

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejconline.com

NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: A randomised phase III trial of a novel treatment modality

Roger Stupp^{a,*}, Eric T. Wong^b, Andrew A. Kanner^c, David Steinberg^d, Herbert Engelhard^e, Volkmar Heidecke^f, Eilon D. Kirson^g, Sophie Taillibert^h, Frank Liebermannⁱ, Vladimir Dbalý^j, Zvi Ram^c, J. Lee Villano^e, Nikolai Rainov^f, Uri Weinberg^g, David Schiff^k, Lara Kunschner^l, Jeffrey Raizer^m, Jerome Honnoratⁿ, Andrew Sloan^o, Mark Malkin^p, Joseph C. Landolfi^q, Franz Payer^r, Maximilian Mehdorn^s, Robert J. Weil^t, Susan C. Pannullo^u, Manfred Westphal^v, Martin Smrcka^w, Lawrence Chin^x, Herwig Kostron^y, Silvia Hofer^z, Jeffrey Bruce^{aa}, Rees Cosgrove^{ab}, Nina Paleologous^{ac}, Yoram Palti^g, Philip H. Gutin^{ad}

^a Centre Hospitalier Universitaire Vaudois, University of Lausanne, Lausanne, Switzerland

^b Harvard Medical School, Beth Israel Deaconess Medical Center, Boston, MA, United States

^c Tel Aviv Medical Center, Tel Aviv, Israel

^d Department of Biostatistics, Tel Aviv University, Tel Aviv, Israel

^e University of Illinois at Chicago, Chicago, IL, United States

^f Augsburg Clinic, Augsburg, Germany

^g Novocure Ltd., Haifa, Israel

^h Hospital de la Pitié-Salpêtrière, Paris, France

ⁱ University of Pittsburgh Medical Center, Pittsburgh, PA, United States

^j Na Homolce Hospital, Prague, Czech Republic

^k University of Virginia, Charlottesville, VA, United States

^l Allegheny Neurological Brain Tumor Center, Pittsburgh, PA, United States

^m Northwestern University, Chicago, IL, United States

ⁿ Department of Neuro-Oncology, Hospices Civils de Lyon, Université Claude Bernard, Lyon, France

^o University Hospitals of Cleveland, Case Western Reserve University School of Medicine, Cleveland, OH, United States

^p Medical College of Wisconsin, Milwaukee, WI, United States

^q New Jersey Neuroscience Institute at JFK Medical Center, Edison, NY, United States

^r University Graz, Graz, Austria

^s University of Kiel, Kiel, Germany

^t The Cleveland Clinic Foundation-Taussig Cancer Center, Cleveland, OH, United States

^u New York Presbyterian Hospital-Weill Cornell Medical Center, New York, NY, United States

^v University of Hamburg, Hamburg, Germany

^w Brno University Hospital, Brno, Czech Republic

^x Boston Medical Center, Boston, MA, United States

* Corresponding author: Address: Department of Neurosurgery, Centre Hospitalier Universitaire Vaudois (CHUV), 46, rue du Bugnon, Lausanne 1011, Switzerland. Tel.: +41 21 314 0156; fax: +41 21 314 0737.

E-mail address: Roger.Stupp@chuv.ch (R. Stupp).

0959-8049/\$ - see front matter © 2012 Published by Elsevier Ltd.

<http://dx.doi.org/10.1016/j.ejca.2012.04.011>

Please cite this article in press as: Stupp R. 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), <http://dx.doi.org/10.1016/j.ejca.2012.04.011>

^y University of Innsbruck, Austria^z University Hospital Zurich, Switzerland^{aa} Columbia University Medical Center, New York, NY, United States^{ab} Lahey Clinic, Boston, MA, United States^{ac} NorthShore University Health System, Evanston, IL, United States^{ad} Memorial Sloan Kettering Cancer Center, New York, NY, United States**KEYWORDS**

Glioblastoma
Brain tumour
Chemotherapy
Randomised trial

Abstract Purpose: NovoTTF-100A is a portable device delivering low-intensity, intermediate frequency electric fields via non-invasive, transducer arrays. Tumour Treatment Fields (TTF), a completely new therapeutic modality in cancer treatment, physically interfere with cell division.

Methods: Phase III trial of chemotherapy-free treatment of NovoTTF (20–24 h/day) versus active chemotherapy in the treatment of patients with recurrent glioblastoma. Primary endpoint was improvement of overall survival.

Results: Patients (median age 54 years (range 23–80), Karnofsky performance status 80% (range 50–100) were randomised to TTF alone ($n = 120$) or active chemotherapy control ($n = 117$). Number of prior treatments was two (range 1–6). Median survival was 6.6 versus 6.0 months (hazard ratio 0.86 [95% CI 0.66–1.12]; $p = 0.27$), 1-year survival rate was 20% and 20%, progression-free survival rate at 6 months was 21.4% and 15.1% ($p = 0.13$), respectively in TTF and active control patients. Responses were more common in the TTF arm (14% versus 9.6%, $p = 0.19$). The TTF-related adverse events were mild (14%) to moderate (2%) skin rash beneath the transducer arrays. Severe adverse events occurred in 6% and 16% ($p = 0.022$) of patients treated with TTF and chemotherapy, respectively. Quality of life analyses favoured TTF therapy in most domains.

Conclusions: This is the first controlled trial evaluating an entirely novel cancer treatment modality delivering electric fields rather than chemotherapy. No improvement in overall survival was demonstrated, however efficacy and activity with this chemotherapy-free treatment device appears comparable to chemotherapy regimens that are commonly used for recurrent glioblastoma. Toxicity and quality of life clearly favoured TTF.

© 2012 Published by Elsevier Ltd.

