Clinical Practice Experience With NovoTTF-100A™ System for Glioblastoma: The Patient Registry Dataset (PRiDe)

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Recurrent glioblastoma multiforme (GBM) is a highly aggressive cancer with poor prognosis, and an overall survival of 6 to 7 months with optimal therapies. The NovoTTF-100A™ System is a novel antimitotic cancer therapy recently approved for the treatment of recurrent GBM, based on phase III (EF-11) trial results. The Patient Registry Dataset (PRiDe) is a post-marketing registry of all recurrent GBM patients who received NovoTTF Therapy in a real-world, clinical practice setting in the United States between 2011 and 2013. Data were collected from all adult patients with recurrent GBM who began commercial NovoTTF Therapy in the United States between October 2011 and November 2013. All patients provided written consent before treatment was started. Overall survival (OS) curves were constructed for PRiDe using the Kaplan-Meier method. Median OS in PRiDe was compared for patients stratified by average daily compliance ($\geq$75% *v* <75% per day) and other prognostic variables. Adverse events were also evaluated. Data from 457 recurrent GBM patients who received NovoTTF Therapy in 91 US cancer centers were analyzed. More patients in PRiDe than the EF-11 trial received NovoTTF Therapy for first recurrence (33% *v* 9%) and had received prior bevacizumab therapy (55.1% *v* 19%). Median OS was significantly longer with NovoTTF Therapy in clinical practice (PRiDe data set) than in the EF-11 trial (9.6 *v* 6.6 months; HR, 0.66; 95% CI, 0.05 to 0.86, $P = .0003$). One- and 2-year OS rates were more than double for NovoTTF Therapy patients in PRiDe than in the EF-11 trial (1-year: 44% *v* 20%; 2-year: 30% *v* 9%). First and second versus third and subsequent recurrences, high Karnofsky performance status (KPS), and no prior bevacizumab use were favorable prognostic factors. No unexpected adverse events were detected in PRiDe.

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As in the EF-11 trial, the most frequent adverse events were mild to moderate skin reactions associated with application of the NovoTTF Therapy transducer arrays. Results from PRiDe, together with those previously reported in the EF-11 trial, indicate that NovoTTF Therapy offers clinical benefit to patients with recurrent GBM. NovoTTF Therapy has high patient tolerability and favorable safety profile in the real-world, clinical practice setting.
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Glioblastoma multiforme (GBM) is the most aggressive form of human glioma and accounts for approximately 60% to 70% of all malignant gliomas.[1,2] Based on data from the 2013 Central Brain Tumor Registry of the United States (CBTRUS) statistical report on primary brain and CNS tumors in the United States, an estimated 9,600 to 11,200 new cases of GBM will be diagnosed in 2014.[1,2] Virtually all patients with newly diagnosed GBM relapse despite maximal multimodality treatment,[3] with a median time to recurrence of approximately 7 months.[4] The prognosis for patients with recurrent GBM is even worse. The median progression-free survival (PFS) was only 9 weeks in the pre-bevacizumab era.[5] In 2009, bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment for recurrent GBM based on two single-arm studies with favorable response rates and PFS data.[1,6,7] Formal phase III data is not available in the recurrent setting, however phase III comparison of bevacizumab versus placebo in newly diagnosed glioblastoma patients failed to demonstrate prolongation of survival with bevacizumab.[1,8] A major challenge in treatment of recurrent GBM, particularly with bevacizumab, is that the tumor eventually develops resistance to the drug. Moreover, bevacizumab-treated tumors may convert to a more aggressive phenotype and exhibit infiltrative tumor growth as observed on magnetic resonance imaging (MRI).[9,10] Furthermore, patients with recurrent GBM who progress following bevacizumab therapy are typically resistant to subsequent cytotoxic chemotherapies.[1,11,12] Therefore, new treatments that can offer a different mechanism of action and potentially overcome treatment resistance are desperately needed.

