JAMA | Original Investigation

Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

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IMPORTANCE Tumor-treating fields (TTFields) is an antimitotic treatment modality that interferes with glioblastoma cell division and organelle assembly by delivering low-intensity alternating electric fields to the tumor.

OBJECTIVE To investigate whether TTFields improves progression-free and overall survival of patients with glioblastoma, a fatal disease that commonly recurs at the initial tumor site or in the central nervous system.

DESIGN, SETTING, AND PARTICIPANTS In this randomized, open-label trial, 695 patients with glioblastoma whose tumor was resected or biopsied and had completed concomitant radiochemotherapy (median time from diagnosis to randomization, 3.8 months) were enrolled at 83 centers (July 2009-2014) and followed up through December 2016. A preliminary report from this trial was published in 2015; this report describes the final analysis.

INTERVENTIONS Patients were randomized 2:1 to TTFields plus maintenance temozolomide chemotherapy (n = 466) or temozolomide alone (n = 229). The TTFields, consisting of low-intensity, 200 kHz frequency, alternating electric fields, was delivered (≥ 18 hours/d) via 4 transducer arrays on the shaved scalp and connected to a portable device. Temozolomide was administered to both groups (150-200 mg/m^2) for 5 days per 28-day cycle (6-12 cycles).

MAIN OUTCOMES AND MEASURES Progression-free survival (tested at α = .046). The secondary end point was overall survival (tested hierarchically at α = .048). Analyses were performed for the intent-to-treat population. Adverse events were compared by group.

RESULTS Of the 695 randomized patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the trial. Median progression-free survival from randomization was 6.7 months in the TTFields-temozolomide group and 4.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.52-0.76; *P* < .001). Median overall survival was 20.9 months in the TTFields-temozolomide group vs 16.0 months in the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; *P* < .001). Systemic adverse event frequency was 48% in the TTFields-temozolomide group and 44% in the temozolomide-alone group. Mild to moderate skin toxicity underneath the transducer arrays occurred in 52% of patients who received TTFields-temozolomide vs no patients who received temozolomide alone.

CONCLUSIONS AND RELEVANCE In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

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Glioblastoma is the most common and aggressive primary brain tumor with an annual incidence of 3.19 per 100 000.[1-5] The disease course is typically rapid, with only approximately 1 in 4 patients alive 2 years after diagnosis, and only 5% to 10% of patients alive at 5 years.[1,6,7]

Since the current standard of care was established, consisting of surgical resection or biopsy, followed by radiotherapy with concomitant temozolomide chemotherapy, followed by maintenance temozolomide for 6 to 12 months,[6] little progress has been made in the treatment of this disease.[3,8,9] Most trials have shown median progression-free survival and median overall survival from diagnosis of 6.2 to 7.5 months and 14.6 to 16.7 months, respectively.[4-6,8]

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively affects dividing glioblastoma cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the scalp.[10,11] Tumor-treating fields cause mitotic arrest and apoptosis of rapidly dividing cells.[10,11] Preclinical studies demonstrated increased sensitivity to chemotherapy with the addition of TTFields in human glioblastoma cell lines and in animal tumor models.[12] In a randomized phase 3 trial involving 237 patients with recurrent glioblastoma whose several lines of prior therapy had failed, TTFields monotherapy was compared with the treating physicians' best choice of salvage chemotherapy. Although no survival difference was observed, the higher objective response rate (12% vs 7%) suggested single-modality activity of TTFields.[13]

In 2009, this randomized phase 3 clinical trial was initiated, comparing maintenance temozolomide alone with maintenance temozolomide in combination with TTFields among patients with glioblastoma. A preplanned interim analysis involving the first 315 patients randomized was previously reported and demonstrated improved progression-free and overall survival.[14] This article reports the final analysis involving all 695 randomized patients, with a median follow-up of 40 months and a minimum follow-up of 24 months.

Key Points

Question Does the use of tumor-treating fields (TTFields), consisting of low-intensity, alternating electric fields delivered via transducer arrays applied to the scalp, when added to maintenance temozolomide chemotherapy, improve progression-free survival for patients with glioblastoma?

Findings In this randomized clinical trial involving 695 patients with glioblastoma who had completed initial radiochemotherapy, median progression-free survival from randomization was 6.7 months in the TTFields plus temozolomide group and 4.0 months in the temozolomide-alone group (hazard ratio, 0.63), a significant difference.

Meaning Among patients with glioblastoma, the addition of TTFields to maintenance temozolomide chemotherapy resulted in statistically significant improvement in survival. These results are consistent with those reported in a previous interim analysis.

Methods

The study was approved by the institutional review boards or ethics committees of all participating centers, and all patients provided written informed consent before entering the study. The trial protocol and statistical analysis plan are included in Supplement 1.

