Response Patterns of Recurrent Glioblastomas Treated With Tumor-Treating Fields

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Glioblastoma multiforme (GBM) is the most common form of primary malignant brain cancer. Median overall survival (OS) for newly diagnosed patients is only about 12 to 18 months. GBM tumors invariably recur, and there is no widely recognized and effective standard treatment for recurrent GBM. NovoTTF Therapy is a novel and US Food and Drug Administration (FDA)-approved antimitotic treatment for recurrent GBM with potential benefits compared with other options. Recurrent GBM patients from two prior trials with demonstrated radiologic tumor response to single-agent NovoTTF Therapy were analyzed to better characterize tumor response patterns and evaluate the associations between response, compliance, and OS. In addition, a compartmental tumor growth model was developed and evaluated for its ability to predict GBM response to tumor-treating fields (TTFields). The overall response rate across both trials was 15% (4% complete responses): 14% in the phase III trial (14/120) and 20% (2/10) in a pilot study. Tumor responses to NovoTTF Therapy developed slowly (median time to response, 5.2 months) but were durable (median duration, 12.9 months). Response duration was highly correlated with OS ($r^2 = .92$, $P < .0001$), and median OS for responders was 24.8 months. Seven of 16 responders exhibited initial tumor growth on magnetic resonance imaging. Compliance appeared to be linked with both improved response and survival. The tumor growth model predicted tumor arrest and shrinkage only after several weeks of continuous NovoTTF Therapy, consistent with the observed clinical findings of initial transient tumor growth in some patients. NovoTTF Therapy is a novel antimitotic treatment for recurrent GBM associated with slowly developing but durable tumor responses in approximately 15% of patients. Some responders exhibit initial tumor growth before shrinkage, indicating treatment should not be terminated prior to allowing for the full effect of NovoTTF Therapy to be realized. OS is longer in responders than in nonresponders. High daily compliance rates may be associated with increased likelihood of an objective response and are predictive of improved survival.
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Glioblastoma (GBM) is the most common type of primary malignant brain cancer.[1,2] Approximately 10,000 new cases of GBM are diagnosed in the United States each year, and the estimated worldwide incidence rate is 3.5 per 100,000 people.[3] Median overall survival (OS) for patients with newly diagnosed GBM is only 12 to 18 months, with standard therapy consisting of surgical resection together with adjuvant chemotherapy (temozolomide) and radiotherapy.[1,3–6] Of patients with GBM, 90% to 95% die within 5 years of diagnosis.[1,2,5] Nearly all patients with GBM experience disease progression despite aggressive first-line therapy, with a median time to progression of 6 to 11 months.[1,4,7] Treatment options for GBM at the time of recurrence are limited, and there is no widely accepted standard treatment.[7–9] The NovoTTF-100A System (Novocure Ltd., Haifa, Israel) is an approved

antimitotic treatment for patients with recurrent GBM.[10] It utilizes low-intensity, intermediate-frequency alternating electric fields, or tumor-treating fields (TTFields), to selectively kill or arrest the growth of rapidly dividing GBM cells by inhibiting the proper formation of the mitotic spindle and by causing rapid membrane breakdown during cytokinesis.[10–13] TTFields are delivered, in conjunction with magnetic resonance imaging (MRI) guidance, via noninvasive transducer arrays attached to the patient's scalp. Recommended usage is ≥18 hours per day in each 4-week treatment cycle.[14] A phase III trial comparing NovoTTF monotherapy with chemotherapy according to physician's choice in patients with recurrent GBM reported similar median OS in the intention-to-treat (ITT) population, 6.6 versus 6.0 months respectively (hazard ratio [HR], 0.86; P =.13), but NovoTTF monotherapy resulted in significantly fewer severe adverse events (6% v 16%; P = .022) and a higher quality of life.[15] Furthermore, unlike chemotherapies, TTFields are a physical modality of treatment without a half-life (unlike biochemical therapy) and therefore they need to be continuously applied for maximal effect.[16] A post hoc analysis of the OS data on the modified ITT (mITT) population, corrected for the number of patients in the NovoTTF Therapy arm who failed to receive at least one full treatment course (see Kanner et al in this supplement), demonstrated significantly longer median OS with NovoTTF Therapy compared with chemotherapy, 7.7 versus 5.9 months, respectively (HR, 0.69; 95% confidence interval [CI], 0.52–0.91; P = .0093). Additional analyses performed by Kanner et al also linked higher NovoTTF Therapy compliance with longer OS. Recently, there have been reports of a limited but notable number of patients with recurrent GBM treated with NovoTTF Therapy in the phase III trial[17] and in an earlier pilot study[12,18] who experienced durable tumor responses with long-term survival, some 10 years in duration until today. Identifying such patients, as well as characterizing their tumor response pattern, would help the future selection of patients likely to receive particularly benefit from NovoTTF Therapy. Therefore, the purpose of the current analysis was to define the response pattern in patients who exhibited objective tumor responses to NovoTTF Therapy in these two studies and to better evaluate their efficacy outcomes in the context of kinetic modeling exploring response to TTFields. In addition, the present study examined baseline characteristics linked with higher probability of response to NovoTTF Therapy, and further explored the relationship between compliance and efficacy outcomes. All analyses were restricted to patients with recurrent GBM who received NovoTTF Therapy alone (as monotherapy), and did not include patient responders from the same pilot study who had newly diagnosed GBM treated by NovoTTF Therapy with temozolomide.[12]

METHODS

Clinical Trial Conduct and Analysis

In both the pilot and phase III trials, patients 18 years old or older with histologically confirmed GBM (World Health Organization grade IV astrocytoma) were eligible after radiologically confirmed disease progression according to the Macdonald criteria.[19] Patients had Karnofsky performance status (KPS) of ≥70% and adequate hematologic, renal, and hepatic function: absolute neutrophil count, ≥1,000/μL; hemoglobin, ≥100 g/L; platelet count, ≥100,000/μL; serum creatinine level, ≤1.7 mg/dL (<150 μmol/L); total serum bilirubin level, ≤ upper limit of normal; and liver function values, <3 times 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 infratentorial tumor were excluded, as were patients with implanted electronic medical devices (eg, pacemaker, programmable ventriculoperitoneal shunt). All patients provided written informed consent, and the studies were approved by the institutional review boards or ethics committees of all participating centers.

