

Preliminary Communication

Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma

A Randomized Clinical Trial

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IMPORTANCE Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Most patients die within 1 to 2 years of diagnosis. Tumor-treating fields (TTFields) are a locoregionally delivered antimitotic treatment that interferes with cell division and organelle assembly.

OBJECTIVE To evaluate the efficacy and safety of TTFields used in combination with temozolomide maintenance treatment after chemoradiation therapy for patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS After completion of chemoradiotherapy, patients with glioblastoma were randomized (2:1) to receive maintenance treatment with either TTFields plus temozolomide (n = 466) or temozolomide alone (n = 229) (median time from diagnosis to randomization, 3.8 months in both groups). The study enrolled 695 of the planned 700 patients between July 2009 and November 2014 at 83 centers in the United States, Canada, Europe, Israel, and South Korea. The trial was terminated based on the results of this planned interim analysis.

INTERVENTIONS Treatment with TTFields was delivered continuously (>18 hours/day) via 4 transducer arrays placed on the shaved scalp and connected to a portable medical device. Temozolomide (150-200 mg/m²/d) was given for 5 days of each 28-day cycle.

MAIN OUTCOMES AND MEASURES The primary end point was progression-free survival in the intent-to-treat population (significance threshold of .01) with overall survival in the per-protocol population (n = 280) as a powered secondary end point (significance threshold of .006). This prespecified interim analysis was to be conducted on the first 315 patients after at least 18 months of follow-up.

RESULTS The interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 randomized to temozolomide alone, and was conducted at a median follow-up of 38 months (range, 18-60 months). 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 and 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (hazard ratio [HR], 0.62 [98.7% CI, 0.43-0.89]; P = .001). Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFields plus temozolomide group (n = 196) and 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group (n = 84) (HR, 0.64 [99.4% CI, 0.42-0.98]; P = .004).

CONCLUSIONS AND RELEVANCE In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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Glioblastoma is the most devastating primary malignancy of the central nervous system in adults. Standard treatment consists of maximal safe surgical resection or a diagnostic biopsy, followed by radiotherapy (60 Gy) with concomitant daily temozolomide chemotherapy, and then maintenance treatment with temozolomide for 6 to 12 months.¹ However, most patients will die within 1 to 2 years. Median progression-free survival from diagnosis of 6.2 to 7.5 months and median overall survival from diagnosis of 14.6 to 16.7 months have been reported in clinical trials.¹⁻⁴ The reported 2- and 5-year survival rates⁵ are 27% and 10%, respectively. During the last decade, all attempts to improve the outcome for patients with glioblastoma have failed when evaluated in large randomized trials.^{2-4,6,7}

Tumor-treating fields (TTFields) are an antimitotic treatment that selectively disrupts the division of cells by delivering low-intensity, intermediate-frequency (200 kHz) alternating electric fields via transducer arrays applied to the shaved scalp.⁸⁻¹⁰ In preclinical models, TTFields have been shown to cause mitotic arrest and apoptosis by disrupting mitotic spindle formation during metaphase and causing dielectrophoretic movement of polar molecules during cytokinesis.^{8,10-12} In a randomized phase 3 trial in which TTFields were compared with chemotherapy in 237 patients with recurrent glioblastoma, the use of TTFields did not prolong progression-free survival or overall survival, but the therapy was associated with better quality of life without the typical chemotherapy-associated toxic effects.¹³

Based on preclinical data demonstrating a synergistic antitumor effect with chemotherapy and TTFields, and pilot clinical feasibility data in combination with temozolomide,⁹ we initiated this phase 3 trial. The objective was to evaluate the efficacy and safety of TTFields used in combination with maintenance temozolomide in patients with glioblastoma after initial treatment with temozolomide and radiotherapy.

Methods

Study Population

Patients eligible for this study (1) had histologically confirmed supratentorial glioblastoma (World Health Organization grade IV astrocytoma¹⁴), (2) were progression-free after having undergone maximal safe debulking surgery when feasible or biopsy, and (3) had completed standard concomitant chemoradiotherapy with temozolomide. Other eligibility criteria were (1) age of 18 years or older, (2) Karnofsky Performance Status (KPS) score of 70% or higher (the KPS score describes the general condition of a patient; a KPS score $\geq 70\%$ ensures some independence in activities of daily living), and (3) adequate bone marrow, liver, and renal function.

Prior use of implanted carmustine wafers was allowed. Patients with infratentorial tumor location and severe comorbidities were excluded. All patients provided written informed consent before entering the study; the study was approved by the institutional review boards or ethics committees of all 83 participating centers. The trial protocol appears in [Supplement 1](#).