1. Background

Glioblastoma is the most prevalent primary malignant brain tumour in adults. Median survival with optimal therapy is only 15 months from diagnosis, and most tumours recur within 9 months of initial treatment.¹ At the time of disease recurrence, treatment options for glioblastoma patients are limited. Repeat surgery may be considered in approximately 20% of patients,^{2–4} and re-irradiation is possible in rare circumstances. For most patients chemotherapy is indicated at disease recurrence, with the choice of drug varying greatly. In the United States, bevacizumab has been provisionally approved for recurrent glioblastoma, while the European Medicines Agency (EMA) rejected the application in the absence of a controlled trial.^{5,6} Cytotoxic agents most frequently used are alkylating agents like nitrosoureas (e.g. lomustine [CCNU] or carmustine [BCNU],⁷ procarbazine⁸ or re-treatment with temozolomide.^{9,10} Response rates are below 10%, progression-free survival rates at 6 months <20%.^{7,8} In the absence of an established and satisfactory standard treatment, bevacizumab

alone and in combination with irinotecan and experimental treatments are commonly used.^{11–13}

Overall survival (OS) from recurrence is commonly short and without effective therapy rarely exceeds 3–5 months.^{14–19} In a randomised trial of repeat surgery with implantation of carmustine wafers versus placebo median survival was 6.5 versus 4.7 months.²⁰ With active therapy, a median survival of 7 months (range 5–9.2 months)^{7–10,12,13,21–24} has been reported. A recent randomised comparison of enzastaurin versus lomustine at first recurrence demonstrated a median survival of 7.1 months, with 19% of patients alive and progression-free at 6 months when treated with lomustine.⁷ Based on these results active chemotherapy as salvage treatment for patients with recurrent glioma is recommended, which strives to improve survival and quality of life despite inherent chemotherapy-related toxicity.

The NovoTTF-100A system (Novocure Ltd., Haifa, Israel) is a portable device delivering low intensity, intermediate frequency, alternating electric fields (Tumour Treating Fields; TTF) using non-invasive, disposable transducer arrays (Fig. 1A). These fields physically

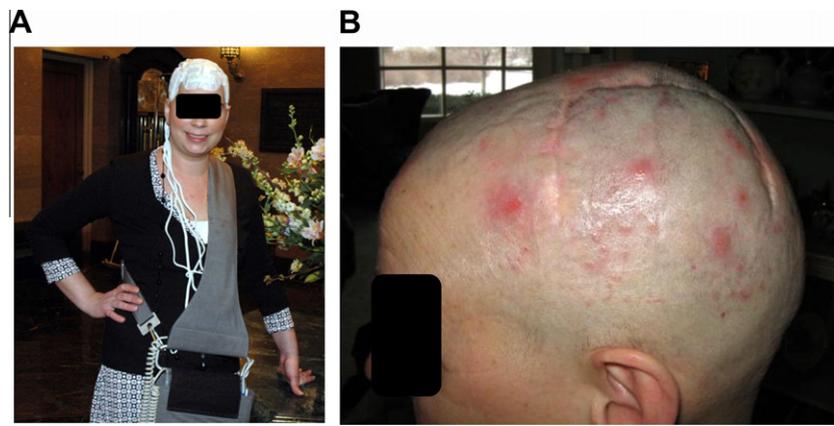


Fig. 1. Female patient wearing the portable NovoTTF-100A device (A). Grade 2 skin rash underneath transducer arrays in a different patient (B). With the patients' permission.

interfere with cell division by causing misalignment of microtubule subunits in the mitotic spindle during the metaphase to anaphase transition²⁵ and by dielectrophoretic movement of intracellular macromolecules and organelles during telophase.^{26,27} This causes failure of cytokinetic furrow formation and resultant mitotic blebbing, leading to the disruption of chromosome segregation and eventual cell death. The exact pathways by which spindle disruption and physical aggregation of macromolecules lead to cell death are unknown. TTF has been tested in several pilot clinical studies^{26,28,29} including a small single arm study as monotherapy for recurrent glioblastoma. The results of this pilot trial were promising²⁶ and served as the basis of this phase III trial comparing NovoTTF-100A monotherapy (TTF) to best active chemotherapy according to the physician's best choice (active treatment control group). This report describes for the first time the efficacy and safety of this entirely novel treatment modality compared to widely accepted active chemotherapies for the treatment of recurrent glioblastoma patients.

2. Methods

2.1. Patient selection

Patients 18 years or older with histologically confirmed glioblastoma (World Health Organization grade IV astrocytoma) were eligible following radiologically confirmed disease progression (Macdonald criteria). Patients had a Karnofsky performance status $\geq 70\%$ and adequate haematologic, renal and hepatic function (absolute neutrophil count $\geq 1000/\text{mm}^3$; haemoglobin $\geq 100 \text{ g/L}$ platelet count, $\geq 100,000/\text{mm}^3$; serum creatinine level $\leq 1.7 \text{ mg/dL}$ ($<150 \mu\text{mol/L}$); total serum bilirubin level \leq the upper limit of normal and liver-function values, <3 times the upper limit of normal). Prior therapy must have included radiotherapy (with and without concomitant and/or adjuvant temozolomide). There was no limit on number or type of prior

therapies or recurrences. Patients with infra-tentorial tumour location were excluded, as were patients with implanted electronic medical devices (e.g. pacemaker, programmable ventriculo-peritoneal shunt). All patients provided written informed consent, and the study was approved by the institutional review boards or ethics committees of all participating centres.

2.2. Study design and treatment

Patients were randomised at a 1:1 ratio to receive either TTF monotherapy (without chemotherapy) or the best available active chemotherapy according to the local physician's choice (active control). Randomisation was performed using random block sizes and was stratified by centre and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomisation, and was to be continued until disease progression or intolerance.

For patients assigned to the TTF group four transducer arrays were placed on the patient's shaved scalp and connected to a portable, battery or power supply operated device (NovoTTF-100A) which was set to generate 200 kHz electric fields within the brain in two perpendicular directions (operated sequentially). Field intensity was set at $>0.7 \text{ V/cm}$ at the centre of the brain. Patients were trained on how to operate the device and then continued treatment at home. Treatment was continuous while maintaining normal daily activity. Transducer arrays were replaced by the patients, their caregivers or device technicians once or twice a week. Prior to placement, the scalp was shaved carefully with an electric razor in order to avoid skin wounding, transducer arrays were supplied sterile. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to an hour, twice per day, for personal needs (e.g. shower). In addition, they were allowed to take 2–3 days off treatment at the end of each 4 weeks of treatment (which is the minimal

required treatment duration for TTF therapy to reverse tumour growth).³⁰

Patients assigned to the active control received chemotherapy at the local investigators discretion. The best available chemotherapy was prescribed according to local practice and depending on prior treatment exposure.