Study Population

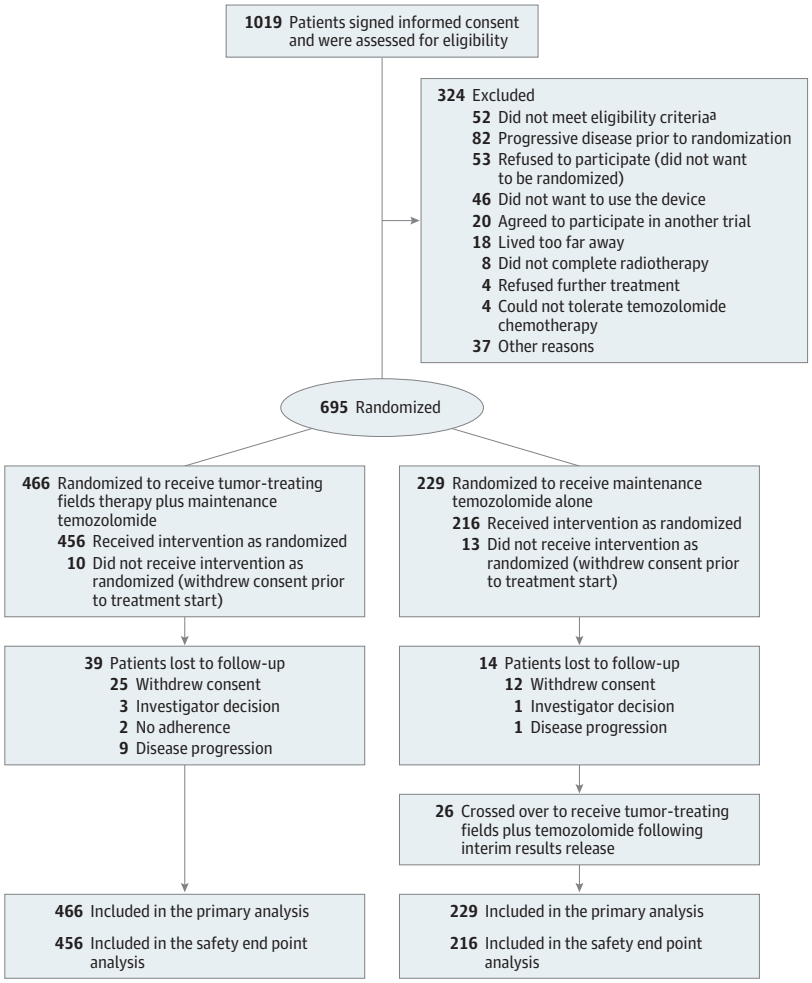
Patients eligible for this study were aged 18 years or older, had a Karnofsky performance score of 70 or higher (a score of ≥70 ensures independence in activities of daily living), and had newly diagnosed and histologically confirmed supratentorial glioblastoma (World Health Organization [WHO] grade IV astrocytoma[15]). All participants had undergone maximal safe debulking surgery when feasible or biopsy and had completed standard radiotherapy with concomitant temozolomide at the time of enrollment. Prior use of implanted carmustine wafers was allowed. Patients with evidence of progressive disease following radiochemotherapy, infratentorial tumor location, and severe comorbidities were excluded. Adequate hematological, liver, and kidney function tests to allow for temozolomide chemotherapy were required.[6,14,16]

Study Design and Treatment

This multicenter, open-label, randomized clinical phase 3 trial, recruited 695 patients at 83 sites in North America, Europe, the Republic of Korea, and Israel. The trial was designed to test the efficacy and safety of TTFields in combination with best standard of care in the treatment of newly diagnosed glioblastoma. Patients were randomized after the end of radiochemotherapy at a ratio of 2:1 to receive standard maintenance temozolomide chemotherapy (150-200 mg/m^2/d for 5 days every 28 days for 6 cycles) with or without the addition of TTFields. Tumor treating fields treatment was to be initiated at least 4 weeks but not more than 7 weeks from the last day of radiotherapy. Maintenance temozolomide was delivered in 28-day cycles according to the protocol established by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group.[6] Extension of the duration of maintenance temozolomide beyond 6 cycles was allowed per local practice. Randomization was performed using a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by the methylation status of the O6-methylguanine-DNA methyltransferase (*MGMT*) gene promoter (methylated, unmethylated, unknown).

Treatment with TTFields was delivered through 4 transducer arrays with 9 insulated electrodes each placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Inc). Transducer array layouts were determined using a TTFields mapping software system to optimize field intensity within the treated tumor (NovoTAL, Novocure Inc). Patients were trained by the nursing staff and device technician to operate the device independently, replace transducer arrays, and troubleshoot any

Figure 1. Recruitment and Inclusion of Patients in the Study



[a] Ten patients were out of randomization window; 8 had low platelet counts; 17, infratentorial disease; 4, elevated liver enzymes; 3, programmable shunts; 10, pacemakers or defibrillators.

alarm conditions (eg, disconnected cables). All treatment was delivered on an outpatient basis and at home. The transducer arrays were supplied in individual sterile packages, and replaced by the patient, a caregiver, or a device technician twice a week. Although uninterrupted treatment was recommended, the patient could take short treatment breaks to tend to personal needs. The patient was advised to continue treatment for no fewer than 18 hours a day.

If tumor progression occurred, second-line therapy was offered per local practice. However, in the experimental group, TTFields could be continued until second radiologic progression occurred or for a maximum of 24 months.

Patient Surveillance and Follow-up

Patients diagnosed with glioblastoma who had undergone surgical resection or biopsy and had received standard radiochemotherapy were randomized to receive either TTFields plus temozolomide or temozolomide alone between July 2009 and December 2014 (**Figure 1**). The database was locked for final analysis on December 28, 2016. Baseline contrast-enhanced magnetic resonance imaging (MRI) of the brain was required within 2 weeks before starting treatment with maintenance temozolomide with or without TTFields. A complete physical examination and laboratory parameters were performed within 1 week of treatment start. Evaluation also included the EORTC QLQ-C30 quality-of-life questionnaire with its brain-specific module (BN-20)[17,18] and a Mini-Mental State Examination (a test result of 27-30 points is considered normal function). Patients were seen monthly for medical follow-up and routine laboratory examinations. Quality of life was assessed every 3 months.

Adverse events were recorded for 2 months after treatment discontinuation according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) v3.0. Adverse events were presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the analysis.

Independent Radiological Review

Magnetic resonance imaging was performed at 2-month intervals until second progression. In the event of clinical progression, MRI was to be performed within 1 week after the investigator had become aware of it. All MRIs were reviewed by 2 blinded central independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression (Macdonald criteria[19]). For cases

in which the 2 reviewers were not in agreement, a third blinded radiologist adjudicated between them.