In the pilot trial, a total of 10 patients with recurrent GBM were accrued and treated with NovoTTF monotherapy without concurrent chemotherapy. In the phase III trial, 237 patients were randomized at a 1:1 ratio to receive either NovoTTF monotherapy or the best available chemotherapy according to the local physician's choice. Randomization was performed using random block sizes and was stratified by center and according to whether patients underwent surgery for their latest recurrence prior to trial entry. Assigned treatment had to start within 1 week of randomization and was to be continued until disease progression or intolerance.

For patient receiving NovoTTF Therapy in either study, four transducer arrays were placed on the shaved scalp and connected to a portable, battery- or power supply–operated device. Treatment parameters were preset to generate alternating electric fields at a frequency of 200 kHz. This frequency is associated with an electric field intensity distribution across the entire supratentorial brain exceeding 0.7 V/cm. Thus, there were no electrical adjustments required. Patients were trained to operate the device and then continued treatment at home. Treatment was continuous while patients were maintaining normal daily activity. Transducer arrays were

replaced by the patients, their caregivers, or device support specialists once or twice per week. Although uninterrupted treatment was recommended, patients were allowed to take treatment breaks of up to 1 hour twice per day for personal hygiene needs (eg, shower) or when severe scalp irritation was observed. In addition, patients were allowed to take 2 to 3 days off from treatment at the end of each 4 weeks of treatment.

Follow-up was once a month and included laboratory tests. MRI was repeated every month in the pilot trial and every two months in the phase III trial until disease progression, and then according to local practice. Tumor response and progression were determined by blinded central radiology review, according to Macdonald criteria.[19] MRI was performed in at least two planes and included T1- and T2-weighted sequences. T1-weighted sequences were repeated after administration of contrast agent. Fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging studies were not mandated in either study and were performed according to local practice.

In the present analysis, all NovoTTF Therapy scans from both studies were reviewed by a neuroradiologist (J.V.). Tumors were measured in two dimensions based on T1 sequences with contrast enhancement. T2, FLAIR, and diffusion-weighted imaging sequences were assessed qualitatively. Time to response, response duration, and OS in responders were calculated using the Kaplan-Meier method. Correlations between response times and OS were based on Pearson linear correlation.

Compliance Measures

The NovoTTF-100A device exerts its therapeutic effect by physically disrupting tumor cells during mitosis. Therefore, this treatment does not have a half-life and is active only when the system is delivering TTFields to the patient. In both trials, a monthly compliance assessment was performed for each patient by downloading an internal log file that captures device "on" time. Patient compliance was calculated as the average percentage of each day the system was delivering fields out of each 24-hour period. We hypothesized that compliance with treatment would correlate with patient response and survival, and tested our hypothesis by using the Pearson linear correlation.

Compartmental Tumor Growth Model

A kinetic model of tumor volume changes under NovoTTF Therapy versus in the absence of this therapy was developed to help us better understand the response pattern in our patients. Like other published models,[20–24] our model assumes that changes in tumor volume and size, for any given time interval, are determined by the number of tumor cells in the dormant or latent (L) state, cells that leave the dormant state to enter mitosis and are replicating (R), cells that die (D) within this time interval, and cells that are cleared (C) from the tumor microenvironment. It is assumed that the volume of the individual cells in all states is constant and that there are no significant tumor volume changes caused by edema or other stromal changes. The cell division cycle time for GBM is on the order of 24 to 72 hours[25] and is assumed to be constant in the kinetic model. After division, a prespecified fraction of the cells continue to the next cycle, while others return to the dormant state (as expressed by the mitotic index). Because GBM frequently has a necrotic center, and the most actively proliferating tumor cells are located peripheral to the center,[26] we made a corresponding adjustment in the model to closely approximate the biological behavior of the tumor in a patient. This constitutes a major difference between our model and the previously published models. Therefore, we modeled the replicating cells and the clearance of dead cells to a vascular outer layer of a constant width such that the volume of this layer, relative to the entire tumor volume, decreases as the tumor grows. In contrast, natural cell death occurs only within the avascular core of the tumor such that the number of cells undergoing natural death increases with tumor volume. Replicating cell death also occurs at rates that are affected by NovoTTF Therapy.

For us to solve this model mathematically, the minimal cell division cycle time (1 day) was taken as the elementary time interval and served as the basic iteration time. The need for an iterative rather than analytical solution arises from the fact that the system is not at equilibrium or even steady-state. The number of dormant, dividing, and dead cells in the tumor at each time point was summed and used to represent the actual tumor volume at any time t.