2.3. Patient surveillance and follow up

Baseline examinations included a gadolinium-enhanced magnetic resonance imaging (MRI) of the brain, full blood counts, blood chemistry tests, blood coagulation tests, electrocardiogram (ECG), physical examination including a detailed neurological examination and quality of life (QoL) questionnaire (European Organisation for Research and Treatment of Cancer (EORTC) QLQ C-30).

Patients were followed once a month, including laboratory tests. MRI was repeated every 2 months. QoL questionnaires were completed at baseline and then every 3 months. Tumour response and progression were determined by blinded central radiology review, according to Macdonald criteria.³¹ When an MRI could not be obtained, progression was assessed clinically based on neurological status, steroid dosing, adverse events and investigator assessment of progression.

Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria (NCI CTC V3.0)

2.4. Statistical analysis

The primary end-point was OS. Secondary end-points were progression free survival (PFS), the percentage of patients alive and progression-free at 6 months (PFS6), 1-year survival rate, radiological response rate (RR), QoL and safety. OS and PFS were computed from the day of randomisation until event or censored at last follow-up according to the Kaplan–Meier method, with 2-sided logrank statistics for comparison. The study had an 80 per cent power at a significance level of 0.05 to detect a 60 per cent increase in median OS (hazard ratio for death, 0.63). All analyses were performed using the intent to treat population of all randomised patients, patients lost to follow-up were censored at the time of last contact. A Cox proportional hazards model was used to adjust for confounding baseline variables (continuous and categorical). The survival data were tested for proportional hazards and the assumption of proportionality met. The Cox model was performed in two steps; first, all protocol pre-specified baseline variables were tested directly for interactions with OS; then a reduced model was performed testing the effect of all variables with significant interactions ($p < 0.05$) with OS together on the treatment effect of TTF versus active chemotherapy. Secondary end-points are presented without adjustment. QoL is pre-

sented as change from baseline to 3 months for each of the subscale domains and symptom scales of the QLQ-C30 questionnaire.

2.5. Organisational aspects

The trial was registered on www.clinicaltrials.gov, NCT#00379470. The trial was funded and sponsored by Novocure Ltd. Statistical analysis was performed by David Steinberg. The manuscript was written by Roger Stupp and Eilon Kirson, with substantial input by all co-authors. The final manuscript was reviewed and approved by all authors. The statistician and the corresponding author had unrestricted access to all data.

2.6. Role of the funding source

Representatives of the study sponsor were involved in the study design, data collection, data analysis, data interpretation and writing of the report. Data analysis was performed by David Steinberg, a compensated independent biostatistician. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

3. Results

3.1. Patients

From September 2006 until May 2009, 237 patients from 28 institutions in 7 countries were randomly assigned to receive TTF monotherapy (120 patients) or active control chemotherapy (117 patients). The baseline patient characteristics were balanced (Table 1). The median age was 54, and a quarter of the patients had undergone some surgical resection of the recurrent tumour prior to enrolment into the trial. More than 80% of patients had failed two or more prior lines of chemotherapy (\geq second recurrence) and 20% of the patients had failed bevacizumab prior to enrolment. Histology was per local pathological diagnosis; in 8% a history of a prior lower grade glioma had been reported (secondary glioblastoma). *Methyl-guanine methyl-transferase (MGMT)* gene promoter methylation, an important predictive factor for benefit of temozolomide chemotherapy in newly diagnosed glioblastoma, was not assessed in this trial of patients with recurrent disease.

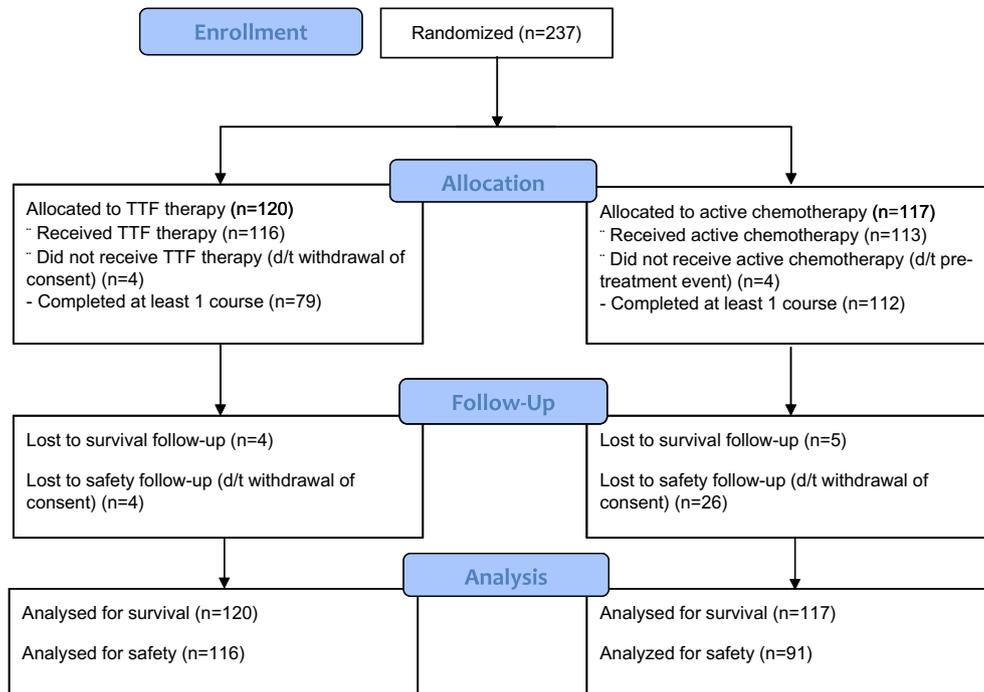
3.2. Patient disposition, treatment and compliance