The NovoTTF-100A™ System (Novocure, Ltd., Haifa, Israel) is a novel antimitotic cancer therapy approved in 2011 by the US FDA for the treatment of recurrent supratentorial GBM,[13,14] based on the results of a phase III trial comparing NovoTTF Therapy with best chemotherapy according to physician choice.[15] The unique mechanism of action of NovoTTF Therapy involves localized delivery of alternating low-intensity, intermediate-frequency, tumor-treating fields (TTFields) via non-invasive transducer arrays attached to the patient's scalp.[14] In preclinical studies, TTFields have been shown to selectively kill or arrest the growth of rapidly dividing cancer cells including glioblastoma cell lines by disrupting both mitotic spindle formation and normal cytokinesis by interrupting cytoplasmic furrow formation.[16–20]

The pivotal phase III (EF-11) trial that led to FDA approval of the device compared NovoTTF Therapy (n = 120) with best chemotherapy according to physician's choice (n = 117) in recurrent GBM patients from 28 institutions in seven countries.[15] More than 80% of patients in the study had failed two or more prior chemotherapies, and 20% had experienced recurrence while on bevacizumab. Seventy-eight percent of the 116 patients who started NovoTTF Therapy completed at least one full-treatment course (4 weeks). The results demonstrated comparable median OS with NovoTTF Therapy compared with chemotherapy (6.6 *v* 6.0 months; hazard ratio [HR], 0.86; 95% confidence interval [CI], 0.66 to 1.12; $P = .27$), together with fewer severe adverse events (6% *v* 16%, $P = .022$) and improved quality-of-life measures for the NovoTTF Therapy arm compared with the chemotherapy arm. The most common adverse events with NovoTTF Therapy were mild to moderate skin irritation associated with the transducer arrays. Systemic adverse events commonly associated with chemotherapy were generally absent in patients receiving NovoTTF Therapy.

Given the mechanism of action of TTFields and the results of preclinical studies, optimal device compliance is required for therapeutic effectiveness with NovoTTF Therapy. NovoTTF Therapy does not have a half-life, therefore it requires continuous application to exert a therapeutic effect. This differs from systemic chemotherapy, which exerts anticancer effects between administrations due to the drug pharmacokinetics. Based on modeling of tumor growth kinetics and supporting preclinical and clinical data, NovoTTF Therapy must be administered almost "continuously" for at least 4 weeks in order to halt tumor growth and subsequently demonstrate an objective response.[21,22] Recommended administration of NovoTTF Therapy

is ≥18 hours per day for each 4-week treatment cycle.[21] A post hoc analysis of the phase III trial data recently showed significantly longer median OS in NovoTTF Therapy patients with a maximal monthly compliance rate ≥75% (≥18 hours daily) versus those with a <75% compliance rate (7.7 *v* 4.5 months, $P = .042$) (see Kanner et al in this supplement). A recent responder analysis also demonstrated very high compliance rates >90% in EF-11 responders.[23]

The Patient Registry Dataset (PRiDe) is a registry of 457 recurrent GBM patients who received NovoTTF Therapy in the clinical practice setting on the US commercial prescription-use program between October 2011 and November 2013. Patients treated in clinical trials often differ from those who receive treatment in the real-world setting due to patient selection criteria and frequently represent a less homogenous group. Hence registry data can be an important source of additional information about the efficacy and safety of a newly approved therapy. This report analyzes data from PRiDe to help us better understand the potential benefits of NovoTTF Therapy for patients with recurrent GBM, including analyses of median OS, tolerability, and the relationship between survival and compliance as well as other prognostic factors.

METHODS

Patients and Data Collection

PRiDe data were collected from all patients ≥18 years old with recurrent GBM who began commercial treatment with NovoTTF Therapy in the United States between October 2011 and November 2013. All participating patients provided written informed consent to use protected health information to advance the understanding of NovoTTF Therapy. Recurrent GBM was defined as histologically-confirmed, supratentorial GBM (World Health Organization grade IV astrocytoma) with radiologically confirmed evidence of disease progression, as defined by the Macdonald criteria,[24] following treatment with radiotherapy with or without concomitant and/or adjuvant chemotherapy. Patients who received NovoTTF Therapy were not restricted to the number or types of prior therapies or recurrences. Information about combination use of NovoTTF Therapy as part of the prescription-use program was not captured. Therefore some patients may have received combination therapy (chemotherapy or anti-vascular endothelial growth factor [VEGF] agents) rather than monotherapy.