Similar to first-order chemical kinetics, at any given time the number of cells leaving a compartment is the multiple of the rate constant and the number of cells in the compartment. The model consists of 4 functional compartments that are in constant dynamic interaction. Dormant or latent (L) cells are in a reversible transition with the dividing or replicating (R) cells, with respective rate constants of k_1 and k_2. The rate constants are balanced to keep the constituents of the two compartments at a fixed ratio consistent with the histologically determined fraction of dividing cells in GBM tumors.[27]

Tumor cells are assumed to die or move to the third compartment through two mechanisms. The first is apoptosis, which mainly depends on nutrient

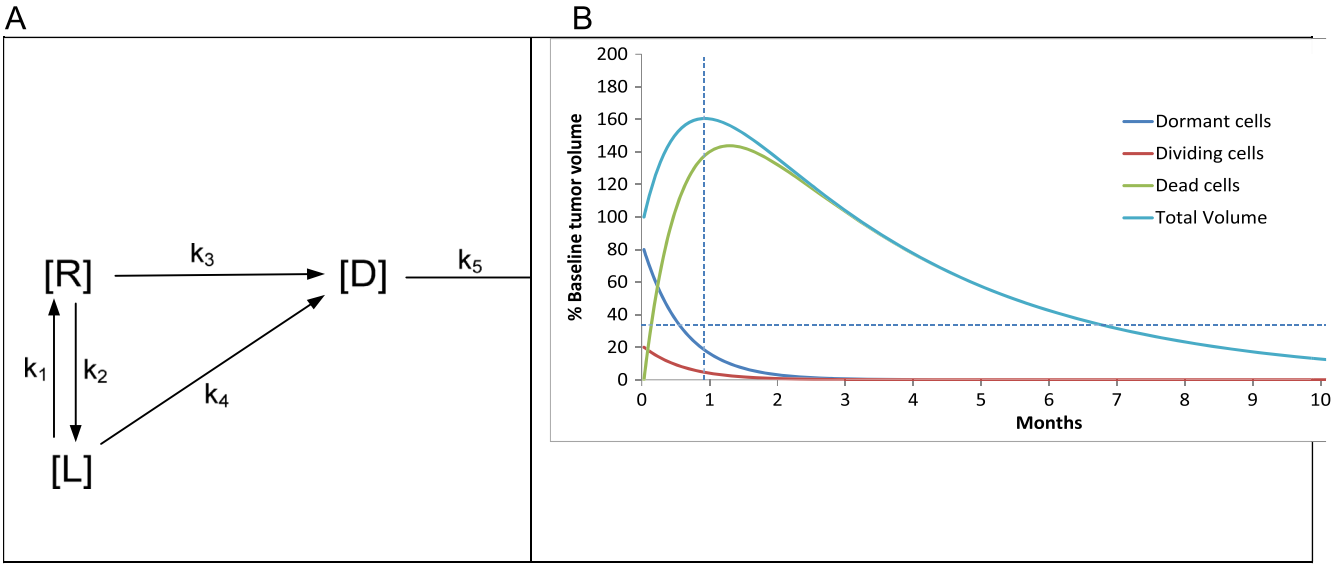

Figure 1. (A) Scheme representing the different compartments in the model and the rate constants associated with the interactions between them. [L] = Latent/Nondividing cells; [R] = Replicating/Dividing cells; [D] = Dead cells; [C] = Cells cleared from tumor by physiological mechanisms. TTFields were modeled as effecting K_3. (B) Results of kinetic model simulation. Relative changes in size of compartments of a tumor. Volume changes during the initial 9 months of NovoTTF Therapy are characterized by growth of tumor volume in the initial month, with a maximum near 1 month followed by a gradual decline. A reduction of tumor volume to 35% is observed at about 6.8 months, and this is equivalent to a 50% decrease in bi-dimensional tumor measurement or partial response according to the Macdonald or RANO criteria. Nondividing cells compartment (black); Dividing cells (green); Dead cells (blue); Total tumor volume (red); Vertical dashed line = peak tumor volume and time of tumor growth reversal (28 days).

and oxygen supply (blood flow); to simplify the model, a single death rate constant (k_4) was chosen. The second mechanism is the rate of killing replicating (R) cells by NovoTTF Therapy, which is represented by a rate constant k_3. The dead cells are removed from the vascular layer of the tumor (at least in part via phagocytosis[28]) by transferring them into a virtual fourth compartment with a rate constant k_5 (Figure 1).

Assuming the tumor to be a perfect sphere with a radius r, we limited cell replication and clearance to a vascular circumferential layer of a constant width Δr, while natural cell death is limited to the avascular core with a radius of $r - \Delta r$. Thus, the apparent kinetic constants k_1 and k_5 decrease as tumor volume increases and k_4 increases. This can be represented mathematically as:

$$k_1 = \frac{(r^3-(r-\Delta r)^3)}{r^3}\cdot k_1' \quad k_5 = \frac{(r^3-(r-\Delta r)^3)}{r^3}\cdot k_5'$$

$$k_4 = 1-\left(\frac{(r^3-(r-\Delta r)^3)}{r^3}\right)\cdot k_4'$$

To solve the model by iteration, these equations were used:

$$R(t) = RR * R(t-1) \quad (1)$$

$$R(t+1) = R(t) - k_3 * R(t) - k_2 * R(t) + k_1 * L(t) \quad (2)$$

$$L(t+1) = L(t) - k_1 * L(t) - k_4 * L(t) + k_2 * R(t) \quad (3)$$

$$D(t+1) = D(t) + k_3 * R(t) + k_4 * L(t) - k_5 * D(t) \quad (4)$$

$$C(t+1) = C(t) + k_5 * D(t) \quad (5)$$

$$Tumor\ Volume\ (t) = L(t) + R(t) + D(t) \quad (6)$$

$$r(t) = \sqrt[3]{\frac{3}{4\cdot\pi}\cdot TumorVolume(t)} \quad (7)$$

RR = replication rate.

