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PTEN mutations predict benefit from tumor treating fields (TTFields) therapy in patients with recurrent glioblastoma

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Abstract

Introduction—Optimal treatment for recurrent glioblastoma isocitrate dehydrogenase 1 and 2 wild-type (rGBM IDH-WT) is not standardized, resulting in multiple therapeutic approaches. A phase III clinical trial showed that tumor treating fields (TTFields) monotherapy provided comparable survival benefits to physician's chemotherapy choice in rGBM. However, patients did not equally benefit from TTFields, highlighting the importance of identifying predictive biomarkers of TTFields efficacy.

Methods—A retrospective review of an institutional database with 530 patients with infiltrating gliomas was performed. Patients with IDH-WT rGBM receiving TTFields at first recurrence

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Author contributions Study design: AD, YE, and LYB. Data collection: AD, SM, MS, and TT. Data analysis: AD, SM, and TT. Manuscript draft writing: AD and SM. Manuscript editing: A., TT, JJZ, NT., CBP, YE, and LYB. Manuscript approval: all authors.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethical approval This study was approved by the institutional review board of The University of Texas Health Science Center at Houston and Memorial Hermann Hospital, Houston, TX and it was in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of interest CBP declares patent applications with Novocure, Ltd. and support from the AACR-Novocure Career Development Award for TTFields Research.

were included. Tumors were evaluated by next-generation sequencing for mutations in 205 cancer-related genes. Post-progression survival (PPS) was examined using the log-rank test and multivariate Cox-regression analysis.

Results—149 rGBM patients were identified of which 29 (19%) were treated with TTFields. No significant difference in median PPS was observed between rGBM patients who received versus did not receive TTFields (13.9 versus 10.9 months, $p = 0.068$). However, within the TTFields-treated group (n = 29), PPS was improved in *PTEN*-mutant (n = 14) versus *PTEN*-WT (n = 15) rGBM, (22.2 versus 11.6 months, $p = 0.017$). Within the *PTEN*-mutant group (n = 70, 47%), patients treated with TTFields (n = 14) had longer median PPS (22.2 versus 9.3 months, $p = 0.005$). No PPS benefit was observed in *PTEN*-WT patients receiving TTFields (n = 79, 53%).

Conclusions—TTFields therapy conferred a significant PPS benefit in *PTEN*-mutant rGBM. Understanding the molecular mechanisms underpinning the differences in response to TTFields therapy could help elucidate the mechanism of action of TTFields and identify the rGBM patients most likely to benefit from this therapeutic option.

Keywords

Tumor treating fields (TTFields); *PTEN*; Recurrent glioblastoma; IDH-wildtype; Predictive biomarker

Introduction

Glioblastomas (GBMs) are malignant brain tumors associated with poor prognosis and a short time to recurrence after initial treatment. The current standard of care involves maximal safe resection followed by concurrent radiotherapy and temozolomide [1]. Treatment at the time of recurrence is variable but commonly involves re-resection, re-irradiation, multiple chemotherapy regimens, and/or clinical trial enrollment. However, no treatments for rGBM have been demonstrated to improve overall survival (OS) in phase III randomized clinical trials (RCTs) [2].

Tumor treating fields (TTFields) are low-intensity electric fields (1–4 V/cm) that alternate at an intermediate frequency (100–300 kHz) to disrupt mitosis and inhibit tumor growth. However, the mechanism of action of TTFields is not entirely understood [3]. TTFields is the only FDA-approved GBM therapy in the past decade to demonstrate prolonged progression-free survival (PFS) and overall survival (OS) when added to the standard of care [4]. In addition, the EF-11 RCT demonstrated that TTFields monotherapy provides comparable survival to physician's choice chemotherapy in the setting of rGBM [5]. However, as not all GBM patients respond equally to TTFields, understanding which patients will benefit the most from this therapy by identifying predictors of response would have important clinical implications.

In addition, both EF-11 and EF-14 RCTs were performed prior to the routine incorporation of molecular alterations in the diagnosis of infiltrating gliomas [4, 5]. The increased understanding of the clinical implications of mutations in isocitrate dehydrogenase 1 or 2 (*IDH1* or *IDH2)*, among other genes, has led to a refinement of the classification of gliomas

[6–8]. Therefore, it is important to consider genetic alterations when evaluating the effects of therapeutic interventions, including TTFields.

The goal of this study was (1) to evaluate the survival effects of TTFields in a cohort of patients with IDH wild-type (IDH-WT) recurrent GBM (rGBM) and (2) to investigate possible clinical characteristics or genomic alterations that may predict responsiveness to TTFields. Our results show that mutations in *PTEN*, a tumor suppressor gene frequently altered in GBM, predict benefit from TTFields in patients with rGBM IDH-WT.

Methods

Patients and tumor samples

We retrospectively searched for patients with infiltrating gliomas using an institutional glioma registry of cases diagnosed between 2010 and 2019. The inclusion criteria for this study were (1) histological diagnosis of IDH-WT GBM; (2) treatment with TTFields at first recurrence; (3) TTFields treatment for more than 4 weeks; and (4) available tumor genomic alteration information (Online Resource 1).