Study Design and Treatment

This multicenter, open-label, randomized phase 3 trial was designed to test the efficacy and safety of TTFields in combination with temozolomide for treatment of glioblastoma after initial treatment with chemoradiation. After the completion of treatment with temozolomide and radiotherapy, patients were randomized at a ratio of 2 to 1 (**Figure 1**) to receive standard maintenance temozolomide chemotherapy (150-200 mg/m²/d for 5 days every 28 days for 6-12 cycles according to the protocol¹ from the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group) with or without the addition of TTFields. Treatment with TTFields was to be initiated within 4 to 7 weeks from the last dose of concomitant temozolomide and radiotherapy. Randomization was performed through a central web-based randomization system and was stratified by extent of resection (biopsy, partial resection, gross total resection) and by O⁶-methylguanine-DNA methyltransferase (*MGMT*) methylation status (methylated, unmethylated, or unknown).

For patients with available paraffin-embedded tumor tissue, evaluation of *MGMT* gene promoter methylation status was performed as described previously^{7,15,16} by a central laboratory blinded to treatment group (MDxHealth). If *MGMT* methylation status could not be determined centrally prior to randomization, local *MGMT* methylation status was used for stratification.

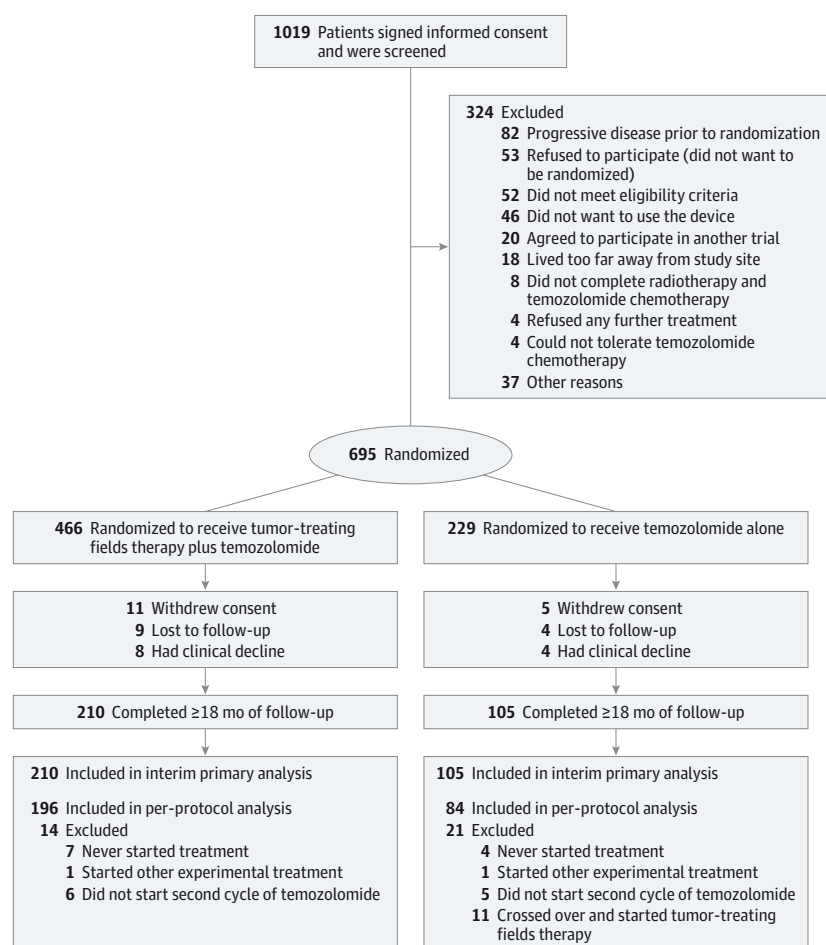
Patients in the TTFields plus temozolomide group received continuous TTFields combined with standard maintenance temozolomide. Patients receiving TTFields had 4 transducer arrays placed on the shaved scalp and connected to a portable device set to generate 200-kHz electric fields within the brain (Optune, Novocure Ltd). Transducer array layouts were determined using a mapping software system for TTFields to optimize field intensity within the treated tumor (NovoTAL, Novocure Ltd). After being trained to operate the device, the patient continued treatment at home. The transducer arrays were supplied in sterile packaging and replaced by the patient, a caregiver, or a device technician twice per week. Although uninterrupted treatment was recommended, short treatment breaks for personal needs were allowed.

If a patient experienced tumor progression, second-line chemotherapy was offered per local practice. However, in the TTFields plus temozolomide group, TTFields could be continued until the second radiological progression, or clinical deterioration, for a maximum of 24 months.