Central *MGMT* Testing, Pathology Review, and Molecular Analyses

In patients with paraffin-embedded tumor tissue available, evaluation of the *MGMT* methylation status was performed using quantitative methylation-specific polymerase chain reaction[3,20] by a central laboratory licensed by MDxHealth. If the *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification. All data analyses were based on the central blinded assessment.

Patients were included based on initial local histological diagnosis. A retrospective pathology review and evaluation of molecular testing was performed by a neuropathologist (B.L.) and molecular biologist (M.E.H.). Deletion of chromosomal arms 1p and 19q and amplification of the epidermal growth factor receptor (*EGFR)* were evaluated by fluorescent in situ hybridization (FISH), immunohistochemistry (IHC), or both; and the mutation status of the isocitrate dehydrogenase 1 (*IDH1)* gene was determined by immunohistochemistry for the most common mutant *IDH1-R132H* as described previously.[21] For cases in which insufficient tissue was available for *EGFR* FISH, the result of *EGFR* IHC was used as a surrogate (Hirsch score, ≥200 amplified; <200, not amplified).[22]

Outcomes

Primary and Secondary End Points

The primary end point was progression-free survival, and the secondary end point was overall survival, with analyses conducted in the intent-to-treat population.

The protocol defined that overall survival would be analyzed in a per-protocol population including only patients who received their original allocated treatments. However, 26 patients (11%) in the temozolomide-alone control group crossed over and received TTFields after December 2014, following release of the results of the interim analysis of the trial. These 26 patients had more favorable baseline characteristics than the rest of the control patients (*MGMT* methylated, 48%; Karnofsky performance score, 80-100; time from end of radiotherapy to randomization, 31 days) and received more cycles of temozolomide (median, 10.5 cycles). To avoid possible bias, these patients were analyzed as randomized in the control group according to the intent-to-treat principle.

Exploratory End Points

Other predefined exploratory end points were percentage of patients alive and progression free at 6 months, annualized survival rates, quality of life, Mini-Mental State Examination, and Karnofsky performance score. The quality-of-life data are not reported in this article.

Statistical Analysis

Primary and Secondary End Points

For the primary end point of progression-free survival, the calculated sample size was 700 patients aimed to detect a hazard ratio (HR) of 0.78 or less, with 80% power allowing for 10% loss to follow-up and a 2-sided $\alpha = .05$. Overall survival was a powered secondary end point in the study (80% power; HR, 0.76; 2-sided $\alpha = .05$). To avoid multiplicity, overall survival was to be tested statistically only if the primary end point of the study was met.

To allow for 2 analyses in the trial, the final type I error of 0.05 was split between the interim and final analyses based on a standard α spending function (Lan and DeMets[23,24]). The primary end point at the final analysis would be achieved if progression-free survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test (stratified by the randomization strata) with an α of .046 (an α of 0.014 was spent on the interim analysis).

The secondary end point would be achieved at the final analysis if overall survival was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α of .048 (an α of .006 was spent on the interim analysis).

Missing Data

For the analysis of progression-free survival patients were censored for progression when treatment was changed before evidence of progression (at the date of treatment change), at the date of their last MRI if lost to follow up, or upon reaching the cutoff date without progression. For the analysis of overall survival, patients without a known date of death were censored at the last known date they were documented to be alive.

Exploratory End Points

The exploratory end points of annual survival rates and the rate of progression-free survival at 6 months were compared between groups using a 1-sided *Z* distribution of the Kaplan-Meier estimates of the survival rates at the defined time point. In addition, the Cox proportional hazards model was used to analyze both progression-free survival and overall survival controlling for treatment group, age, sex, *MGMT* methylation status (as determined by the central laboratory), tumor location in the brain, and country of residence (United States vs all other countries). The threshold for significant interactions in the model was specified at an α of .05.

Post Hoc Analysis

Post hoc analyses of prespecified subgroups (*MGMT* promoter methylation status, extent of resection (complete, partial resection, or biopsy), age (continuous), performance status (90-100 vs ≤80), sex, and geographic region (United States vs the rest of the world) was performed using a multivariate analysis testing the difference between treatment groups while controlling for the other prognostic factors.

Analysis of Adverse Events and Tolerability

Differences in the incidence of adverse events between groups was tested using a χ^2 test at an α of .05. The incidence of adverse events was also compared between groups after normalizing the incidence to the average treatment duration per group. Differences in the time to decline in Karnofsky performance score and Mini-Mental State Examination were tested using a log-rank test at an α of .05. All analyses were performed using SAS version 9.4.