RESULTS

Patient Characteristics and Tumor Responses

In this analysis, we examined a total of 130 patients with recurrent GBM receiving NovoTTF Therapy as monotherapy: 10 from the pilot study and 120 from the phase III trial. In the pilot study, a 20% radiologic response rate was reported (2 of 10 patients); in the phase III trial, a 14% radiologic response rate was reported (14 of 100). Thus, across both trials, a total of 16 responders (of which four had durable complete responses) were reported out of the 110 patients with baseline and at least one follow-up MRI (15% response rate, 4% complete response rate). Responders to NovoTTF Therapy had similar baseline characteristics as the rest of the population in the two clinical trials

Table 1. Baseline Characteristics for Recurrent GBM Patients Treated With NovoTTF Therapy in the Phase III and Pilot Studies and for Responders Across the Two Studies

Characteristic	Phase III NovoTTF Therapy Patients (n = 120)	Pilot Trial NovoTTF Therapy Patients (n = 10)	Responders to NovoTTF Therapy (n = 16)
Age, years Median (range)	54 (24–80)	53 (28–68)	53.5 (36–75)
KPS, median (range)	80 (50–100)	90 (70–100)	90 (70–100)
Gender, % male	77%	70%	88%
Tumor area, cm^2 Median (range)	14.4 (0.7–64.3)	NA	10.0 (1.3–24.9)
Prior bevacizumab (%)	19%	0%	6%
Prior low grade (%)	8%	10%	31%
Prior lines of therapy Median (range)	2 (1–5)	1 (1–3)	2 (1–3)
Patients at first recurrence, %	9%	50%	19%
RT/TMZ at initial diagnosis, %	83%	80%	100%
TMZ cycles Median (range)	4 (0–19)	NA	5 (0–12)

Abbreviations: KPS, Karnofsky performance status; RT, radiotherapy; TMZ, temozolomide.

(Table 1). Some of the baseline prognostic characteristics appeared more favorable in responders than nonresponders, including higher KPS (90 *v* 80), fewer prior bevacizumab treatments (6% *v* 19%), more patients with secondary GBM that were transformed from prior low-grade gliomas (31% *v* 8%), and smaller median tumor size (10.0 cm^2 *v* 14.4 cm^2). These differences were not statistically significant in comparison with the general study populations (multivariate analysis of variance, $P > .05$). As both trials included only patients with recurrent GBM, biopsy at recurrence was not required, and genetic analysis of tumor tissue was not routinely performed.

Response Patterns

Figures 2 to 4 show exemplary T1-weighted MRI scans of responders to NovoTTF Therapy. With respect to response patterns, the most prominent findings were that tumor responses to NovoTTF Therapy developed relatively slowly but in most cases were durable. As seen in Figure 5, the median time to objective radiographic response in the 16 patients was 5.2 months (95% CI, 3.2–7.6 months). The median response duration in these patients was 12.9 months (95% CI, 2.1–not available [NA] months). Twelve of the 16 responders (75%) had durable responses lasting longer than 12 months. Also, response duration was highly correlated with OS ($r^2 = .97$, $P < .0001$). Median OS for responders was 26.5 months (95% CI, 17.1–NA months).

Delayed Response

Of note, for seven of the 16 responders (44%), MRI showed the initial tumor growth. An exemplary MRI of such a delayed responder can be found in Figure 6. Median time to reversal of tumor growth in delayed

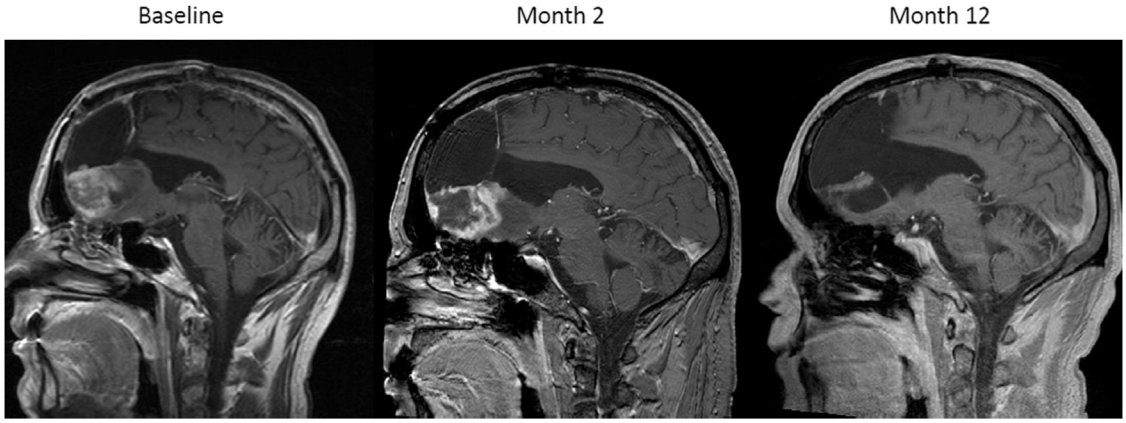

Figure 2. Exemplary T1-weighted images after contrast agent administration of a 48-year-old male with prior grade II astrocytoma, which transformed to glioblastoma (based on tissue biopsy). The subject progressed after receiving chemoradiotherapy and adjuvant temozolomide (3 courses) and subsequently responded to NovoTTF Therapy (PR at 12 months) and remained stable for an additional 20 months on TTFields.