Patient Surveillance and Follow-up

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 with collection of laboratory parameters was performed within 1 week of treatment initiation. The evaluation also included a quality-of-life questionnaire (QLQ-C30) that has a brain-specific module (BN-20), which was developed by the European Organisation

Figure 1. Recruitment and Inclusion of Patients in the Study



for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups.^{17,18} A Mini-Mental State Examination (a short bedside test used to evaluate cognition and memory) also was administered (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. Magnetic resonance imaging was to be performed every second month after the baseline MRI until second radiological progression in all patients. In the event of clinical progression, MRI was to be performed within 1 week after the study investigator became aware of it. All MRIs were reviewed centrally by 2 blinded independent radiologists (BioClinica Inc) and were evaluated for tumor response and progression using the criteria developed by Macdonald et al.¹⁹ In cases in which the central reviewers were not in agreement, a third blinded radiologist adjudicated between them. The third radiologist was involved in 17% of the cases in the TTFields plus temozolomide group and in 18% of the cases in the temozolomide alone group.

The results of the central review were not communicated to the study investigator, and all treatment decisions were based on local imaging interpretation. Eight patients in the

TTFields plus temozolomide group (4%) compared with 6 patients in the temozolomide alone group (3%) were considered stable by blinded central review; however, treatment had been changed by the study investigator due to local interpretation of tumor progression. Patients were removed from the progression-free survival analysis at the date of treatment change when this occurred before evidence of tumor progression or when patients reached the cutoff date without tumor progression.

Adverse events were recorded prospectively according to the National Cancer Institute's Common Terminology Criteria (version 3.0) until 2 months after treatment discontinuation. Adverse events are presented descriptively as number and percentage of patients with each adverse event term for all patients available at the time of the interim analysis. Treatment adherence with TTFields was recorded electronically by the device as average daily use in hours per day and information was reviewed and transferred at the monthly follow-up visit.

Statistical Considerations

The primary end point was progression-free survival in the intent-to-treat (ITT) population assessed by an independent review panel (80% power; hazard ratio [HR], 0.78; 2-sided α level

of .05). The study was also designed to have 80% power (HR, 0.76; 2-sided a level of .05) to examine overall survival as a secondary end point. To avoid an increase in the risk of a false-positive result, overall survival was to be tested statistically only if the primary end point was met.

This prespecified interim analysis was to be performed after the first 315 randomized patients reached a minimum 18-month follow-up. The final type I error rate of 0.05 was split between the interim and final analyses based on a standard a spending function.²⁰⁻²² The protocol prespecified that overall survival would be analyzed in an as-treated population, excluding all patients in both treatment groups who (1) never started maintenance temozolomide, (2) had major protocol violations, (3) crossed over to the other treatment group, or (4) received TTFields outside the protocol setting.

The primary end point would be achieved in the interim analysis if progression-free survival in the ITT population was significantly longer in the intervention group compared with the control group using a stratified log-rank test with an α level of .01. The secondary end point would be achieved in the interim analysis if overall survival in the as-treated population (per-protocol population) was significantly longer in the TTFields plus temozolomide group using a stratified log-rank test with an α level of .006. The confidence intervals that go with the HRs are presented as 1 minus the prespecified α level for each analysis. For example, the α level in the per-protocol interim analysis for overall survival was .006. Therefore, the corresponding confidence interval used for presenting the HRs was 1.000 – 0.006 (99.4% confidence interval). An upper confidence limit of less than 1 indicates the prespecified statistical threshold was met. An independent data and safety monitoring committee was chartered to stop the trial if the interim analysis of progression-free survival (ITT population) and overall survival (per-protocol population) surpassed these predetermined thresholds, as well as for futility or safety concerns.

In addition to these prespecified analyses, an analysis of overall survival in the ITT population was performed. Furthermore, a robustness analysis including all 695 patients enrolled in the trial served to validate the findings of the interim analysis (database lock: December 29, 2014; eAppendix 1 in Supplement 2).

Multiple imputation analyses also were performed for the trial's primary end point of progression-free survival in the ITT population to test the sensitivity of the results to possible bias using informative and interval censoring. These analyses included (1) treating all patients with informative censoring as treatment failures in the TTFields plus temozolomide group, (2) censoring all patients with informative censoring in the temozolomide alone group (worst case scenario), and (3) treating all events in the TTFields plus temozolomide group and in the temozolomide alone group as occurring differentially at different periods during the inter-MRI interval before the date of tumor progression.