Table 1. Patient and Treatment Characteristics

Characteristics	No. (%) of Patients	
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)
Age, y		
Median (range)	56.0 (19-83)	57.0 (19-80)
≥65	89 (19)	45 (20)
<65	377 (81)	184 (80)
Karnofsky performance score[a]		
Median (range)	90.0 (60-100)	90.0 (70-100)
90-100	308 (66)	149 (65)
≤80	154 (33)	74 (32)
Missing	4 (1)	6 (3)
Sex		
Men	316 (68)	157 (69)
Women	150 (32)	72 (31)
Region		
United States	221 (47)	118 (52)
Outside the United States	245 (53)	111 (48)
Race/ethnicity		
White	416 (89)	201 (88)
African American	3 (1)	1 (<1)
Asian	27 (6)	19 (8)
Hispanic	18 (4)	7 (3)
American Indian	1 (<1)	1 (<1)
Antiepileptic drug use at baseline	205 (44)	95 (41)
Corticosteroid use at baseline	135 (29)	64 (28)
Mini-Mental State Examination score[b]		
27-30	356 (76)	160 (70)
≤26	88 (19)	48 (21)
Missing	22 (5)	21 (9)
Extent of resection		
Biopsy	60 (13)	29 (13)
Partial resection	157 (34)	77 (33)
Gross total resection	249 (53)	123 (54)
MGMT promotor region methylation status		
Tissue available and tested	386 (83)	185 (81)
Methylated	137 (36)	77 (42)
Unmethylated	209 (54)	95 (51)
Invalid	40 (10)	13 (7)
Slides available for central pathology review	296 (64)	138 (60)
Confirmed glioblastoma	285 (96)	134 (97)
WHO grade II or III glioma	4 (1)	2 (1)
Insufficient quality for diagnosis	7 (2)	2 (1)
IDH1-R132H status		
Tissue available and tested	260 (56)	119 (52)
Mutated	19 (7)	6 (5)
Negative test results	240 (92)	113 (95)
Invalid	1 (<1)	
EGFR status		
Tissue available and tested	252 (54)	112 (49)
Amplified	102 (41)	43 (38)
Not amplified	147 (58)	68 (61)
Invalid	3 (1)	1 (1)
Tumor tissue chromosomes 1p and 19q		
Tissue available and tested	259 (56)	112 (49)
Codeletion	2 (1)	
Loss 1p only	4 (2)	1 (1)
Loss 19q only	3 (1)	3 (3)
Retained	239 (92)	102 (91)
Invalid	11 (4)	6 (5)

(continued)

Table 1. Patient and Treatment Characteristics (continued)

Characteristics	No. (%) of Patients	
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)
Tumor position[c]		
Corpus callosum	25 (5)	12 (5)
Frontal lobe	190 (41)	84 (37)
Occipital lobe	58 (12)	27 (12)
Parietal lobe	146 (31)	89 (39)
Temporal lobe	191 (41)	90 (40)
Missing	3 (1)	3 (1)
Tumor location[c]		
Left hemisphere	214 (46)	99 (43)
Right hemisphere	249 (53)	127 (55)
Both hemispheres	4 (1)	2 (1)
Corpus callosum	15 (3)	9 (4)
Missing	1 (<1)	1 (<1)
Treatment delivery		
Completed standard radiation therapy		
57-63 Gy	422 (91)	212 (93)
<57 Gy	21 (5)	11 (5)
>63 Gy	18 (4)	3 (1)
Dose not reported	5 (1)	3 (1)
Concomitant radiation therapy and temozolomide		
Yes	433 (93)	212 (93)
No record available	33 (7)	17 (7)
Time from last day of radiation treatment to randomization, median (range), d	37 (15-128)	36 (15-70)
Time from initial diagnosis to randomization, median (range), mo	3.8 (1.7-6.2)	3.7 (1.4-6.3)
Temozolomide cycles, median (range)	6 (0-51)	5 (0-33)
Tumor-treating fields therapy		
Duration, median (range), mo	8.2 (0-82)	
≥18 h/d (first 3 mo of treatment), mean	347 (75)	

Abbreviations: *EGFR*, epidermal growth factor receptor gene; *IDH1*-R132H, socitrate dehydrogenase 1 (*IDH1*) R132H mutation site; *MGMT*, O^6-methylguanine-DNA-methyltransferase gene; TTFields, tumor-treating fields; WHO, World Health Organization.

[a] Karnofsky performance score ranges from 0 to 100 in 10-point increments, with a higher score representing better performance status.

[b] Scores range from 1 to 30, with a higher score representing better cognitive function.

[c] Multiple positions for each patient allowed (for multifocal tumors).

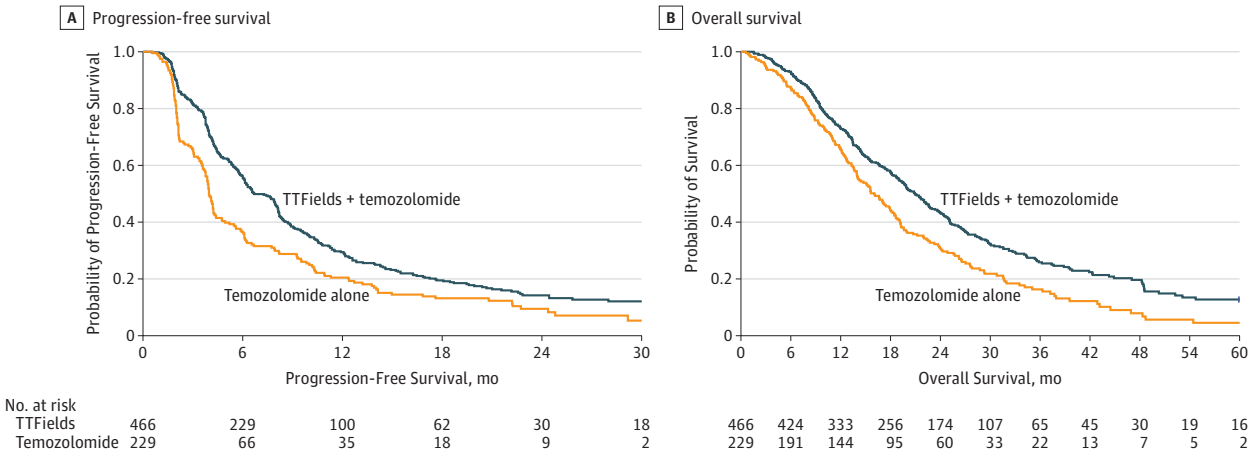
Results

Study Participants

Four hundred and sixty-six patients were randomized to receive TTFields plus temozolomide and 229 to receive temozolomide alone (Figure 1). Patient baseline characteristics were balanced between the 2 groups (**Table 1**). The median age was 56 years (interquartile range [IQR], 48-63 years), 68% were men, and median Karnofsky performance score was 90%. Eighty-nine percent of patients were white, and 49% of the patients were treated in the United States.