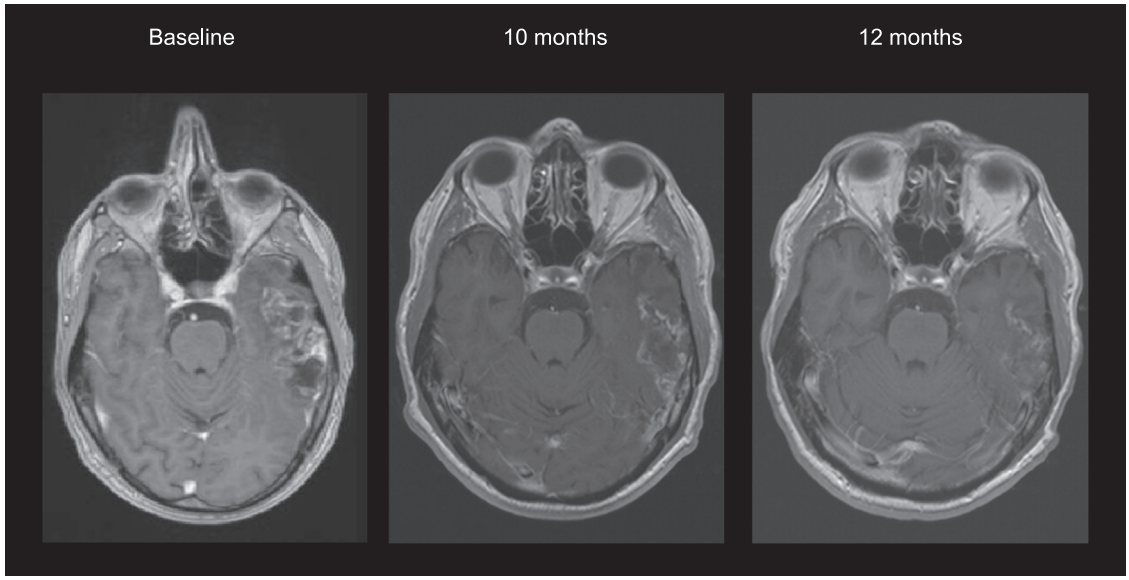

Figure 3. Exemplary T1 images after contrast agent administration of a 51-year-old male with primary GBM who recurred 6 months after chemo-radiation with temozolomide. The patient never underwent surgery (biopsy only). He had a very gradual response, reaching a 50% reduction in tumor size after 10 months on NovoTTF Therapy. He remained stable for an additional 2 months on NovoTTF Therapy.

responders was four months (95% CI, 2.3–7.4 months). The initial tumor growth was accompanied by an increase in T2-weighted and/or FLAIR signal in five of these seven delayed responders (71%; see Figure 6). Diffusion-weighted imaging in three of the seven delayed responders did not demonstrate a diffusion-weighted signal increase in the first 4 months after treatment initiation. The averaged maximal tumor area over time compared to baseline in the delayed responders is shown in Figure 7.

Compliance Versus Response and Survival

Compliance and Kaplan-Meier estimates of median OS were compared in patients with complete responses, partial responses, stable disease,

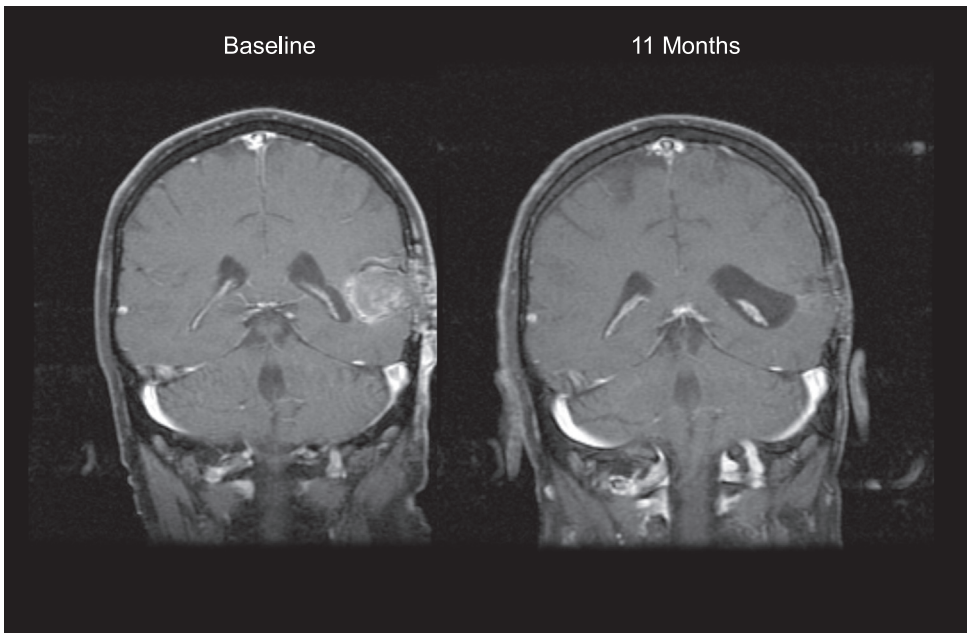

Figure 4. Exemplary T1-weighted images after contrast agent administration of a 55-year-old male with primary GBM who recurred for the third time after receiving chemoradiotherapy, adjuvant temozolomide (2 cycles), bevacizumab with irinotecan (3 months) and erlotinib with sorafenib (one cycle). The subject had a partial response to NovoTTF Therapy after 4 months of treatment and remained stable for an additional 8 months while on NovoTTF Therapy.