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc) and R version 3.1.1.²³ The final analysis will be performed when all 695 patients enrolled in the study have at least 18 months of follow-up and will include prespeci-

fied subgroup analyses and additional secondary end points, including quality of life.

Results

Study Participants

Between July 2009 and November 2014, there were 695 patients with newly diagnosed glioblastoma randomized to receive either TTFields plus temozolomide ($n = 466$) or temozolomide alone ($n = 229$). Data for the interim analysis included 210 patients randomized to TTFields plus temozolomide and 105 to temozolomide alone (Figure 1; database lock: September 5, 2014). The independent data and safety monitoring committee met in October 2014 to review the interim analysis; the trial met the predefined boundaries for success (improvement of both progression-free and overall survival) and the committee recommended study termination, thus allowing patients in the control group to crossover and receive TTFields.

After approval of study termination by the US Food and Drug Administration, the trial was closed to recruitment on November 29, 2014, after 695 patients of the planned 700 patients had already been randomized. All patients in the control group with ongoing maintenance therapy were offered to receive TTFields. At the time of this report, 35 patients in the control group crossed over to receive TTFields. Follow-up for all patients continues according to the protocol.

Patient baseline characteristics were well balanced between the 2 groups (Table 1). The median age was 57 years and 66% were male. The median KPS score was 90%. Sixty-four percent of patients had a gross total resection and 11% had only a diagnostic biopsy. Tumor tissue for central *MGMT* testing was available for 72% of the patients; the *MGMT* methylation frequency was 39% (75/191 valid tests; 39% for the TTFields plus temozolomide group and 41% for the temozolomide alone group). Tumor location in the brain was also comparable.

Carmustine wafers (Gliadel) were used at initial surgery in 2.4% of patients in the TTFields plus temozolomide group vs 2.9% of patients in the temozolomide alone group. Ninety-five percent of the patients were white and 61% were treated in the United States. The rest of the patients were treated at centers in Canada, Europe, Israel, and South Korea. The median time from diagnosis to randomization was 3.8 months (range, 2.0-5.7 months) for patients in the TTFields plus temozolomide group and 3.8 months (range, 1.4-5.7 months) for those in the temozolomide alone group. The median time from the end of treatment with temozolomide and radiotherapy to randomization was 36 days in the TTFields plus temozolomide group and 38 days in the temozolomide alone group; 53% of patients were randomized after having started the first cycle of maintenance temozolomide. The median time from randomization to initiation of TTFields was 5 days.

Treatment Delivery

All patients had completed radiotherapy and concomitant temozolomide as per local practice. The median number of temozolomide cycles until evidence of first tumor progression was 6 cycles (range, 1-26 cycles) for patients in the TTFields

Table 1. Patient Baseline Characteristics and Treatment Details

	All Patients (N = 315)	TTFields Plus Temozolomide (n = 210)	Temozolomide Alone (n = 105)
Age, y			
Mean (SD)	55.8 (11.1)	55.3 (11.3)	56.8 (10.5)
Median (range)	57 (20-83)	57 (20-83)	58 (21-80)
Karnofsky Performance Status score, median (range), % ^a	90 (60-100)	90 (60-100)	90 (70-100)
Sex, No. (%)			
Male	207 (66)	140 (67)	67 (64)
Female	108 (34)	70 (33)	38 (36)
Use at baseline, No. (%)			
Antiepileptic medication	126 (40)	88 (42)	38 (36)
Corticosteroid therapy	77 (24)	51 (24)	26 (25)
Mini-Mental State Examination score, No. (%) ^b			
≤26	45 (15)	31 (15)	14 (13)
27-30	247 (78)	174 (83)	73 (70)
Unknown	23 (7)	5 (2)	18 (17)
Extent of resection, No. (%)			
Biopsy	34 (11)	23 (11)	11 (10)
Partial resection	79 (25)	52 (25)	27 (26)
Gross total resection	202 (64)	135 (64)	67 (64)
Tissue available and tested, No. (%)			
MGMT methylation	75 (33)	49 (32)	26 (35)
No methylation	116 (51)	79 (52)	38 (51)
Invalid test result	36 (16)	24 (16)	11 (15)
Region, No. (%)			
United States	191 (61)	127 (60)	64 (61)
Rest of world	124 (39)	83 (40)	41 (39)
Completed radiation therapy, No. (%)			
<57 Gy	18 (6)	13 (6)	5 (5)
60 Gy (standard; ±5%)	291 (92)	191 (91)	100 (95)
>63 Gy	6 (2)	6 (3)	0 (0)
Concomitant temozolomide use, No. (%)			
Yes	308 (98)	207 (99)	101 (96)
Unknown	7 (2)	3 (1)	4 (4)
Time from event to randomization, median (range), d			
Last day of radiotherapy	37 (13-68)	36 (13-53)	38 (13-68)
Initial diagnosis	114 (43-171)	115 (59-171)	113 (43-170)
No. of maintenance temozolomide cycles until first tumor progression, median (range)	6 (1-26)	6 (1-26)	4 (1-24)
Duration of treatment with TTFields, median (range), mo	9 (1-58)	9 (1-58)	
Adherence to TTFields therapy ≥75% during first 3 mo of treatment		157 (75)	