Baseline characteristics were assessed by manual patient chart review. OS was collected using the Social Security Death Date Registry and obituaries. Novocure started collecting compliance data centrally in January 2013, so such data are only available for under two thirds of patients in the registry. A monthly compliance assessment was performed for each patient by computer download of an internal log file which captures the cumulative amount of time therapy is delivered to the patient. Patient compliance was calculated as the average percentage of each day the system was delivering fields (out of each 24-hour period). In addition, other prognostic factors, such as the number of prior recurrences, age, KPS, prior bevacizumab use, and any debulking surgery were captured and analyzed. Adverse events were recorded prospectively according to National Cancer Institute Common Toxicity Criteria. Quality-of-life measures were not assessed in PRiDe.

Statistical Analysis

The OS and treatment duration curves were constructed using the Kaplan-Meier method. OS in PRiDe was compared to OS for patients receiving NovoTTF Therapy or best chemotherapy in the phase III EF-11 trial (ITT population) using a log-rank (Mantel-Cox) test. Patient or disease characteristics prognostic for survival with NovoTTF Therapy were assessed using a Cox proportional hazards model (P value of .15 for significant interactions). Subgroup analyses were performed on patient/clinical characteristics found to be significantly correlated with OS. A log-rank test was used to compare the relationship between OS and daily compliance (<75% *v* ≥75%), prior debulking surgery (yes, no), KPS (90–100, 70–80, 10–60), recurrence number (1st, 2nd, 3rd–5th recurrence) and prior bevacizumab use (prior use *v* naïve).

RESULTS

Patient Characteristics

Four-hundred fifty-seven patients with recurrent GBM were treated with NovoTTF Therapy between October 2011 and November 2013 at 91 oncology centers. This population is more than three times the 120 subjects treated with NovoTTF monotherapy, as well as the 117 subjects treated with chemotherapy, in the phase III EF-11 trial, from which we were making a comparison. Baseline patient characteristics are presented in Table 1. Patient characteristics (age and gender) were generally similar in PRiDe and the two treatment groups in the EF-11 trial. Approximately one third of patients treated commercially with NovoTTF Therapy were women, which is an important observation given the perceived cosmetic considerations of head shaving and array placement.

Table 1. Baseline Patient Characteristics in PRiDe and EF-11 Trial

Characteristic		PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
Age (y)	Median (range)	55 (18–86)	54 (24–80)	54 (29–74)
Gender	Male	67.6%	77%	62%
	Female	32.4%	23%	38%
KPS	Median (range)	80 (10–100)	80 (50–100)	80 (50–100)
	10–60	19.0%	NA	NA
	70–80	46.6%	NA	NA
	90–100	30.9%	NA	NA
	Unknown	3.5%	NA	NA
Recurrence	Median (range)	2 (1–5)	2 (1–5)	2 (1–4)
	First	33.3%	9%	15%
	Second	26.9%	48%	46%
	Third to Fifth	27.4%	43%	39%
	Unknown	12.5%	0%	0%
Prior treatments	Bevacizumab	55.1%	19%	18%
	RT + temozolomide	77.9%	86%	82%
	Debulking surgery	63.9%	79%	85%
	Carmustine wafers	3.7%	NA	NA

Abbreviations. KPS, Karnofsky performance status; NA, not available; RT, radiotherapy.

Tolerability and Safety

No new adverse events were detected in PRiDe compared to those found in EF-11. The most common device-related adverse events associated with NovoTTF Therapy in the registry were skin reactions/irritation and heat sensations on the scalp beneath the transducer arrays (Table 2). Patients sometimes described these events as "warmth" or "tingling" sensations, none of which were associated with injury to the patient. Systemic adverse events, which were often associated with chemotherapy (eg, gastrointestinal, hematologic, and infectious adverse events), were rare for patients treated with NovoTTF Therapy in the registry.

Survival Rates

Figure 1 presents Kaplan-Meier curves of OS for patients treated with NovoTTF Therapy in the clinical practice setting (PRiDe) and those who received NovoTTF Therapy or best chemotherapy as part of the EF-11 trial (ITT population; see Kanner et al in current supplement). Median OS on NovoTTF Therapy appeared to be markedly longer in PRiDe than in the EF-11 trial (9.6 *v* 6.6 months). Median OS was also significantly longer with NovoTTF Therapy in PRiDe than with best chemotherapy group in the EF-11 trial (9.6 *v* 6.0 months). One- and 2-year OS rates for NovoTTF Therapy patients in PRiDe were more than double those seen with either NovoTTF Therapy or best chemotherapy in the EF-11 trial (Table 3).[15,25]

Median treatment duration for patients in PRiDe was 4.1 months (95% CI, 3.5–4.8). In comparison, the median treatment duration in the EF-11 study was 2.3 months (95% CI, 2.1– 2.4) for NovoTTF Therapy arm and 2.1 months (95% CI, 2.0–2.9) for best chemotherapy. Figure 2 shows the fraction of NovoTTF Therapy patients still on treatment over time. Roughly 50% were still on NovoTTF Therapy after 4 months from treatment start, and roughly 10% were still on NovoTTF Therapy at 2 years after treatment start.

