatively affect QoL. TTFields may have favorably impacted QoL by delaying lesion-related loss of neurologic function. Furthermore, a similar proportion of AEs leading to the discontinuation of TTFields therapy were likely treatable or preventable grade 1/2 skin AEs,

suggesting that the ceiling for new intracranial lesions and QoL improvements was not reached.

Study limitations include the lack of sham device use and open-label design. The lack of a sham device is common in RT trials and reflects the practical, logistical, and ethical concerns of potentially using sham RT treatments.[35] The use of central assessment blinded to to treatment, negates any meaningful impact on the primary endpoint; therefore, the lack of blinding for patients and investigators is not expected to significantly affect the results of the primary endpoint. The patient population enrolled was broad, and neither the type nor number of prior lines of treatment for primary disease nor molecular pathology (ie, programmed death-ligand 1 and oncogenic driver) was defined. Consequently, this study may be considered to lack the specificity needed to define a specific patient subpopulation eligible for therapy, as has been the case with trials of systemic therapies for NSCLC.[44] However, this study reflects the designs of trials of other platform technologies, such as SRS, that have shaped the basis of treatment for patients with BMs. Future trials and real-world evidence may provide more granularity, eg, on molecular pathology.

In conclusion, this study indicates that TTFields therapy is effective in patients with BMs of NSCLC who have undergone SRS, extending time to intracranial progression without adding to the toxicity of systemic therapy for primary disease or causing a decline in neurocognitive function or QoL. TTFields therapy has the potential to safely improve intracranial control of BMs, allowing the therapeutic focus to be on the primary tumor. We speculate that application of TTFields therapy may delay or reduce the need for salvage SRS or WBRT or systemic salvage therapies.

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