Abbreviations: MGMT, O⁶-methylguanine-DNA methyltransferase; TTFields, tumor-treating fields.

^a A higher score indicates better functional status.

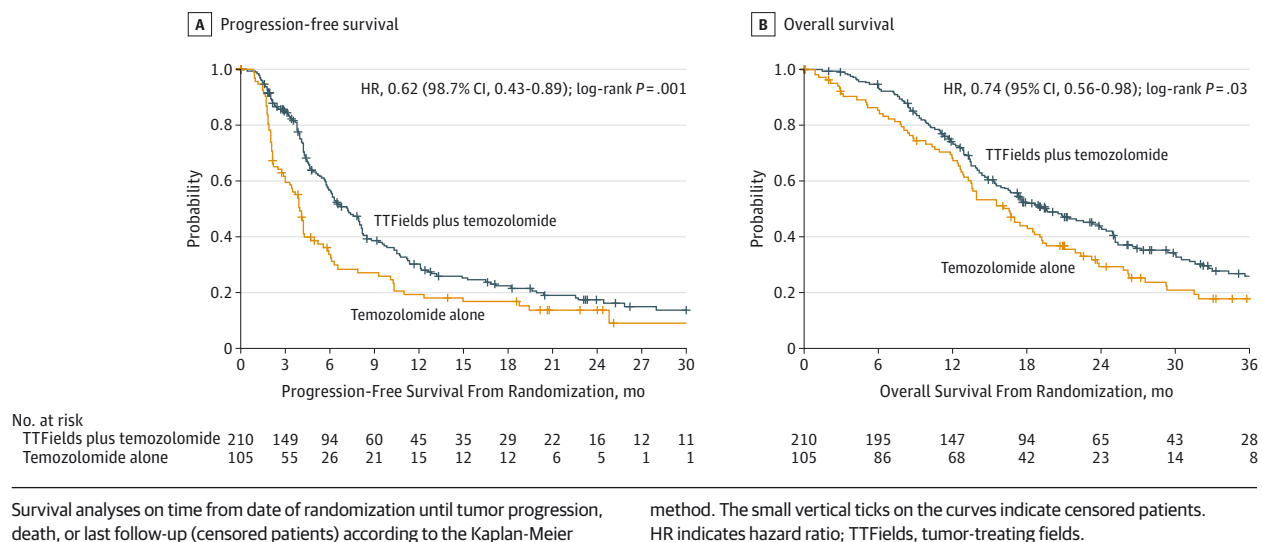
^b A higher score indicates better cognitive capability.

plus temozolomide group and 4.0 cycles (range, 1-24 cycles) for patients in the temozolomide alone group; the median duration of treatment with TTFields was 9 months (range, 1-58 months). Two-thirds (n = 141) of patients in the TTFields plus temozolomide group continued treatment with TTFields after first tumor progression. Three-quarters (n = 157) of patients receiving treatment with TTFields were adherent to therapy (ie, wearing the device >18 hours per day on average during the first 3 treatment months).

Efficacy End Points

As prespecified, the primary end point for the efficacy results was based on progression-free survival in the ITT population of the interim analysis data set. After a median follow-up of 38 months (range, 18-60 months), the median progression-free survival from randomization was 7.1 months (95% CI, 5.9-8.2 months) in the TTFields plus temozolomide group compared with 4.0 months (95% CI, 3.3-5.2 months) in the temozolomide alone group (HR, 0.62 [98.7% CI, 0.43-0.89];

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



stratified log-rank $P = .001$; **Figure 2A**). Thus, adding TTFIELDS to temozolomide treatment increased median progression-free survival in the ITT population by 3.1 months.

As per the statistical analysis plan, overall survival was to be tested in a prespecified per-protocol population only after the primary end point was found to surpass the threshold for significance in the interim analysis. Median overall survival in the per-protocol population was 20.5 months (95% CI, 16.7-25.0 months) in the TTFIELDS plus temozolomide group ($n = 196$) compared with 15.6 months (95% CI, 13.3-19.1 months) in the temozolomide alone group ($n = 84$) (HR, 0.64 [99.4% CI, 0.42-0.98]; stratified log-rank $P = .004$). The details on the per-protocol population and analyses are summarized in eAppendix 2 in [Supplement 2](#).