In the TTF group, 116 of 120 patients (97%) started treatment and 93 patients (78%) completed 4 weeks of therapy (1 cycle). Twenty-seven patients discontinued treatment early, often within a few days, due to non-compliance or inability to handle the device (trial flow

diagram). Four patients had pre-treatment events related to the progressive nature of their disease and never started therapy with the device. In the TTF patients who started treatment (116 patients) mean compliance was measured by downloading a log file from the device, which recorded the actual time TTF therapy was delivered. Median compliance was 86 per cent (range 41–98%) of the time in each treatment month, translating into a mean use of 20.6 h per day.

apy (6.6 versus 6.0 months, respectively). One-year survival proportion was 20% in both groups, the 2- and 3-year survival rates were 8% (95% CI 4, 13) and 4% (95% CI 1, 8) versus 5% (95% CI 3, 10) and 1% (95% CI 0, 3), for TTF versus active control, respectively (Fig. 1A). The hazard ratio for death was 0.86 (95% CI 0.66, 1.12) in favour of NovoTTF ($p = 0.27$). Adjusting for baseline characteristics using a Cox proportional hazards model did not substantially

trial flow diagram



In the active control group, 113 of 117 patients (97%) started chemotherapy and all but 1 patient completed one full treatment course of the chosen chemotherapy. In four patients disease related adverse events and tumour progression prevented the initiation of the planned chemotherapy, they only received supportive care (hospice care). Twenty-one patients randomised to the control group decided not to return to the investigational site for treatment, thus details on disease progression and toxicity are not available. Most of patients received single agent or a combination chemotherapy regimen containing bevacizumab (31%), or irinotecan (31%), followed by nitrosoureas (25%), carboplatin (13%), temozolomide (11%) or various other agents (5%; Supplementary Table 1).

3.3. Survival, progression and radiological response

At a median follow up of 39 months, 220 patients had died (93%). Median survival was marginally higher in the TTF group compared to active control chemother-

apy. In the active chemotherapy control arm of the trial, survival was not significantly affected by the choice of chemotherapy (Cox proportional hazards test; $p = 0.66$).

More objective radiological responses (partial and complete responses) were seen in the TTF group than in the active control chemotherapy group (14 versus 7, respectively), translating into a response rate in evaluated patients of 14.0% (95% CI 7.9–22.4%) versus 9.6% (95% CI 3.9–18.8%), respectively (chi squared $p = 0.19$). All three complete responses were observed in the TTF group. Two exemplary partial responses from TTF are shown in Fig. 3.

The trial had been designed for superiority. Since the control group in the trial is an active chemotherapy control which showed similar efficacy to that seen in previous trials and the device was used as monotherapy it is reasonable to analyse the results also in the context of a non-inferiority analysis. The HR for death in the TTF group compared to the active control chemotherapy group was below 1.0 (0.86; 95% CI 0.66–1.12), indi-

Table 1
Baseline characteristics.

	Tumour Treatment Fields (TTF) (n = 120) # pts (%)	Active control (n = 117) # pts (%)
<i>Characteristics</i>		
Age, median (range)	54 years (24–80)	54 years (29–74)
Gender		
Male	92 (77)	73 (62)
Female	28 (23)	44 (38)
Histology		
Glioblastoma	100%	100%
Prior lower grade glioma	10 (8)	9 (8)
Karnofsky performance status, median (range)	80% (50–100)	80% (50–100)
Steroid use at enrolment		
Yes	55 (46)	62 (53)
No	55 (46)	49 (42)
Unknown	10 (8)	6 (5)
Largest tumour diameter at randomisation, median (range)	6.1 cm (0–15.2)	5.5 cm (0–16.2)
Interval from initial glioma diagnosis, median (range)	11.8 months (3.2–99.3)	11.4 months (2.9–77.1)
<i>Prior therapy</i>		
1st recurrence	11 (9)	17 (15)
2nd recurrence	58 (48)	54 (46)
3rd or greater recurrence	51 (43)	46 (39)
<i>Surgery</i>		
Debulking before enrolment	33 (28)	29 (25)
Debulking at any stage	95 (79)	99 (85)
Biopsy only	25 (21)	18 (15)
<i>Radiotherapy</i>		
100%	100%	100%
With concomitant temozolomide	103 (86)	96 (82)
No concomitant temozolomide	15 (13)	20 (17)
Unknown	2 (1)	1 (1)
<i>Prior adjuvant (maintenance) temozolomide</i>		
100 (83)	100 (83)	89 (76)
Median no of cycles	4 (0–19)	3 (0–27)
Prior bevacizumab	23 (19)	21 (18)