Compliance as a Prognostic Factor and Its Relationship to OS

Because of the major difference in the OS in patients registered in PRiDe as compared to the OS of subjects treated with NovoTTF monotherapy in EF-11, we sought to identify the prognostic factors in the former cohort. The first prognostic factor we analyzed was NovoTTF treatment compliance because it was found to be prognostically important in EF-11 in a post hoc analysis. Compliance data were collected centrally starting in January 2013 and, therefore, were only available for 287 of the 457 patients (63%) in the registry. The median daily compliance was 70% for patients treated with NovoTTF Therapy in PRiDe (range, 12%–99%). One

Table 2. Adverse Events in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe

Adverse event	Percentage of Patients PRiDe (n = 457)
Skin reaction	24.3
Heat sensation	11.3
Neurological disorder	10.4
Seizure	8.9
Electric sensation	7.7
Headache	5.7
Pain/discomfort	4.7
Fall	3.9
Psychiatric disorder	2.9
Gastrointestinal disorder	2.9
Fatigue	2.5
Vascular disorder	1.6
Weakness	1.4
Infections	1.4
Eye disorder	1.3

hundred twenty-seven (44%) achieved daily compliance of ≥75% of each day, while 160 (56%) had daily compliance of <75%. As illustrated in Figure 3, median OS was significantly longer in patients with a NovoTTF Therapy daily compliance ≥75% than in those with <75% daily compliance (13.5% *v* 4.0%; HR, 0.43; 95% CI, 0.29–0.63; $P < .0001$).

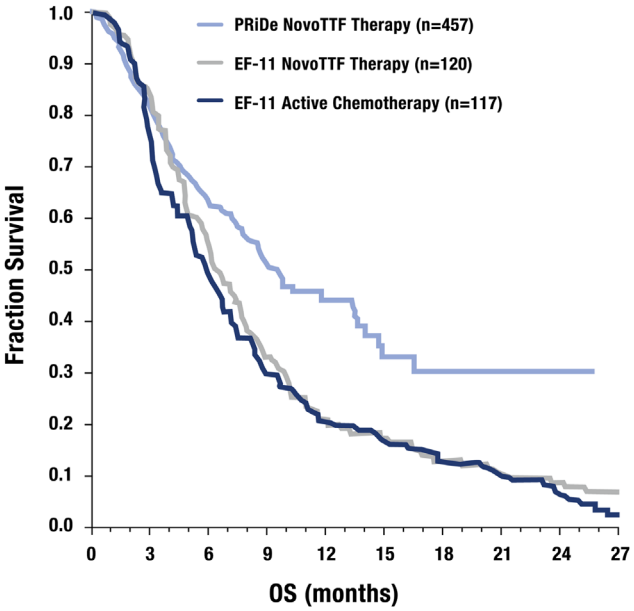

Figure 1. Kaplan-Meier overall survival (OS) curves for patients with recurrent glioblastoma multiforme treated with NovoTTF Therapy in PRiDe or with NovoTTF Therapy or best chemotherapy in the EF-11 trial ($P = .0003$).