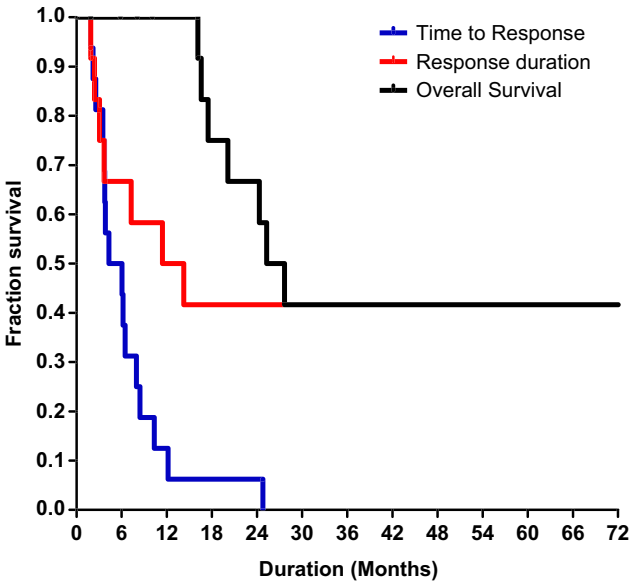

Figure 5. Kaplan Meier curves of the time to radiological response according to Macdonald criteria (blue line), response duration (red line), and overall survival (black line) of the 16 responders from the two clinical trials.

and progressive disease. As seen in Table 2, an increase in compliance was associated with better response to treatment and longer OS. The extent of response from treatment (PR+CR, SD, PD, and NA) was also significantly dependent on compliance (ANOVA $P < .001$, Figure 8).

Kinetic Modeling of Delayed Responses

Tumor growth kinetics were studied by means of a multicompartment model. The model reflects the balance between the changes occurring in the number of dormant and replicating cells, on the one hand, and cells that die "naturally" or as a result of TTFields treatment (Figure 1A). The rate constants when cells shift from one compartment to the other, and the replication rate and other parameters used in the numerical solution, were derived from published data (Table 3). The model predicts that, when GBM tumors are continuously exposed to TTFields, they will cease to increase in size and begin to shrink only after 4 weeks of continuous TTFields exposure (Figure 1B). This behavior is consistent with the data presented above for the seven patients with delayed response to NovoTTF Therapy (Figure 7).[12,25,27,29–31]

DISCUSSION

NovoTTF Therapy is new antimitotic treatment that kills or arrests the growth of recurrent GBM tumors by delivering TTFields that disrupt mitotic spindle formation during metaphase to anaphase transition and by potentiating aberrant dielectrophoretic movement of intracellular macromolecules and organelles during anaphase and telophase, resulting in chromosome missegregation and cell death.[16,32] Because of this unique mechanism of action, NovoTTF Therapy is selective for dividing cells and requires continuous application for maximal benefit.

We report here that 15% of patients with recurrent GBM tumors responded to NovoTTF Therapy with a complete or partial radiological response, and that these responses typically developed slowly (median time to response, 5.2 months) and are in most cases durable (median duration, 12.9 months). By way of comparison, only 9.6% of patients treated with best active chemotherapy in the phase III trial exhibited an objective radiological response (seven partial responses v 3 complete and 11 partial responses in the NovoTTF Therapy cohort).[15] Moreover, a response assessment of the phase III trial data by Wong et al showed that response duration was highly correlated with OS in the NovoTTF Therapy cohort (r^2=0.92, $P < .0001$), but not in the best active chemotherapy cohort (r^2=0.06, P=.6226).[33] The current analyses also demonstrated that roughly half (44%) of the GBM tumors responding to NovoTTF Therapy initially exhibit growth on MRI, before reversing and shrinking in size 2 to 7 months (median, 4 months) later with continuous therapy. Therefore, these results suggest that NovoTTF Therapy effects a response slowly, and when it occurs, the response is often durable.

To better characterize our observation on tumor shrinkage induced by NovoTTF Therapy, we constructed a kinetic model based on the states of cells, between latency and replication as well as their progression to death and clearance, within the tumor microenvironment. Using rate constants obtained from published literature, we were able to construct a tumor volume kinetics curve that showed a doubling of the baseline tumor volume at 4 weeks before a reduction approximating a two-dimensional reduction in the tumor measurement near 7 months. This kinetics closely approximate our observed time to GBM shrinkage in patients as shown in Figure 7, in which there was an initial increase in tumor size that constitutes progressive disease, and tumor shrinkage that qualifies for a partial response did not occur until >8 months after NovoTTF Therapy. Therefore, these results from the kinetics model help to better characterize tumor response to NovoTTF Therapy, which predicts GBM tumors will cease to grow and start to shrink only after at least several weeks of continuous TTFields exposure. However, objective tumor response may not occur until at least 7 to 8 months later.