Fifty-four percent had undergone a gross total resection (>95% of the tumor removed; as assessed and reported by the surgeon), 13% of patients had a diagnostic biopsy only. Histological slides for central pathology review were available for

Figure 2. Kaplan-Meier Survival Curves for Patients Included in the Final Analysis in the Intent-to-Treat Population



A, Median progression-free survival from randomization for the tumor-treating fields (TTFields) plus temozolomide group was 6.7 months and was 4.0 months for the temozolomide-alone group (hazard ratio [HR], 0.63; 95% CI, 0.52-0.76; $P < .001$). B, Median survival from randomization was 20.9 for the TTFields plus temozolomide group vs 16.0 months for the temozolomide-alone group (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$). Median follow up was 44 months (range, 25-91 months) in both groups.

434 of 695 patients (62%). The local diagnosis of glioblastoma was confirmed in 419 of 434 patients (97%). For 6 cases WHO grade II or III diagnoses were made, and for the remaining 9 patients, the available tissue for review did not allow for a definitive diagnosis or showed no tumor, yet all these patients were included in the intent-to-treat analysis. Tumor tissue for *MGMT* testing was available for 82% of the patients; of the cases with a valid test (518 of 571) 41% were *MGMT* methylated (40% TTFields plus temozolomide group and 45% for the temozolomide-only group). In 7% of tumors, expression of the *IDH1*-R132H mutant was demonstrated by a positive immunohistochemistry, *EGFR* was amplified in 40%.

Tumor location (lobe, hemisphere) in the brain was also comparable between the groups. The median time from histological diagnosis to randomization was 3.8 months (range, 1.7-6.2 months) for patients in the TTFields plus temozolomide group, and 3.7 months (range, 1.4-6.3 months) for those in the temozolomide-only group. Median time from the end of radiotherapy to randomization was 37 days in the TTFields plus temozolomide group and 36 days in the temozolomide-only group and occurred in most patients after starting of the first cycle of maintenance temozolomide. Median time from randomization to TTFields was 5 days (IQR, 3-7 days).

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until first tumor progression was 6 (range, 0-51) for the TTFields plus temozolomide group and 5 (range, 0-33) for the temozolomide-only group; the median duration of TTFields treatment was 8.2 months (range, 0-82 months), 51% (n = 237) of patients continued TTFields after the first progression.

Efficacy End points

After a median follow-up of 40 months (IQR, 34-66 months), and a minimum follow-up of 24 months, the primary end point of median progression-free survival was 6.7 months (95% CI, 6.1-8.1 months) for patients treated with TTFields plus temozolomide vs 4.0 months (95% CI, 3.8-4.4 months) for patients treated with temozolomide alone, for a proportional hazard ratio (HR) of 0.63 (95% CI, 0.52-0.76; $P < .001$; stratified log-rank test; **Figure 2**A). For the secondary end point of overall survival, the median survival duration from randomization was 20.9 months (95% CI, 19.3-22.7 months) in the TTFields plus temozolomide group vs 16.0 months (95% CI, 14.0-18.4 months) in the temozolomide-only group, proportional HR of 0.63 (95% CI, 0.53-0.76; $P < .001$; stratified log-rank test; Figure 2B).

In exploratory analyses, the percentage of patients alive at 2 years from randomization was 43% (95% CI, 39%-48%); at 3 years, 26% (95% CI, 22%-31%), and at 5 years, 13% (95% CI, 9%-18%) in the TTFields plus temozolomide group and for the temozolomide-only group at 2 years was 31% (95% CI, 25%-38%; $P < .001$); at 3 years, 16% (95% CI, 12%-23%; $P = .009$); and at 5 years, 5% (95% CI, 2%-11%; $P = .004$). Progression-free survival at 6 months was 56% (95% CI, 51%- 61%) for patients treated with TTFields plus temozolomide and 37% (95% CI, 30%-44%) with temozolomide only ($P < .001$) (**Table 2**).

An exploratory Cox proportional hazards model adjusting for Karnofsky performance score, *MGMT* promotor methylation status, geographic region, age, tumor location, and extent of resection were consistent with the findings of the progression-free and overall survival analyses. The following factors were associated with longer overall survival: TTFields plus temozolomide treatment (HR, 0.63; 95% CI, 0.53-0.76; $P < .001$), female sex (HR, 0.76, 95% CI, 0.63-0.92; $P = .005$), methylated *MGMT* promoter (HR, 0.50; 95% CI, 0.41-0.62; $P < .001$), younger age (as a continuous variable; HR, 0.978 per year; 95% CI, 0.969-0.985; $P < .001$) and higher Karnofsky performance score (as a categorical variable in 10 point increments; $P < .001$). Patients with frontal tumors had nonsignificantly longer survival (HR = 0.82, CI 0.67-1.01, $P = .061$). Country of treatment and extent of resection were not

Table 2. Summary of Study End Points[a]

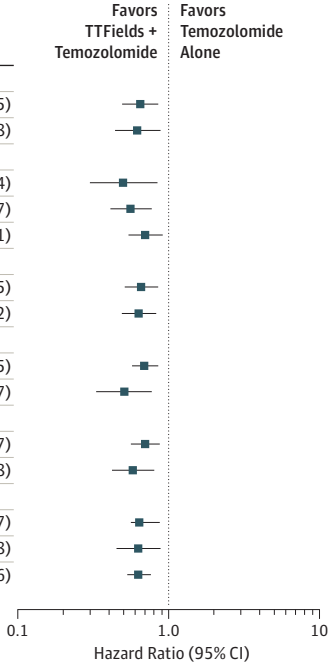
	TTFields + Temozolomide (n = 466)	Temozolomide Alone (n = 229)	Between-Group Differences
Progression-free survival			
Primary end point, median (95% CI), mo	6.7 (6.1-8.1)	4.0 (3.8-4.4)	2.7 (2.1-4.2)
Overall survival			
Secondary end point, median (95% CI), mo	20.9 (19.3-22.7)	16.0 (14.0-18.4)	4.9 (2.3-7.9)
Exploratory end points, % (95% CI)			
Progression-free 6-mo survival rate	56 (51-61)	37 (30-44)	19 (15-23)
Annual survival rates, y			
1	73 (69-77)	65 (59-72)	8 (0-16)
2	43 (39-48)	31 (25-38)	12 (4-18)
3	26 (22-31)	16 (12-23)	10 (3-17)
4	20 (16-25)	8 (4-14)	12 (5-19)
5	13 (9-18)	5 (2-11)	8 (2-14)

Abbreviation:
TTFields, tumor-treating fields.