Other Prognostic Factors

The Cox proportional hazards model identified the presence or absence of debulking surgery, number of prior recurrences, compliance, KPS, and prior bevacizumab therapy as significant independent predictors of OS in patients treated with NovoTTF Therapy in PRiDe ($P < .15$). Table 4 presents log-rank OS testing between patient subgroups in PRiDe for each of these prognostic factors; Figure 4 presents Kaplan-Meier survival curves for these same factors. First, no difference in median OS was observed between patients who did not have surgical debulking and those who did (8.9 *v* 9.8, respectively; HR, 1.1; 95% CI, 0.8–1.5; $P = .7927$). Second, recurrent GBM patients treated with NovoTTF Therapy in clinical practice at their first recurrence experienced a significantly longer median OS as compared to patients treated at their second, third, or subsequent recurrence (20 months compared to 8.5 and 4.9 months, respectively; HR, 0.6; 95% CI, 0.4–0.9; $P = 0.0271$ and HR, 0.3; 95% CI, 0.2–0.5; $P < .0001$). It should be noted that a greater percentage of patients in PRiDe were at their first GBM recurrence compared with patients treated with NovoTTF Therapy or best chemotherapy in the EF-11 trial (33.3% *v* 9% and 15%, respectively). In addition, differences were also apparent between patients in PRiDe and those in the EF-11 trial with respect to prior treatments. More than half of NovoTTF Therapy patients in PRiDe had previously received bevacizumab (55.1%), compared with only 19% of NovoTTF monotherapy and 18% of best active chemotherapy cohorts in the EF-11 trial. Third, recurrent GBM patients with KPS ≥90 exhibited a near doubling of median OS compared with patients with a KPS of 70–80, median OS 14.8 versus 7.7 months, respectively, HR 0.6 (95% CI, 0.4–0.9), $P = .0070$. Lastly, the survival of bevacizumab-naïve patients was significantly longer compared to patients who had received prior bevacizumab before starting NovoTTF Therapy, with a respective median OS 13.4 versus 7.2 months, HR 0.5 (95% CI, 0.4–0.7), $P < .0001$. These data suggest that, within this

Table 3. One- and 2-Year Overall Survival Rates for Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe and EF-11 Trial, and With Best Chemotherapy in the EF-11 Trial

Endpoint	PRiDe NovoTTF Therapy (n = 457)	EF-11 NovoTTF Therapy (n = 120)	EF-11 Chemotherapy (n = 117)
1-Year survival	44%	20%	20%
2-Year survival	30%	9%	7%

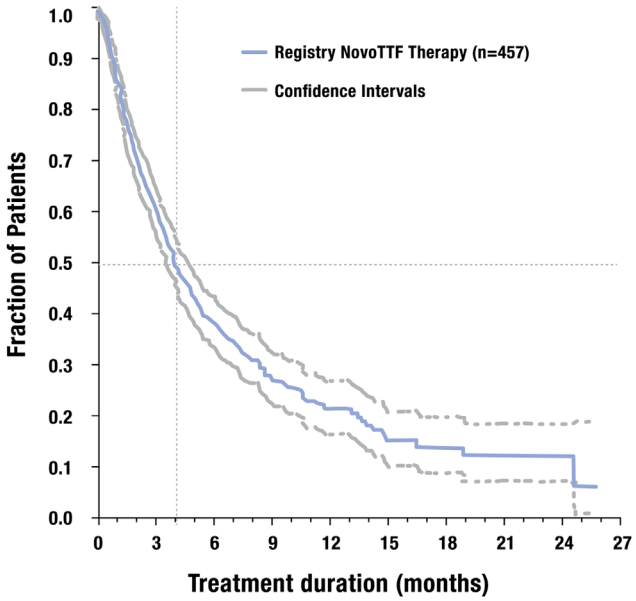

Figure 2. Fraction of NovoTTF Therapy patients alive by treatment duration (PRiDe).

heterogeneous group of patients registered in PRiDe, there were subsets of patients who derived significant benefit from NovoTTF Therapy.

DISCUSSION

The Patient Registry Dataset, or PRiDe, represents 457 unselected patients with recurrent GBM who received NovoTTF Therapy in a real-world, clinical practice setting across 91 cancer centers in the United States between October 2011 and November 2013. No new, unexpected adverse events were detected with NovoTTF Therapy in this cohort. Similar to the EF-11 trial,[15] the most common adverse events associated with NovoTTF Therapy were mild to moderate skin reactions localized to the scalp beneath the transducer arrays. These reactions were easily treated with topical corticosteroids or antibiotics, were not associated with serious injury to the scalp, and typically did not require interruption of treatment. Some patients in PRiDe reported subjective sensations beneath the transducer arrays, often described as "warmth" or "tingling." These heat or electric sensations were captured as adverse events in PRiDe ("skin reaction"), but not in the EF-11 trial. These sensations occur when the contact between transducer arrays and the skin is suboptimal, and usually indicate the presence of hair regrowth. In these instances, re-shaving the head can re-establish optimal contact between the skin and transducer arrays. Furthermore, systemic adverse events commonly observed with chemotherapy were largely absent in patients treated with NovoTTF Therapy in PRiDe as they were in the EF-11 trial.[15]