The current study provides an association between patient outcomes and treatment compliance with

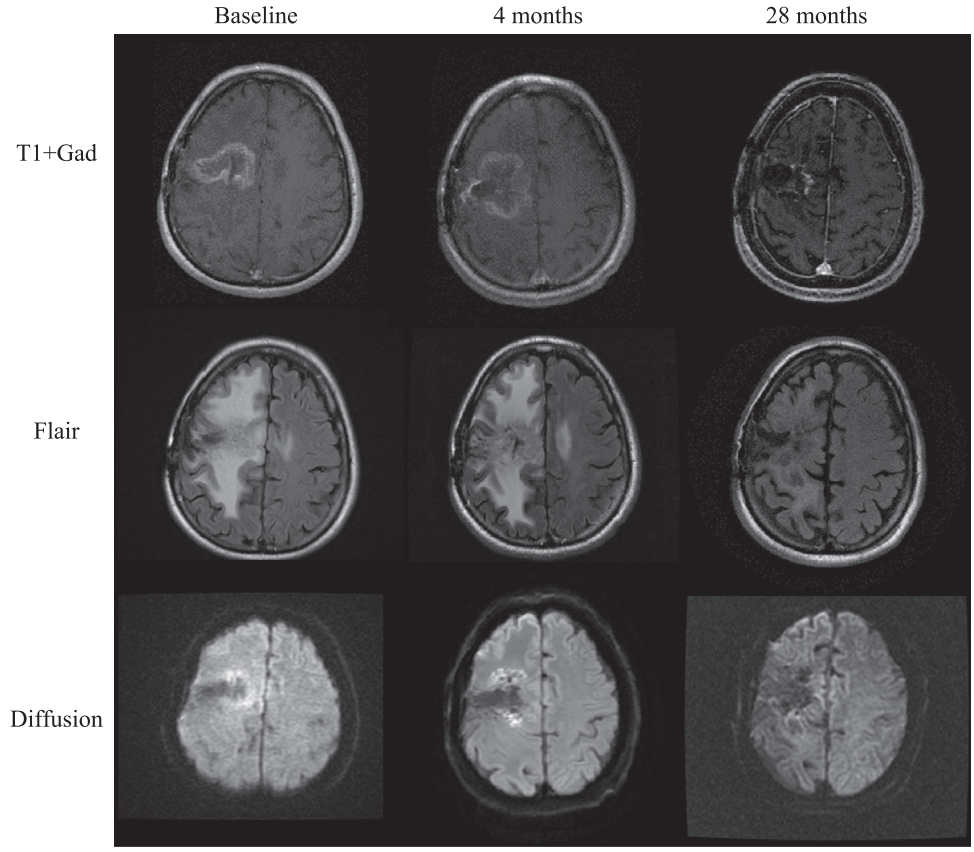

Figure 6. Exemplary T1-weighted images after contrast agent administration with their corresponding FLAIR and Diffusion MRI scans of a heavily pretreated 48-year-old man with secondary GBM. The patient underwent three debulking surgeries, chemo-radiation with temozolomide, and gamma knife boost. The patient's tumor showed heterozygous deletions of 1p and 19q and was MGMT promoter methylated. The patient was treated with NovoTTF Therapy for 28 months until radiological response was achieved and has been on treatment since (for 45 months so far). Notably, the patient's tumor grew for the first 8 months on NovoTTF Therapy and only then started to decrease in size. Additional MRI sequences show that while the tumor was growing initially, this was accompanied by an increase in FLAIR signal, but not in diffusion signal.

NovoTTF Therapy. Our data show that the likelihood of a radiological response increases with increased compliance with NovoTTF Therapy, ie, the closer the patient comes to "continuous" application of TTFields, and that responders have a longer median OS than nonresponders (24.7 months for responders *v* 7.6 and

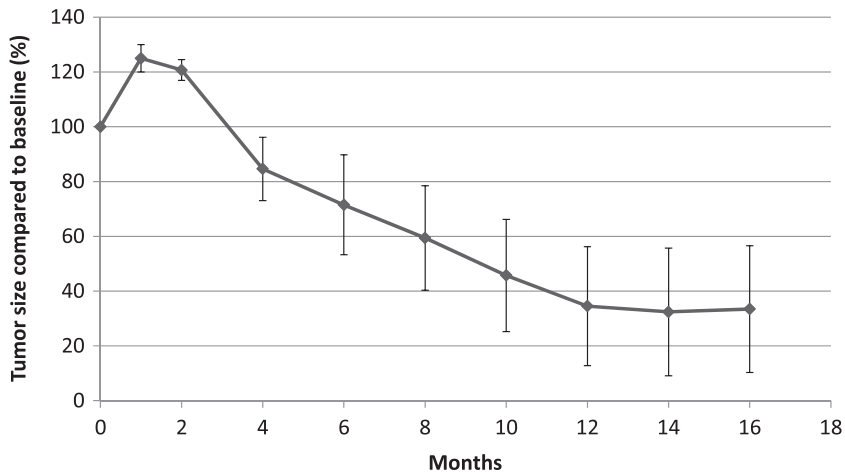

Figure 7. Time course of normalized tumor size in the seven delayed responders to NovoTTF Therapy. Data are presented as average tumor area ± standard deviation normalized to baseline (pretreatment) tumor area.

Table 2. Response, Median Overall Survival, and Compliance With NovoTTF Therapy in the Phase III Trial

Response	Median OS (mo)	Average Compliance (average % per 24 h)	n	Comparison to Responders (PR+CR) Hazard Ratio (95% CI)	Comparison to Responders (PR+CR) Log Rank *P* Value
PR and CR	24.7	92	14		
SD	7.6	85	34	0.28 (0.14–0.58)	.0006
PD	5.5	79	59	0.24 (0.14–0.42)	<.0001
No follow-up MRI (NA)	2.4	60	13	0.08 (0.02–0.26)	<.0001
All patients	6.6	83	120		

Abbreviations: OS, overall survival; CI, confidence interval; PR, partial response; CR, complete response; SD, stable disease; PD, progressive disease.