[a] Survival rates are actuarial estimates according to the Kaplan-Meier method.

Figure 3. Overall Survival for Each Prognostic Patient Subgroup of Patients Treated With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone

Subgroup	TTFields + Temozolomide: No. of Patients	TTFields + Temozolomide: No. (%) Alive at End of Study	Temozolomide Alone: No. of Patients	Temozolomide Alone: No. (%) Alive at End of Study	Median Survival (IQR), mo: TTFields + Temozolomide	Median Survival (IQR), mo: Temozolomide Alone	Hazard Ratio (95% CI)
MGMT promoter region methylation status							
Unmethylated	209	18 (9)	95	3 (3)	16.9 (9.7-28.2)	14.7 (9.8-24.8)	0.66 (0.49-0.85)
Methylated	137	26 (19)	77	9 (12)	31.6 (21.1-48.5)	21.2 (12.3-37.9)	0.62 (0.44-0.88)
Resection							
Biopsy	60	5 (8)	29	0 (0)	16.5 (9.0-24.7)	11.6 (7.1-18.1)	0.50 (0.30-0.84)
Partial	157	20 (13)	77	3 (4)	21.4 (9.9-37.6)	15.1 (7.8-23.3)	0.56 (0.41-0.77)
Gross total	249	32 (13)	123	13 (11)	22.6 (13.4-39.8)	18.5 (12.1-31.6)	0.70 (0.54-0.91)
Region							
Outside United States	245	32 (13)	111	9 (8)	20.1 (11.3-32.2)	15.5 (9.3-25.6)	0.66 (0.51-0.85)
United States	221	25 (11)	118	7 (6)	22.0 (11.3-48.2)	17.1 (9.8-29.2)	0.63 (0.49-0.82)
Age, y							
<65	377	47 (12)	184	14 (8)	21.6 (12.0-39.4)	17.3 (10.6-29.3)	0.69 (0.57-0.85)
≥65	89	10 (11)	45	2 (4)	17.4 (9.0-31.5)	13.7 (7.6-24.8)	0.51 (0.33-0.77)
Karnofsky performance score							
90-100	308	39 (13)	149	11 (7)	23.3 (13.5-41.9)	17.8 (11.9-29.3)	0.70 (0.56-0.87)
≤80	154	16 (10)	74	5 (7)	14.9 (8.4-29.8)	11.0 (5.7-23.3)	0.58 (0.45-0.88)
Sex							
Women	150	21 (14)	72	6 (8)	24.6 (14.4-48.2)	18.5 (11.3-27.6)	0.64 (0.56-0.87)
Men	316	36 (11)	157	10 (6)	19.1 (10.0-34.1)	15.5 (8.4-26.5)	0.63 (0.45-0.88)
Overall	466	57 (12)	229	16 (7)	20.9 (11.3-37.6)	16.0 (9.3-27.5)	0.63 (0.53-0.76)



Data points represent Cox hazard ratios of overall survival in each subgroup of patients treated with tumor-treating fields (TTFields) plus temozolomide compared with temozolomide alone and were adjusted for the other subgroups. Error bars represent 95% CIs of the hazard ratios. The Karnofsky performance score is measured from 0 to 100 in 10-point increments, with higher scores indicating better the patient performance status.