Patients receiving NovoTTF Therapy for recurrent GBM demonstrated a median OS of 9.6 months in clinical practice. This compares favorably to the reported median OS for the EF-11 pivotal trial cohort treated with NovoTTF monotherapy, where median OS was 6.6 months, and to OS of patients who received treatments for recurrent GBM in other clinical trials.[26–29] For example, recent reports of median OS in recurrent GBM patients treated with bevacizumab are in the range of 6 to 10.5 months,[7,12,26–28,30] and those treated with temozolomide in the range 6 to 9 months.[31–33] It should be noted that many of the longer term survival outcomes noted in clinical trials of bevacizumab and temozolomide in recurrent GBM included small sample sizes and none were randomized.

The difference between the OS seen in clinical practice and in the EF-11 trial may in part be due the greater percentage of patients with a first GBM recurrence in PRiDe versus patients in the EF-11 study (33.3% *v* 9%, respectively). This observation is also supported by a prior post hoc analysis of EF-11 that showed a significantly longer median OS in patients treated with NovoTTF Therapy at their first or second recurrence compared to those treated at third or subsequent recurrences. Furthermore, when used as intended (daily compliance $\geq$75% or $\geq$18 hours daily), the median OS for patients treated with NovoTTF Therapy in PRiDe was remarkably high at 13.5 months compared to only 4.0 months in those who had suboptimal compliance (daily compliance

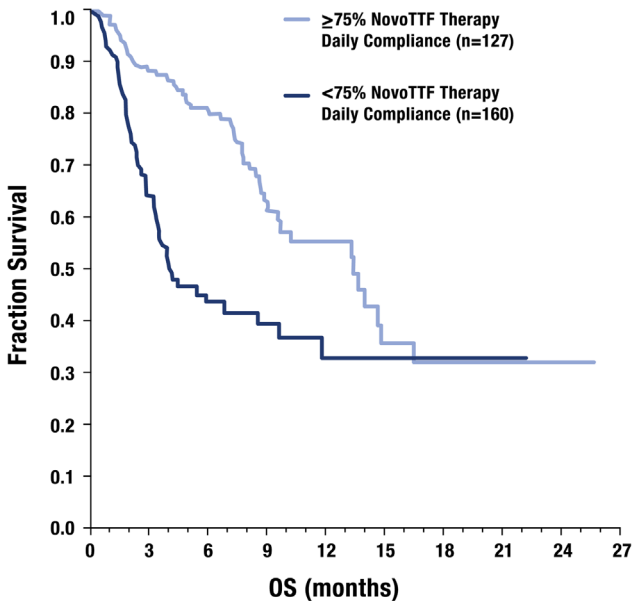

Figure 3. Overall survival (OS) by daily compliance with NovoTTF Therapy for recurrent glioblastoma multiforme patients in PRiDe.

Table 4. Overall Survival (OS) in Patients With Recurrent Glioblastoma Multiforme Treated With NovoTTF Therapy in PRiDe Based on Prognostic Factors Significantly Correlated With OS in the Cox Proportional Hazards

Variable	Median OS (mo)	Hazard Ratio	*P* Value
No. of recurrences			
1st	20	—	—
2nd	8.5	0.6 (95% CI, 0.4–0.9)	.0271[a]
3rd-5th	4.9	0.3 (95% CI, 0.2–0.5)	<.0001[b]
Compliance			
≥75%	13.5	0.4 (95% CI, 0.3–0.6)	<.0001
<75%	4.0		
Karnofsky performance status (KPS)			
90–100	14.8	—	—
70–90	7.7	0.6 (95% CI, 0.4–0.9)	.0070[c]
10–60	6.1	0.4 (95% CI, 0.2–0.6)	<.0001[d]
Bevacizumab use			
Naïve	13.4	0.5 (95% CI, 0.4–0.7)	<.0001
Prior use	7.2		
Debulking surgery			
No	8.9	1.1 (95% CI, 0.8–1.5)	.7927
Yes (any surgery)	9.8		

[a] First recurrence compared to 2nd recurrence.
[b] First recurrence compared to 3rd–5th recurrence.
[c] KPS 90–100 compared to KPS 70–80.
[d] KPS 90-100 compared to KPS 10–60.