5.5 months for patients with stable disease or progressive disease, respectively). These compliance data are consistent with those reported by Kanner and colleagues (corresponding article in this supplement), which show significantly longer median OS in NovoTTF Therapy-treated recurrent GBM patients with a maximal monthly compliance rate of ≥75% versus <75% (7.7 *v* 4.5 months, *P*=.042). Kanner et al also report a significant trend for improved median OS with stepwise increases in compliance (5.8, 6.0, and 7.7 months for <60%, 60%–79%, and 80%–99% compliance, respectively; *P*=.039).

A number of recurrent GBM patients with delayed and durable responses from NovoTTF Therapy have been described.[17,18] Villano et al recently presented in detail the case of a 48-year-old man with recurrent GBM who received NovoTTF Therapy during the phase III trial. His tumor response pattern was characterized by a slow but continuous increase in tumor size over 10 months, followed by a period of stabilization and then partial response that lasted for another 4 years. Notably, this patient survived more than 6 years from the time of initiation of NovoTTF Therapy.[17] Similarly, Rulseh et al also reported delayed responses in two patients that occurred 5 and 7 months from NovoTTF Therapy initiation, and they lived 6 and 5 years thereafter, respectively.[18] These two patients are still alive, currently 10 years after their initial diagnosis. Taken together, these cases suggest that certain patients respond to NovoTTF Therapy only after a delay, but once they respond, the response is durable.

Another important question that remains to be answered is if patients who eventually respond to NovoTTF Therapy can be identified by their clinical or tumor characteristics. Kanner et al performed a number of post hoc analyses of the phase III trial data, identifying prior failure of bevacizumab therapy, prior low-grade glioma, and tumor size ≥18 cm^2 as potentially relevant variables for further study. Examination of baseline patient characteristics in the present study highlighted a number of variables possibly linked with tumor response (and, by extension, OS) that might be worthy of further study, including higher KPS, prior bevacizumab therapy, and prior low-grade glioma. Lower cumulative dexamethasone dose has also been

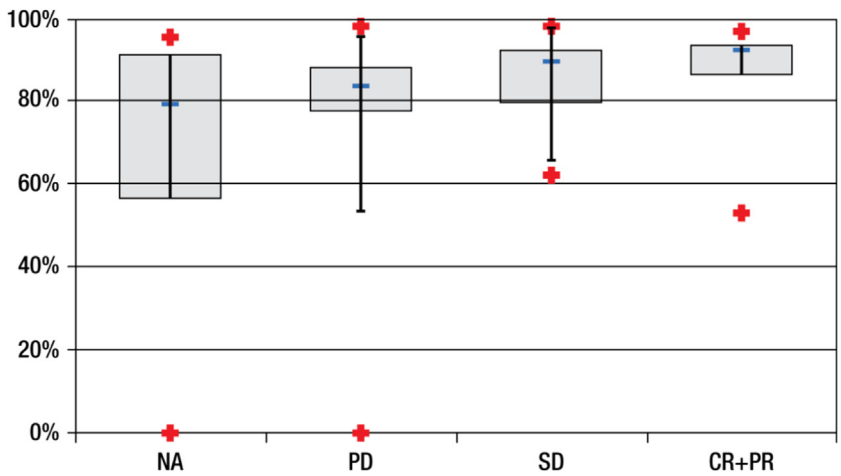

Figure 8. ANOVA analysis of the extent of response is significantly different among the four major groups, PR+CR, SD, PD, and NA (*P* <.001).

Table 3. Comparison of Literature and Model Kinetic Parameters

Parameter	Model	Literature	Reference
RR	× 1.29 / d	× 1–2 / d	Hoshino, 1992[27]
K_1	0.28 / d	0.18–0.40	Chiesa-Vottero et al, 2003[28]
K_2	0.48 / d	Calculated	Calculated to maintain R/L = K_1
K_3	0.50 / d	0.40–0.60	Kirson et al, 2007[14]
K_4	0.022 / d	0.034 ± 0.022	Mizoguchi et al, 2000[32]
K_5	0.007 / d	(0.016 – 0.26) / d	Gong et al, 1999[31]
Δr	0.20	Estimated	Chen et al, 2006[30]

Abbreviations: RR, replication rate; K1 and K2, forward and reverse rate constants of cells between latency and replication; K3, rate constant for killing replicating cells by TTFields; K4, single rate constant for killing replicating cells; K5, rate constant for removal of dead cells from vascular layer of tumor; Δr, wide of vascular circumferential layer where tumor cell replication and clearance occur.

linked with response to NovoTTF Therapy in recurrent GBM.[33] Therefore, by identifying patients for whom NovoTTF Therapy might provide long-term survival benefit would be potential means of providing them personalized therapy. In addition, compliance has been linked not only in this study but also in the ones by Kanner et al and Mrugala et al (current supplement) with improved median OS. The present study also associated NovoTTF Therapy compliance with increased likelihood of achieving a tumor response, and tumor response—and particularly response duration—was correlated with OS. Since compliance and dexamethasone are modifiable variables, these hypotheses can be readily tested in future clinical trials.

In summary, NovoTTF Therapy represents a novel treatment option for patients with recurrent GBM. About 15% of patients experience slowly developing but durable tumor responses, a number of which have now been linked with survival of 7 years or longer. Tumor responses develop gradually and initial tumor growth may even be observed in eventual responders to NovoTTF Therapy. In addition, compliance has been linked with increased likelihood of tumor response and improved OS. Taken together, these results suggest physicians should impress the importance of compliance upon their patients receiving NovoTTF Therapy, and should not rely solely on early radiographic changes as a reason for discontinuing treatment.

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