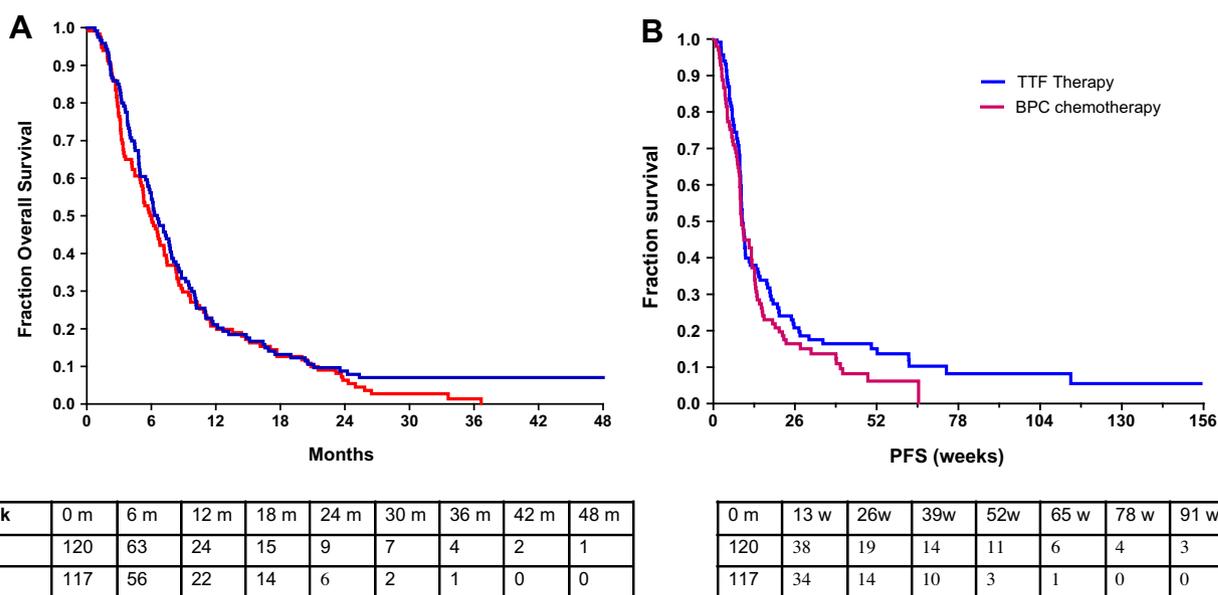


Fig. 2. Overall survival (A) and progression free survival (B) Kaplan–Meier curves.

cating that TTF may be at least equivalent to active chemotherapy.

PFS showed a similar trend in favour of TTF patients as seen for OS (Fig. 1B). Median PFS was 2.2 and

2.1 months for TTF and active control groups, respectively (Fig. 2; HR 0.81, 95% CI 0.60–1.09; log rank $p = 0.16$). PFS6 was 21.4 per cent (95% CI 13.5–29.3) in the TTF group and 15.1 per cent (95% CI 7.8–22.3) in the active control group (chi squared $p = 0.13$).

3.4. Safety and toxicity

As expected from the mechanism of action of TTF therapy and the fact that its delivery is localised to the head, the typical systemic side-effects of chemotherapies were not observed in the TTF treated patients. Mild to moderate (grade 1 and 2) contact dermatitis on the scalp beneath the transducer arrays occurred in 16% of TTF patients (Fig. 1B). This condition was easily treated with topical corticosteroids, resolved completely after treatment, was stopped and did not require substantial treatment breaks.

Patients receiving active control chemotherapy experienced toxicity related to pharmacologic mechanism of the agents used. A list of grade 2–4 adverse events by organ system and adverse event terms seen in more than 2% of patients in either group is presented in Table 2. As expected, there were significantly more gastrointestinal, haematological and infectious adverse events seen in the chemotherapy group than in the TTF group. Severe

(grades 3 and 4) toxicity was observed in only 3% of patients.

3.5. Quality of life

Longitudinal Quality of Life (QOL) could be analysed in the patients who remained on study therapy for ≥ 3 months and for whom QoL data were available (63 patients, 27%). In the domains of global health and social functioning no meaningful differences between chemotherapy and TTF were observed. However, cognitive and emotional functioning favoured TTF. Physical functioning may be slightly worse with TTF, while role functioning favoured TTF (Fig. 4A). Symptom scale analysis is in accordance to treatment-associated toxicity; appetite loss, diarrhoea, constipation, nausea and vomiting were directly related to the chemotherapy administration. Increased pain and fatigue was reported in the chemotherapy-treated patients and not in the TTF treatment group (Fig. 4B).

3.6. Treatment after progression

In order to rule out the effect of subsequent treatments on the OS results reported above, we compared the number and type of post-progression treatments patients received after failing the trial therapy. Due to

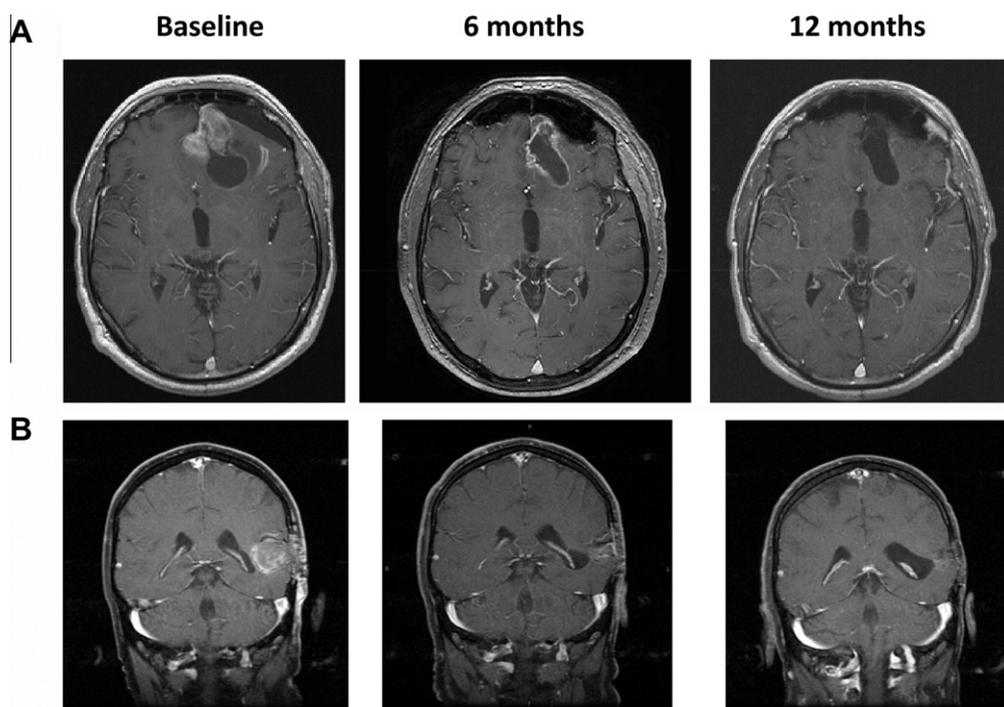


Fig. 3. Exemplary T1 weighted magnetic resonance imaging (MRI) images with gadolinium from two Tumour Treatment Fields (TTF) patients with partial response to therapy. (A) A 48 years old male with prior grade II astrocytoma which transformed to glioblastoma (based on tissue biopsy). The subject progressed 7 months after receiving chemoradiotherapy, and subsequently responded to TTF therapy (partial response at 12 months) and remained stable for an additional 36+ months on TTF. (B) A 55 years old male with primary glioblastoma who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and erlotinib with sorafenib (one cycle). The subject had a partial response to TTF therapy after 4 months of treatment and remained stable for an additional 8 months while on TTF.