<75% or <18 hours daily). Kanner et al (see accompanying Kanner article in this supplement) recently reported similar findings when re-examining data from the EF-11 trial: median OS was significantly longer with a monthly compliance rate for NovoTTF Therapy ≥75% than <75% (7.7 *v* 4.5 months, $P = .042$). The compliance findings from each of these studies are consistent with the mechanism of action of NovoTTF Therapy, which depends on almost continuous administration (≥18 hours per day) for a prolonged period of time (≥4 weeks).[21,22] However, patients in PRiDe who had suboptimal compliance were also found to have lower KPS and were, in general, at later stages of their disease. It is unclear whether they also may have had larger tumors or inadequate social support. Nevertheless, consistent with previous findings, our data suggest that applying NovoTTF Therapy to patients with higher performance status, earlier in their recurrence and ensuring treatment compliance, can maximize clinical benefit.

Additional analyses uncovered other prognostic factors that were important for patients in PRiDe. Of interest, in our subgroup analysis, 55.1% of patients in PRiDe who received prior bevacizumab therapy demonstrated a shorter median OS of 7.2 months, as compared to a median OS of 13.4 months in bevacizumab-naïve patients. The shorter survival in patients treated previously with bevacizumab may be a result of acquired tumor resistance and development of a more aggressive phenotype with infiltrative tumor progression on MRI.[9,10] Moreover, patients with recurrent GBM tumors that progress while on bevacizumab therapy are typically resistant or refractory to subsequent cytotoxic chemotherapy,[1,11,12] and have a median OS of just 2.7 months. Therefore, the PRiDe data suggest that at least a percentage of bevacizumab-resistant tumors remain responsive to NovoTTF Therapy. Future analysis of responders and nonresponders to NovoTTF Therapy will need to include molecular genetic analysis of the tumor (and especially MGMT methylation status), the estimated tumor size (volume) as measured by fluid attenuated inversion recovery sequence on MRI, and more detailed analysis of the extent of resection.

Our analysis of KPS in PRiDe also demonstrated that higher KPS correlated with longer OS. It is unclear at this time whether or not patients who had KPS 90–100 had smaller tumors than the rest of the cohort or perhaps more extensive resections. KPS is often, but not always, a measure of tumor size, particularly the microscopic invasive component of the glioblastoma. Whether or not the median tumor size, as measured by gadolinium-enhanced T1-weighted and/or FLAIR MRI, differ between the subgroup with KPS 90–100 versus 70–90 and 10–60 remains to be determined. Of note, age was not a predictor of OS in the PRiDe dataset when evaluated either by direct correlation (Pearson correlation coefficient) or a