In additional analyses in the ITT population, the median overall survival was 19.6 months (95% CI, 16.6-24.4 months) in the TTFIELDS plus temozolomide group compared with 16.6 months (95% CI, 13.6-19.2 months) in the temozolomide alone group (HR, 0.74 [95% CI, 0.56-0.98]; stratified log-rank $P = .03$; **Figure 2B**). The percentage of patients alive at 2 years following enrollment was 43% in the TTFIELDS plus temozolomide group and 29% in the temozolomide alone group ($P = .006$).

To assess the robustness of the interim analysis findings, additional analyses on all 695 patients randomized were performed. Patient characteristics of all patients randomized did not differ significantly from the interim data set, and the results for the main end points were similar in these analyses compared with the interim analysis (eAppendix 1 in [Supplement 2](#)).

Second-line treatments, such as nitrosoureas, temozolomide rechallenge, and bevacizumab, were received by 67% of the patients in the TTFIELDS plus temozolomide group compared with 57% in the temozolomide alone group; about 40% of second-line therapies included bevacizumab and about 40% included nitrosoureas. The type of chemotherapy used at recurrence was balanced between treatment groups.

Secondary imputation analyses of progression-free survival with relation to the effects of interval and informational censoring did not change the conclusions of the primary progression-free survival analysis (eAppendix 3 in [Supplement 2](#)).

Safety and Tolerability

The addition of TTFIELDS to temozolomide therapy in patients with newly diagnosed glioblastoma was not associated with any significant increase in systemic toxic effects compared with temozolomide therapy alone (**Table 2**). The overall incidence, distribution, and severity of adverse events were similar in patients treated with TTFIELDS plus temozolomide and in those treated with temozolomide alone. The only notable exception was a higher incidence rate of localized skin toxicity (medical device site reaction beneath the transducer arrays) in patients treated with TTFIELDS plus temozolomide. Mild to moderate skin irritation was observed in 43% of patients treated with TTFIELDS plus temozolomide and severe skin reaction (grade 3) in 2%. Mild anxiety, confusion, insomnia, and headaches were reported more frequently in the patients treated with TTFIELDS plus temozolomide and occurred mainly at the time of therapy initiation. The incidence of seizures was almost identical in the 2 groups (15 [7%] in the TTFIELDS plus temozolomide group vs 8 [8%] in temozolomide alone group). A total of 12 patients died of causes considered unrelated to treatment while receiving adjuvant therapy (8 [3.9%] in the temozolomide plus TTFIELDS group and 4 [4.0%] in the temozolomide alone group; **Table 2**).

Discussion

Glioblastoma is a highly aggressive brain tumor affecting men and women, frequently at the peak of life. Prognosis remains poor with no major treatment advance in more than a decade. In the interim analysis of this randomized clinical trial,

the addition of TTFields to standard maintenance temozolomide significantly improved progression-free and overall survival. The prespecified analyses revealed that patients randomized to receive TTFields plus temozolomide compared with patients randomized to receive temozolomide alone had a median progression-free survival of 7.1 months vs 4.0 months (ITT analyses). Patients who received TTFields plus temozolomide had a median overall survival of 20.5 months compared with 15.6 months in those who received temozolomide alone (as per the prespecified per-protocol analysis; the ITT analysis did not differ substantially).

Based on the results of this planned interim analysis, the trial's independent data and safety monitoring committee recommended termination of the trial. Because almost all patients had been enrolled (695/700) in the study by the time the recommendation was implemented, the full trial population will be followed up for both progression-free and overall survival. Subsequent analyses of all secondary end points and subgroups will be performed when the follow-up data are available.

The trial population and the results in the control group in this study were comparable with other glioblastoma clinical trials. Nevertheless, patients in this trial were randomized only after the end of radiochemotherapy, and for most, the first cycle of maintenance temozolomide had been started at the time of randomization; thus, patients with early tumor progression during radiochemotherapy were excluded. Most glioblastoma trials have reported survival from the date of initial diagnosis or study enrollment before starting radiochemotherapy, thus 3 to 4 months before randomization of the current study.