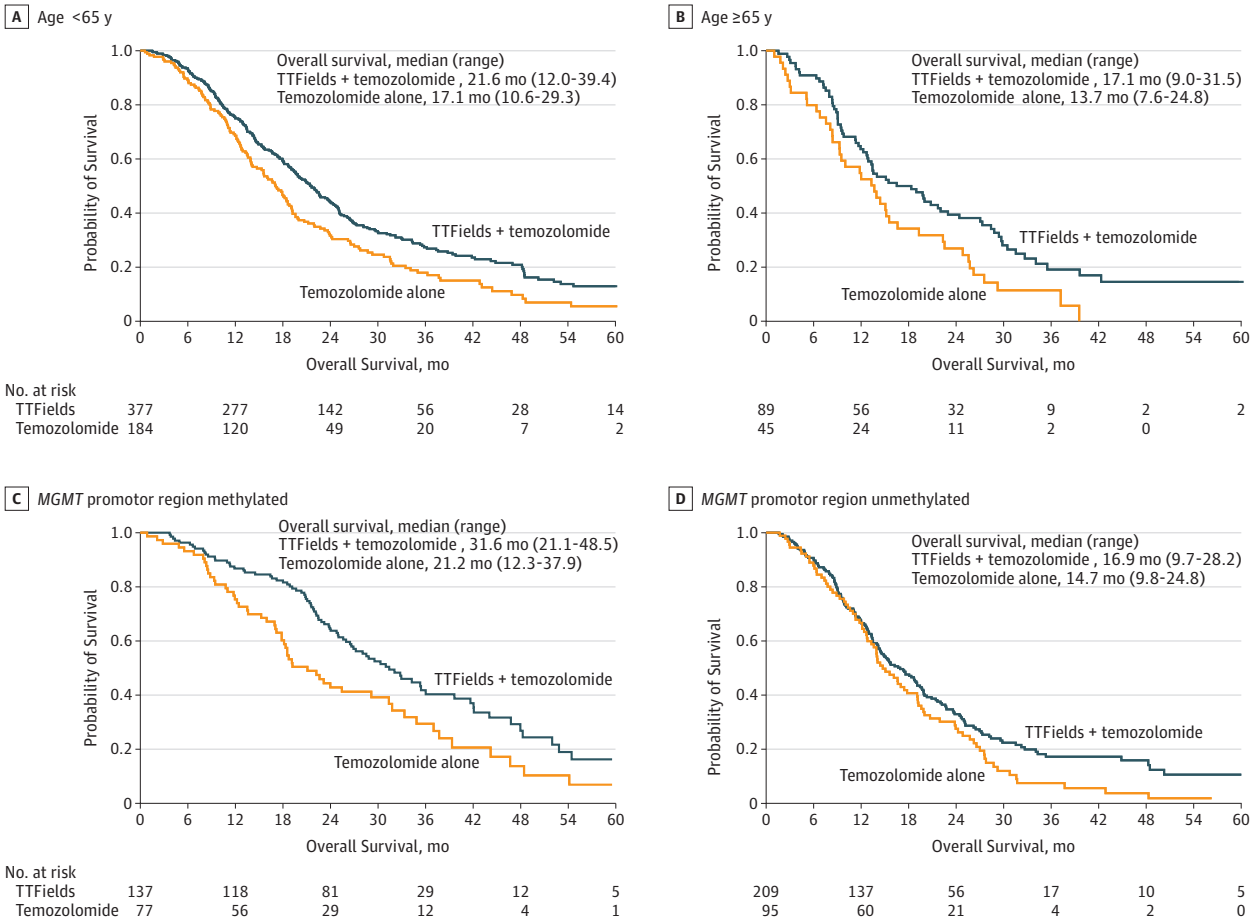
IQR, indicates interquartile range; *MGMT*, O^6-methylguanine-DNA methyltransferase promotor region methylation status.

associated with a significant difference in survival (P = .101 and P = .183, respectively).

Post Hoc Subgroup Analysis

In post hoc analyses, TTFields plus temozolomide was associated with an increase in progression-free survival and overall survival (**Figure 3**; Cox proportional hazards, P < .05 for the treatment effect within each subgroup) in all subgroups of patients regardless of age, sex, Karnofsky performance score, *MGMT* promoter methylation status, geographic region, or extent of resection. Patients 65 years or older had shorter survival than patients younger than 65 years. In both age groups, TTFields plus temozolomide was associated with significantly increased survival compared with temozolomide alone for older (HR, 0.51; 95% CI, 0.33-0.77) and younger patients (HR, 0.67; 95% CI, 0.55-0.82; **Figure 4**A and Figure 4B).

Figure 4. Overall Survival by Patient Age and by *MGMT* Promotor Region Methylation Status



A, In comparing tumor-treating fields (TTFields) plus temozolomide vs temozolomide alone among patients younger than 65 years the hazard ratio (HR) was 0.67 (95% CI, 0.55-0.82). B, In comparing the 2 treatments among patients 65 years or older, the HR was 0.51 (95% CI, 0.22-0.77). C, In comparing the treatments among patients with O^6-methylguanine-DNA methyltransferase *MGMT* promotor region methylation, the HR was 0.62 (95% CI, 0.43-0.88). D, In comparing the treatments among patients without the *MGMT* promotor region methylation, the HR was 0.66 (95% CI, 0.49-0.85). The median follow-up of patients was 44 months (range, 25-91 months) in all groups.

Patients with tumors that lacked *MGMT* promoter methylation had a significantly shorter survival than patients with tumors with *MGMT* promoter methylation, although use of TTFields with temozolomide was associated with longer survival (HR, 0.66; 95% CI, 0.49-0.85 both in patients with tumors that were *MGMT* methylated and tumors that were unmethylated, respectively; Figure 4C and Figure 4D). In the TTFields plus temozolomide group, 265 patients who were treated with TTFields for 18 hours a day or more (monthly average in the first 6 months of treatment) had longer survival than 185 patients treated less than 18 hours a day (22.6 months, 95% CI, 19.7-25.1 months vs 19.1 months, 95% CI, 16.5-21.9; HR, 0.65; 95% CI, 0.49-0.85; $P = .009$).

Adverse Events and Tolerability

The addition of TTFields to temozolomide therapy was not associated with any significant increase in rates of systemic adverse events compared with temozolomide therapy alone (48% vs 44%, respectively; $P = .58$; **Table 3**), and the overall incidence, distribution, and severity of adverse events were not statistically different in patients in the 2 treatment groups. The numerically higher incidence of some adverse events in the TTFields plus temozolomide group was a reflection of the longer duration of temozolomide treatment in this group due to delayed occurrence of progression. When adverse event incidence normalized to duration of treatment was analyzed, these differences disappeared. The only exception was a higher incidence of localized skin toxic effects (medical device site reaction beneath the transducer arrays) in patients treated with TTFields plus temozolomide; mild to moderate skin irritation was observed in 52% of patients, and severe (grade 3) skin involvement occurred in 2%. Anxiety, confusion, insomnia, and headaches which were reported more frequently (statistically nonsignificant) in patients treated with TTFields at the interim analysis were not seen in the final adverse event analysis of the trial. The incidence of seizures was identical in the 2 groups.