Table 2
Treatment-emergent adverse events \geq grade 2 by body system.

System	Adverse event term	Tumour Treatment Fields (TTF) ($n = 116$) % (% gr. 3 + 4)	Active control ($n = 91$) % (% gr. 3 + 4)
Haematological		3 (0)	17 (4)
	Leucopenia	0 (0)	5 (1)
	Neutropenia	0 (0)	2 (1)
	Thrombocytopenia	1 (1) ^a	7 (2)
Gastrointestinal disorders		4 (1)	17 (3)
	Abdominal pain	0 (0)	3 (0)
	Diarrhoea	0 (0)	6 (2)
	Nausea/vomiting	2 (0)	7 (0)
General deterioration and malaise		5 (1)	6 (1)
Infections		4 (0)	8 (1)
Skin rash (transducer arrays)		2 (0)	0 (0)
Metabolism and nutrition disorders		4 (1)	6 (3)
Musculoskeletal disorders		2 (0)	5 (0)
Nervous system disorders		30 (7)	28 (7)
	Brain oedema	0 (0)	2 (0)
	Cognitive disorder	2 (1)	2 (1)
	Convulsion	7 (2)	5 (2)
	Dysphasia	2 (0)	1 (0)
	Headache	8 (1)	6 (0)
	Hemianopsia	1 (0)	3 (1)
	Hemiparesis	3 (1)	2 (1)
	Neuropathy peripheral	2 (0)	2 (0)
Psychiatric disorders		5 (0)	4 (0)
Renal and urinary disorders		3 (1)	3 (0)
Respiratory disorders		1 (0)	3 (1)
Vascular disorders		3 (1)	4 (3)
	Pulmonary embolism	1 (1)	2 (2)
	Hypertension	1 (0)	1 (1)
	Deep vein thrombosis	1 (0)	1 (0)

^a Thrombocytopenia from prior chemotherapy, normalised subsequently.

the very advanced stage they were recruited to the study (most patients were at their second or subsequent recurrence), only 5.8% of the TTF-treated patients and 10.3% of the chemotherapy-treated patients received subsequent salvage antitumour therapy (chi square $p = 0.24$) (mainly bevacizumab, irinotecan, nitrosoureas and temozolomide). The majority of patients received only supportive care once tumour progression developed.

4. Discussion

Tumour treatment with alternating electrical fields that interfere with the metaphase to anaphase transition in dividing tumour cells is an entirely novel cancer treatment modality. We report the first prospective, randomised, controlled study using this new treatment modality in the most aggressive primary brain tumour. Although glioblastoma diffusely infiltrates the brain, it almost never metastasises and is thus amenable to a loco-regional therapy.

Prognosis of patients with recurrent glioblastoma is poor, and chemotherapy is usually recommended. Depending on prior treatments and treatment centre expertise, variable chemotherapy agents alone or in combination are commonly prescribed. Our randomised trial compared this standard chemotherapy per local

practice (active treatment control group) with TTF in a prospective, multicentre phase III trial. Although the trial did not reach its primary end-point of improved survival compared to active chemotherapy, this new minimally invasive and chemotherapy-free local treatment modality demonstrated a statistically non-significant increased response rate (14 versus 9.6%, $p = 0.19$), an improved PFS6 rate (21% versus 15%, $p = 0.13$), and a trend towards reduction of the risk of death (hazard ratio 0.86, 95% CI 0.66–1.12, $p = 0.27$), as well as sustained improvement in QoL.

These results cannot be explained by subsequent salvage chemotherapy, as few patients received additional therapy after failure of protocol treatment. Importantly, the majority of our patients were recruited to the trial at an advanced stage of the disease, after failure of two or more chemotherapy agents, while other trials in recurrent glioblastoma usually only enrol patients at first recurrence. It is also notable that 20% of patients had failed prior bevacizumab therapy, a population that usually fares poorly with most subsequent treatments.

One limitation of the study was the absence of a placebo or treatment-free control arm. In the setting of advanced disease and chemotherapy considered indicated and effective, such a control would hardly have been acceptable to patients and physicians alike. Fur-