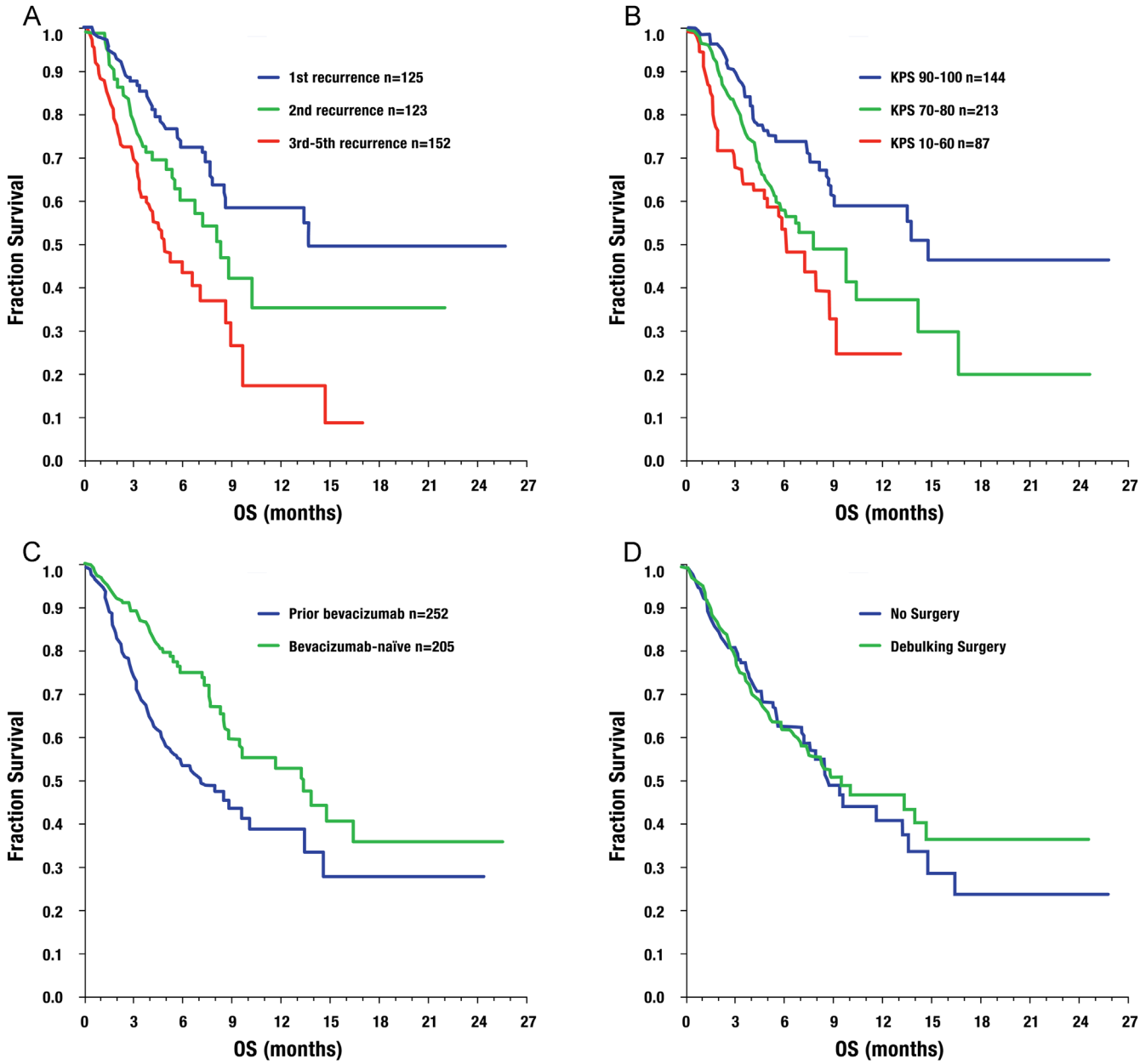

Figure 4. Kaplan-Meier overall survival (OS) curves for recurrent glioblastoma multiforme patients treated with NovoTTF Therapy in PRiDe based on (A) recurrence number, (B) Karnofsky performance status (KPS), (C) prior bevacizumab use, and (D) prior debulking surgery, respectively.

Cox proportional hazards model ($P = .20$). In addition, age was not correlated with compliance in the PRiDe (correlation coefficient = 0.02; $P = .37$). Taken in the context of the overall efficacy results, these findings suggest NovoTTF Therapy works well for patients of all ages and that advanced age is not associated with lower compliance. It would also be interesting to know if marital status (or other measures of patient support) influence compliance and survival, but data on marital status were not collected in PRiDe.

Finally, the PRiDe dataset did not capture patients on combination treatments in which additional biologic therapy or chemotherapy were added to NovoTTF Therapy. It is possible that the longer survival seen in clinical practice with NovoTTF Therapy compared to NovoTTF monotherapy in the EF-11 trial is a reflection of combination use of NovoTTF Therapy with biological agents or cytotoxic chemotherapy. In fact, preclinical data have suggested that TTFields are additive or even synergistic with chemotherapies in cell culture.[34–36] Therefore, the potential benefits of combining NovoTTF Therapy with other systemic therapies warrant further investigation. A phase III trial of NovoTTF Therapy together with temozolomide

compared to temozolomide alone is currently ongoing in patients with newly diagnosed glioblastoma. The results of this trial will shed light on the possible additive or synergistic effects of NovoTTF Therapy and systemic chemotherapy.

In summary, PRiDe and the EF-11 trial represent one of the largest datasets of patients with recurrent GBM published to date, containing 700 patients in total, 567 of whom were treated with NovoTTF Therapy. The results, individually and collectively, provide further support for the use of NovoTTF Therapy to treat recurrent, supratentorial GBM. Observations from the post-marketing registry demonstrate that the safety and efficacy observed with NovoTTF Therapy in a clinical trial extend to the real-world, clinical practice setting. Future investigations may need to include NovoTTF Therapy in combination with other recurrent GBM treatments, which together may have additive or synergistic effects on patient outcomes.

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