To estimate tolerability, prespecified exploratory analyses of the association of TTFields device use with patients'

Table 3. Adverse Events by Body System and Severity (≥5% Incidence in Any Group)

	Grade 3-4 Events, No. (%) of Patients	
	TTFields + Temozolomide (n = 456)	Temozolomide Alone (n = 229)
≥1 Adverse event	218 (48)	94 (44)
Blood and lymphatic system disorders[a]	59 (13)	23 (11)
Thrombocytopenia	39 (9)	11 (5)
Gastrointestinal disorders	23 (5)	8 (4)
Asthenia, fatigue, and gait disturbance	42 (9)	13 (6)
Infections	32 (7)	10 (5)
Injury, poisoning, and procedural complications (falls and medical device site reaction)	24 (5)	7 (3)
Metabolism and nutrition disorders (anorexia, dehydration, and hyperglycemia)	16 (4)	10 (5)
Musculoskeletal and connective tissue disorders	21 (5)	9 (4)
Nervous system disorders	109 (24)	43 (20)
Seizures	26 (6)	13 (6)
Respiratory, thoracic and mediastinal disorders (pulmonary embolism, dyspnea, and aspiration pneumonia)	24 (5)	11 (5)

Abbreviation:
TTFields, tumor-treating fields.

[a] The numerically slightly higher incidence of hematological toxicity, fatigue, and some other adverse effects are due to the longer treatment duration and observation time in the experimental group. The differences disappear when data are normalized to treatment duration.

activities of daily life and cognition were performed using the Karnofsky performance score and the Mini-Mental State Examination. Time to a sustained 6-point decline in the Mini-Mental State Examination score was significantly longer in the TTFields plus temozolomide group than the temozolomide-alone group (16.7 months, 95% CI, 14.7-19.0 months vs 14.2 months, 95% CI, 12.7-17.0 months, respectively; HR, 0.79; 95% CI, 0.66- 0.95; P = .01). Time to a sustained 10-point decrease in Karnofsky performance score was also significantly longer in the TTFields plus temozolomide group than in the temozolomide-alone group (5.5 months;, 95% CI, 5.0-6.3 months vs 3.9 months; 95% CI, 3.1-5.2 months, respectively; HR, 0.80; 95% CI, 0.67-0.95; P = .009).

Discussion

In the final analysis of this randomized phase 3 trial, the addition of the TTFields treatment to standard temozolomide maintenance therapy, compared with standard temozolomide maintenance therapy alone, resulted in increased progression-free survival and overall survival in patients with newly diagnosed glioblastoma. After a median follow-up of 40 months, the addition of TTFields to temozolomide, compared with temozolomide alone, resulted in longer median progression-free survival from the time of randomization, 6.7 months vs 4.0 months and longer median overall survival from randomization, 20.9 months vs 16.0 months, respectively. These findings are consistent with the preliminary results reported based on a planned interim analysis of the first 315 patients enrolled, after a median follow-up of 38 months, in which median progression-free survival in the intent-to-treat population was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group (210 patients analyzed) and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide-alone group (105 patients analyzed).

In the current study, exploratory end points were consistent with the primary and secondary end points in this trial. In a post hoc analysis the effect of TTFields was observed in all clinical and molecular subgroups, including patients older than age 65 years and patients with *MGMT* unmethylated tumors.

To assess whether the improved outcome may have been related to other factors than the TTFields therapy the data were scrutinized for possible imbalances, unexpected poor performance of the control group, or differences in supportive care administered to patients between the 2 groups. Both clinical factors and molecular tumor characteristics were well balanced and comparable between the 2 groups. *MGMT* promoter methylation, the strongest predictive factor for outcome in temozolomide-treated patients,[25] was more prevalent in the control group (45% vs 40% of samples with a valid result). Patients with early tumor progression occurring during the first 3 months after diagnosis were not included in this trial, and so the randomized patient population had a better prognosis, for both groups, compared with other trials that had randomized patients before radiation therapy. The reported survival times were measured from randomization, not from diagnosis, so for an estimation of the overall outcome 3.8 months should be added in both groups. The RTOG 0525/Intergroup study, which evaluated dose-dense temozolomide, also randomized patients only after completion of radiochemotherapy.[8] Outcome of the control group in the current study and of the RTOG study were very similar, and in both studies, the median survival from randomization was 16 months.

In this trial, the rates of systemic adverse effects were not significantly different in the 2 treatment groups. The occurrence of mild to moderate skin irritation related to reaction beneath the transducer arrays of the device occurred in more than half of patients in the TTFields plus temozolomide group.

These findings are in contrast to the more than 23 randomized trials conducted over the last decade that have evaluated novel agents or intensified treatment strategies

(eg, dose-dense temozolomide, cilengitide, nimotuzumab, bevacizumab, and rindopepimut[3,5,8,26]) for treatment of patients with newly diagnosed glioblastoma and have failed to demonstrate improved survival. Innovative treatments for glioblastoma are needed.

Limitations

This study has several limitations. First, the current trial was open-label because it was considered practically unfeasible (heat and easy measure of current associated with TTFields) and ethically unacceptable to expose patients to a sham device. Although a placebo effect may affect subjective end points like quality of life or even progression-free survival by influencing the frequency of imaging and its interpretation, in the current trial a consistent benefit was observed in progression-free survival as assessed by blinded central radiology review, as well as in the gold standard of objective outcome, overall survival. Second, delivery of TTFields therapy requires the patient to continuously carry a device on a shaved scalp and may create burdens for patients. Nevertheless, the majority of patients were able to handle the device independently or with some help from a caregiver. The fact that 75% of patients achieved treatment adherence of 75% or more (ie, using the device for ≥18 hours per day) indicated good tolerability. The effects of the TTFields treatment and the need for continuous use of the device on quality of life will be reported separately.

Conclusions

In the final analysis of this randomized clinical trial of patients with glioblastoma who had received standard radiochemotherapy, the addition of TTFields to maintenance temozolomide chemotherapy vs maintenance temozolomide alone, resulted in statistically significant improvement in progression-free survival and overall survival. These results are consistent with the previous interim analysis.

ARTICLE INFORMATION

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