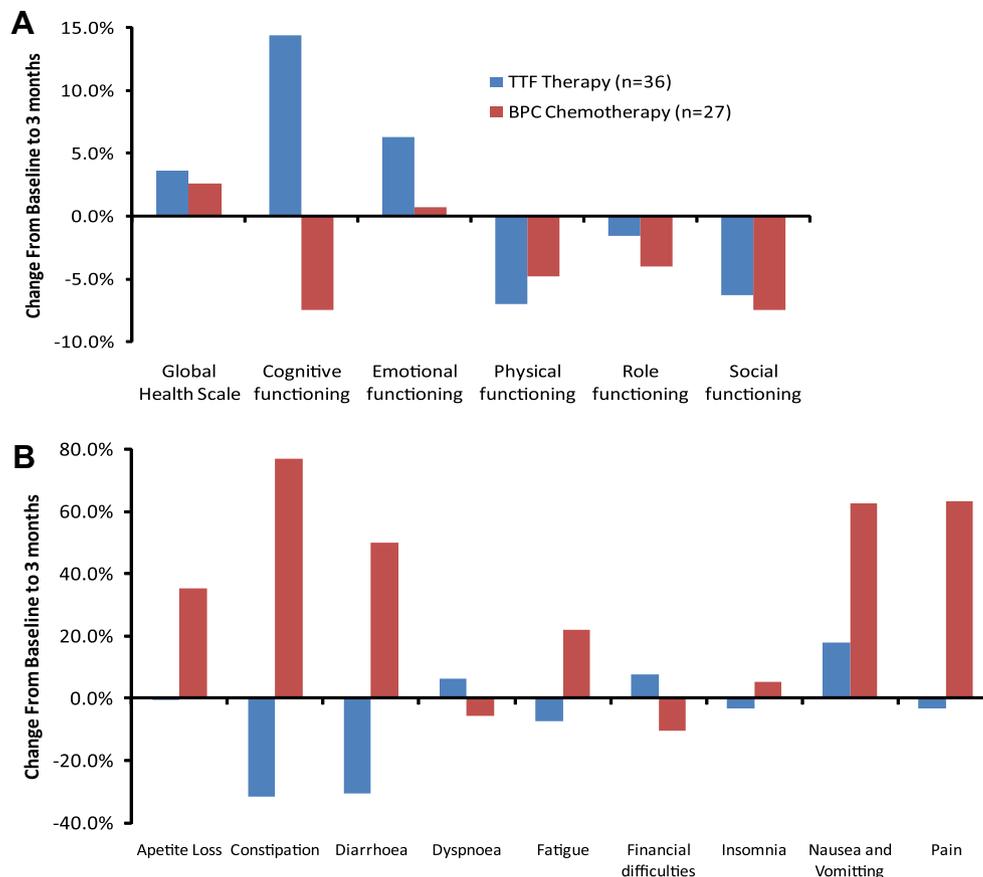


Fig. 4. QLQ C30 longitudinal change from base to 3 months. (A) General functional scales (an increase in percentage corresponds to an increase in QOL). (B) Symptom scales (an increase in percentage corresponds to a decrease in QOL).

thermore, chemotherapy with lomustine has shown superior efficacy versus investigational treatments in two recent randomised trials. And based on high response rates and prolonged survival compared to historical controls bevacizumab has received accelerated Food and Drug Administration (FDA) approval. Furthermore, the observation of objective responses in 14 patients with NovoTTF alone (median time since end of prior RT 7 months, thus unlikely to be all pseudoprogression) strongly suggests singular activity of this device.

Another limitation is the somewhat heterogeneous patient population, with patients included after progression of one or several lines of prior chemotherapy. This underscores the demand from patients for further treatments, even when the expected benefit of a 2 months prolongation in PFS may appear modest. In the ongoing randomised phase III trial for newly diagnosed glioblastoma, only patients non-progressive after completion of chemoradiation are eligible (Novocure EF-14, www.clinicaltrials.gov, NCT#00916409).

As expected with a local treatment, toxicity was limited to skin irritation from transducer arrays (Fig. 1B). After proper instructions, most patients became independent in handling this device and replacing transducer arrays, allowing them to be ambulatory and even going to work. Despite the inconvenience of carrying and

using the device almost permanently, compliance was high and patients reported improvement in QoL in the absence of chemotherapy related toxicities.

In vitro and animal experiments suggest enhanced effect when TTF is combined with chemotherapy.^{28,32} We therefore initiated a subsequent randomised phase III trial currently enrolling newly diagnosed glioblastoma patients after completion of standard radiochemotherapy, parallel to starting the adjuvant or maintenance temozolomide chemotherapy. Patients randomised to the experimental arm will receive TTF in addition to maintenance temozolomide (www.clinicaltrials.gov, NCT#00916409).

Based on the result of this trial TTF therapy has recently been approved in the US and Europe for the treatment of recurrent glioblastoma (www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm251669.htm).

The universal anti-cancer effect of TTF may be applicable to other solid tumour types, alone or in combination with chemotherapy. In particular, in a situation of morbidity induced by a heavy local tumour burden, and in conditions where further radiotherapy is not an option, this non-invasive treatment may allow for a clinical benefit and will substantially expand our treatment armamentarium.

Conflict of interest statement

Eilon Kirson and Uri Weinberg are employees of Novocure Ltd., and have stock options in the company.

Herwig Kostron has received honoraria from Novocure Ltd.

Yoram Palti is the inventor of the Novo-TTF principle. He received consulting honoraria and travel support by Novocure Ltd.

Nina Paleologos has served on advisory boards and speakers bureau to Genentech, Merck & Co (previously Schering-Plough).

Susan Panullo has received research grants from Novocure, NTI Pharma, Eisai, Immunocellular and Parexel, and honoraria for lectures from Merck & Co (previously Schering-Plough).

Zvi Ram is a board member for Novocure, and received consultancy honoraria.

Jeffrey Raizer has received research support from Novocure Ltd., performed consultancy for Merck and Genentech/Roche, and lectures on behalf of Merck & Co, Genentech and Enzon.

David Schiff has performed consultancy for Genentech and Tau Pharmaceuticals.

Andrew Sloan has provided consultancy to Genentech/Roche, Real Bio Inc., Nanfiber Solutions, Surgical Theatre and Monteris Medical Inc.

Roger Stupp has served on scientific advisory boards for Merck-Serono, Roche, Actelion, MDxHealth (previously OncoMethylomeSciences) and Merck and Co (previously Schering-Plough).

Manfred Westphal has received consultancy honoraria from Roche, OncoScience and Ark Therapeutics.

Eric T. Wong has received research support from Novocure Ltd.

The following authors declare no potential conflict of interest: Jeffrey Bruce, Lawrence Chin, Rees Cosgrove, Vladimir Dbaly, Herbert Engelhard, Philip Gutin, Volkmar Heidecke, Silvia Hofer, Andrew Kanner, Lara Kunscher, Joseph Landolfi, Frank Lieberman, Marc Malkin, Maximilliam Mehdorn, Franz Payer, Martin Smrcka, David Steinberg, J. Lee Villano, and Robert Weil.