When the interval from diagnosis to randomization is added to the outcome results in this study, the progression-free survival of 7.8 months in the control group is comparable with most other reported studies, and supports the generalizability of these results. The Radiation Therapy Oncology Group (RTOG) 0525 protocol randomized patients only after the end of treatment with temozolomide and radiotherapy, similar to our study.³ The control groups with standard dose temozolomide only in these 2 trials were comparable: progression-free survival from randomization of 4.0 months in the present study and 5.5 months in the RTOG 0525 trial and overall survival of 16.6 months in both trials. Thus, the benefit observed with TTFields cannot be simply attributed to patient selection. In the present trial, the gain of 3 months in both median progression-free survival (from 4.0 months to 7.2 months; HR, 0.62) and median overall survival (from 16.6 months to 19.6 months; HR, 0.74), translating into a survival gain at 2 years of 14% (from 29% to 43%) in the ITT population is in the range of benefit that is considered clinically meaningful for therapeutic agents in oncology.

The prespecified analysis for overall survival in the interim analysis was to be based on the per-protocol population ($n = 280$); ie, removal in both study groups of the patients who did not start their second course of maintenance temozolomide or had major protocol violations. This analysis met the prespecified threshold for efficacy in the interim analysis for the per-protocol population. In a more conserva-

Table 2. Grade 3 to 4 Treatment-Emergent Adverse Events

	No. (%) of Patients With Adverse Events ^a	
	TTFields Plus Temozolomide ($n = 203$) ^b	Temozolomide Alone ($n = 101$) ^c
Hematological disorders ^d	25 (12)	9 (9)
Anemia	1 (<1)	2 (2)
Leukopenia or lymphopenia	11 (5)	5 (5)
Neutropenia	6 (3)	1 (1)
Thrombocytopenia	19 (9)	3 (3)
Cardiac disorders	2 (1)	3 (3)
Eye disorders	2 (1)	1 (1)
Gastrointestinal disorders ^d	11 (5)	2 (2)
Abdominal pain	2 (1)	0
Constipation	2 (1)	0
Diarrhea	1 (<1)	2 (2)
Vomiting	3 (1)	1 (1)
General disorders	17 (8)	5 (5)
Fatigue	8 (4)	4 (4)
Infections	10 (5)	5 (5)
Injury and procedural complications ^d	14 (7)	5 (5)
Fall	6 (3)	2 (2)
Medical device site reaction	4 (2)	0
Metabolism and nutrition disorders	7 (3)	3 (3)
Musculoskeletal disorders	8 (4)	3 (3)
Nervous system disorders ^d	45 (22)	25 (25)
Seizure	15 (7)	8 (8)
Headache	4 (2)	2 (2)
Psychiatric disorders ^d	9 (4)	3 (3)
Anxiety	2 (1)	0
Bradyphrenia	0	1 (1)
Confusional state	2 (1)	1 (1)
Mental status changes	4 (2)	1 (1)
Psychotic disorder	2 (1)	0
Respiratory disorders	4 (2)	1 (1)
Skin disorders	0	1 (1)
Vascular disorders ^d	8 (4)	8 (8)
Deep vein thrombosis	1 (<1)	3 (3)
Pulmonary embolism	4 (2)	6 (6)

Abbreviation: TTFields, tumor-treating fields.

^a Safety is reported on patients who have received any treatment. Randomized patients who never received any maintenance therapy were excluded from this safety analysis.

^b Eight patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and infection; and 4 patients with central nervous system disorders likely due to tumor progression).

^c Four patients died while receiving adjuvant therapy due to causes unrelated to therapy (1 patient for each of the following reasons: cardiac events, pulmonary emboli, respiratory, and unknown).

^d Patients may have had more than 1 adverse event so subcategories do not total and not all events are subcategorized.

tive analysis using the ITT population, an overall survival benefit was also manifest. Furthermore, an analysis of robustness performed on all randomized patients enrolled at the time

of study termination (eAppendix 1 in Supplement 2) supports the conclusions of the interim analysis.

This clinical trial has some important limitations. Patient enrollment occurred only after the end of radiochemotherapy, leading to some variation in the delivery of standard treatment of temozolomide and radiotherapy. Patients who had progressed early during radiochemotherapy were not eligible for randomization, thus excluding patients with very poor prognoses. There is likely reporting bias for second-line therapies after tumor progression because in the TTFields plus temozolomide group, TTFields were to be continued, and thus, more detailed treatment information has been tracked for this group.

This analysis reports a planned interim analysis on data from the first 315 patients with at least 18 months of follow-up; however, for detailed and meaningful subgroup analyses, the mature data of the full data set will be needed. Treatment failure patterns, effects of second-line therapies, and additional molecular analyses on baseline tumor biopsies will allow for better understanding of the clinical effects of this novel treatment modality. With the last patient randomized on November 29, 2014, however, these data are not expected before the end of 2016.