Acknowledgements

We are indebted to the patients and their families for agreeing to participate in this trial. We thank all the local site co-investigators, and trial coordinators at the participating centres for their hard and diligent work, as well as the nurses at the trial site and Novocure technicians for the great patient care provided. We express our special thanks to Martine Lionnet, Francois Ducray, Stéphanie Cartalat-Carel, Marie Fasol, Valerie Elsig, Mike Ambrogi, Shawn Andrews, Yoram Wasserman and Zoya Gurvich.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2012.04.011>.

References

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;**352**(10):987–96.
2. Brandes AA, Vastola F, Monfardini S. Reoperation in recurrent high-grade gliomas: literature review of prognostic factors and outcome. *Am J Clin Oncol* 1999;**22**(4):387–90.
3. Guyotat J, Signorelli F, Frappaz D, Madarassy G, Ricci AC, Bret P. Is reoperation for recurrence of glioblastoma justified? *Oncol Rep* 2000;**7**(4):899–904.
4. Mandl ES, Dirven CM, Buis DR, Postma TJ, Vandertop WP. Repeated surgery for glioblastoma multiforme: only in combination with other salvage therapy. *Surg Neurol* 2008;**69**(5):506–9 [discussion 509].
5. Verhoeff JJ, van Tellingen O, Claes A, et al. Concerns about antiangiogenic treatment in patients with glioblastoma multiforme. *BMC Cancer* 2009;**9**:444.
6. Wick W, Weller M, van den Bent M, Stupp R. Bevacizumab and recurrent malignant gliomas: a European perspective. *J Clin Oncol* 2010;**28**(12):188–9 [author reply e190–2].
7. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010;**28**(7):1168–74.
8. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 2000;**83**(5):588–93.
9. Balmaceda C, Peereboom D, Pannullo S, et al. Multi-institutional phase II study of temozolomide administered twice daily in the treatment of recurrent high-grade gliomas. *Cancer* 2008;**112**(5):1139–46.
10. Chang SM, Theodosopoulos P, Lamborn K, et al. Temozolomide in the treatment of recurrent malignant glioma. *Cancer* 2004;**100**(3):605–11.
11. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist* 2009;**14**(11):1131–8.
12. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009;**27**(28):4733–40.
13. Vredenburgh JJ, Desjardins A, Herndon 2nd JE, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;**25**(30):4722–9.
14. Rosenthal MA, Gruber ML, Glass J, et al. Phase II study of combination taxol and estramustine phosphate in the treatment of recurrent glioblastoma multiforme. *J Neurooncol* 2000;**47**(1):59–63.
15. Oudard S, Carpentier A, Banu E, et al. Phase II study of lonidamine and diazepam in the treatment of recurrent glioblastoma multiforme. *J Neurooncol* 2003;**63**(1):81–6.
16. Chamberlain MC, Tsao-Wei DD. Salvage chemotherapy with cyclophosphamide for recurrent, temozolomide-refractory glioblastoma multiforme. *Cancer* 2004;**100**(6):1213–20.
17. Kesari S, Schiff D, Doherty L, et al. Phase II study of metronomic chemotherapy for recurrent malignant gliomas in adults. *Neurooncol* 2007;**9**(3):354–63.
18. Puduvalli VK, Yung WK, Hess KR, et al. Phase II study of fenretinide (NSC 374551) in adults with recurrent malignant gliomas: a North American Brain Tumor Consortium study. *J Clin Oncol* 2004;**22**(21):4282–9.

19. Robe PA, Martin DH, Nguyen-Khac MT, et al. Early termination of ISRCTN45828668, a phase 1/2 prospective, randomized study of sulfasalazine for the treatment of progressing malignant gliomas in adults. *BMC Cancer* 2009;**9**:372.
20. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. *Lancet* 1995;**345**(8956):1008–12.
21. Brada M, Hoang-Xuan K, Rampling R, et al. Multicenter phase II trial of temozolomide in patients with glioblastoma multiforme at first relapse. *Ann Oncol* 2001;**12**(2):259–66.
22. Rich JN, Reardon DA, Peery T, et al. Phase II trial of gefitinib in recurrent glioblastoma. *J Clin Oncol* 2004;**22**(1):133–42.
23. Neyns B, Sadones J, Joosens E, et al. Stratified phase II trial of cetuximab in patients with recurrent high-grade glioma. *Ann Oncol* 2009;**20**(9):1596–603.
24. Perry JR, Belanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent malignant glioma: rescue study. *J Clin Oncol* 2010;**28**(12):2051–7.
25. Lee S, Wong E, Swanson K. Mitosis interference of cancer cells during anaphase by electric field from NovoTTF-100A. In: *Society for Neuro Oncology*, 2011, Orange County, CA; 2011. *Neuro Oncol* 2011;**13**(Suppl. 3):1–167 [Abstract CB-17].
26. Kirson ED, Dbaly 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):10152–7.
27. Kirson ED, Gurvich Z, Schneiderman R, et al. Disruption of cancer cell replication by alternating electric fields. *Cancer Res* 2004;**64**(9):3288–95.
28. Kirson ED, Schneiderman RS, Dbaly V, et al. Chemotherapeutic treatment efficacy and sensitivity are increased by adjuvant alternating electric fields (TTFields). *BMC Med Phys* 2009;**9**(1):1.
29. Salzberg M, Kirson E, Palti Y, Rochlitz C. A pilot study with very low-intensity, intermediate-frequency electric fields in patients with locally advanced and/or metastatic solid tumors. *Onkologie* 2008;**31**(7):362–5.
30. Kirson ED, Wasserman Y, Izhaki A, Mordechovich D, Gurvich Z, Dbaly V, et al. Modeling tumor growth kinetics and its implications for TTFields treatment planning. In: *The 2010 Society of Neuro-Oncology Scientific Meeting and Education Day*, Montreal, Canada; 2010. *Neuro Oncol* 2010;**12**(Suppl. 4):1–148 [Abstract NO-54].
31. Macdonald DR, Cascino TL, Schold Jr SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;**8**(7):1277–80.
32. Schneiderman RS, Shmueli E, Kirson ED, Palti Y. TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters. *BMC Cancer* 2010;**10**:229.