This was an open-labeled study. A sham or placebo treatment for the control group was considered neither practical (patients would be able to sense heat when they were receiving TTFields) nor appropriate (due to the burden for patients and caregivers and the need to shave the scalp and have transducer arrays placed). In this respect, the trial resembles studies evaluating radiation therapy. This raises the question of a placebo effect leading to the improved outcome. Although some effect of placebo may be expected on subjective end points, such as cognitive function and quality of life, objective end points, such as overall and progression-free survival (assessed by a blinded review panel), are independent of pla-

cebo effects in cancer therapy.²⁴ The panel did not have information on treatment received and no stigmata of TTFields array pads were evident on MRI.

Recent randomized studies of patients with glioblastoma, which did not use placebo controls, failed to show any increase in progression-free or overall survival^{3,7} despite intensive treatment regimens requiring twice weekly hospital visits.⁷ The magnitude of effect size seen in the present trial (HR of 0.62 for progression-free survival and 0.74 for overall survival) is beyond what could be attributed to a placebo effect. In addition, the support provided to patients in the TTFields plus temozolomide group by device support specialists during the trial was largely technical in nature and did not include medical supportive care. Medical follow-up with monthly visits was the same for both treatment groups.

Because TTFields were applied only to the head, an increase in systemic adverse events was neither seen nor expected. No increase in seizure rate or neurological adverse events was observed. Almost half of the patients treated with TTFields did experience some grade 1 to 2 (mild to moderate) localized skin reaction related to the application of the transducer arrays used to deliver the TTFields. This adverse effect could be managed using published skin care guidelines for patients receiving TTFields.²⁵ Only 2% of patients receiving TTFields had grade 3 to 4 (severe) skin reactions beneath the transducer arrays.

Conclusions

In this interim analysis of 315 patients with glioblastoma who had completed standard chemoradiation therapy, adding TTFields to maintenance temozolomide chemotherapy significantly prolonged progression-free and overall survival.

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REFERENCES

- Stupp R, Mason WP, van den Bent MJ, et al; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
- Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):699-708.
- Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31(32):4085-4091.
- Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):709-722.
- Stupp R, Hegi ME, Mason WP, et al; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459-466.
- Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. *Eur J Cancer*. 2015;51(4):522-532.
- Stupp R, Hegi ME, Gorlia T, et al; European Organisation for Research and Treatment of Cancer (EORTC); Canadian Brain Tumor Consortium; CENTRIC study team. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1100-1108.
- Kirson ED, Dbalý V, Tovarys F, et al. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. *Proc Natl Acad Sci U S A*. 2007;104(24):10152-10157.
- Kirson ED, Schneiderman RS, Dbalý V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys*. 2009;9:1.
- Fonkem E, Wong ET. NovoTTF-100A: a new treatment modality for recurrent glioblastoma. *Expert Rev Neurother*. 2012;12(8):895-899.
- Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res*. 2004;64(9):3288-3295.
- Gutin PH, Wong ET. Noninvasive application of alternating electric fields in glioblastoma: a fourth cancer treatment modality. *Am Soc Clin Oncol Educ Book*. 2012;126-131.
- Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer*. 2012;48(14):2192-2202.
- Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97-109.
- Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med*. 2005;352(10):997-1003.
- Vlassenbroeck I, Califice S, Diserens AC, et al. Validation of real-time methylation-specific PCR to determine O6-methylguanine-DNA methyltransferase gene promoter methylation in glioma. *J Mol Diagn*. 2008;10(4):332-337.
- Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85(5):365-376.
- Taphoorn MJ, Claassens L, Aaronson NK, et al; EORTC Quality of Life Group, and Brain Cancer, NCIC and Radiotherapy Groups. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer*. 2010;46(6):1033-1040.
- Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol*. 1990;8(7):1277-1280.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35(3):549-556.
- DeMets DL, Lan G. The alpha spending function approach to interim data analyses. *Cancer Treat Res*. 1995;75:1-27.
- DeMets DL, Lan KK. Interim analysis: the alpha spending function approach. *Stat Med*. 1994;13(13-14):1341-1352.
- R Development Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2008.
- Chvetzoff G, Tannock IF. Placebo effects in oncology. *J Natl Cancer Inst*. 2003;95(1):19-29.
- Lacouture ME, Davis ME, Elzinga G, et al. Characterization and management of dermatologic adverse events with the NovoTTF-100A System, a novel anti-mitotic electric field device for the treatment of recurrent glioblastoma. *Semin Oncol*. 2014;41(suppl 4):S1-S14.