Data for this study were collected from the electronic medical record of Memorial Hermann Hospital (Houston, TX) and compiled utilizing REDCap electronic data capture tools hosted at the University of Texas Health Science Center at Houston (UTHealth) [9, 10]. Data collected included age, sex, Karnofsky performance status score (KPS), diagnosis, tumor location, volumetric extent of resection, initial treatment strategy, treatment strategy at the time of recurrence, use of TTFields, PFS, OS, and post-progression survival (PPS). Tumors were classified by a board-certified neuropathologist following the 2016 WHO Classification of Tumors of the Central Nervous System [6]. Available TTFields data included: average percent usage and therapy start and end dates, which was obtained from the Optune® (Novocure Ltd., Haifa, Israel) usage database. Radiographic extent of resection was classified as gross-total resection (GTR), near-total resection (NTR), or subtotal resection (STR) as previously described [11]. Recurrence and therapeutic strategy were determined by a review of cases by a multidisciplinary tumor board as previously described [12].

A group of IDH-WT rGBM patients without TTFields treatment was utilized as the control cohort. This group was identified using our institutional registry. Patients who met the following criteria were included: (1) diagnosis of IDH-WT GBM; (2) imaging or histological evidence of recurrence; (3) TTFields therapy-naïve; and (4) available tumor genomic alteration information (Online Resource 1).

Ethics declaration

This study was approved by the Institutional Review Board (ID: HSC-MS-17–0917) of UTHealth and Memorial Hermann Hospital, Houston, TX, USA.

Targeted sequencing

Tumor tissue samples were analyzed for genetic alterations by a targeted next-generation sequencing (NGS) panel interrogating 205 genes and 26 gene rearrangements

(FoundationOne, Foundation Medicine Inc., Cambridge, MA, USA). The FoundationOne assay was performed in a clinical laboratory improvement amendments (CLIA)-certified laboratory, as previously described [13–15].

Digital droplet PCR (ddPCR)

In a subset of patients (n = 5) *TERT* promoter mutation was evaluated through ddPCR. FFPE tissue samples were tested using *TERT* C228T dHsaEXD72405942 and *TERT* C250T dHsaEXD46675715 (Bio-Rad Laboratories, CA, USA) probes as previously described [16].

Statistical analyses

Descriptive analyses were evaluated by Fisher's exact test or Mann–Whitney U-test for categorical or continuous variables, respectively. The primary and secondary study outcomes were PPS and OS, respectively. We anticipated that therapeutic strategies at recurrence could bias OS either by including patients without recurrence (sample bias) or taking into consideration the time before recurrence, which was not affected by the treatment initiated after first recurrence (lead-time bias). This lead time bias has been demonstrated in studies of GBM reoperation [17]. The Kaplan–Meier method was used to plot survival curves and the statistical significance was examined by the log-rank test. Multivariate Cox proportional hazard regression models were used to calculate the hazard ratio (HR) estimates with 95% confidence intervals (95% CI), adjusted for the known variables that affect survival. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed in EZR (v.1.40) [10, 18] and GraphPad Prism (version 9.0, La Jolla, CA, USA).

Results

Cohort characteristics

Five hundred and thirty (530) infiltrating gliomas were identified between 2010 to 2019 from our institutional registry. We selected 29 rGBM patients treated with TTFields that fulfilled the inclusion criteria (Online Resource 1). The median age was 58 years (range 40–70 years). The majority of patients (n = 19, 66%) were male, and 11 (38%) patients had a preoperative KPS ≥ 80. All patients were treated with maximal safe resection with 9 (33%) having gross-total resection (GTR), and 28 (97%) were treated according to the Stupp protocol [1].

The median time to progression from initial diagnosis was 4.7 months. All 29 rGBM patients received TTFields therapy for first GBM recurrence, with a median TTFields start time of 51 days (range 2–161 days) from the diagnosis of recurrence. TTFields was used for a median of 176 days (range 41–961 days), while the median percentage of daily usage was 59% (range 3–88%). The 29 rGBM patients were concurrently treated with reoperation (n = 12, 41%), temozolomide re-challenge (n = 19, 66%), bevacizumab (n = 24, 83%), and/or irinotecan (n = 15, 52%). Table 1 summarizes the demographic and clinical characteristics of the TTFields-treated rGBM cohort.

The most common genomic alterations identified in the tumors of TTFields-treated patients were in *TERT* promoter (76%), *CDKN2A/B* (72%), *EGFR* (55%), *PTEN* (48%), *TP53*

(28%), *PIK3CA* (21%), *NF1* (14%), *PIK3R1* (14%), *RB1* (14%), *CDK4* (10%), *MDM2* (10%), *MDM4* (10%), *BCOR* (7%), *GLI1* (7%), *MYC* (7%), *PDGFRA* (7%), and *BRAF* (7%), which were similar to the frequencies reported in larger series of GBM [19–22]. Detailed information on the genomic alterations in the TTFields-treated patients is included in Online Resource 2.

TTFields therapy in recurrent IDH-WT GBM

The rGBM patients treated with TTFields (n = 29) did not show a statistically significant increase in PPS compared to rGBM patients that did not receive TTFields (n = 120), (13.9 months VS. 10.9 months, $p = 0.068$), Fig. 1a. Similarly, no significant increase in OS was observed in rGBM patients treated with TTFields (Online Resource 3A).

Predictors of survival in rGBM patients treated with TTFields

Univariate analysis did not show a significant correlation between PPS and demographic or clinical characteristics in TTFields-treated patients (Online Resource 4). However, analysis of genetic alterations in rGBM patients treated with TTFields revealed a significantly longer PPS in patients with *PTEN*-mutant tumors (n = 14) compared to patients with *PTEN*-WT (n = 15) tumors (22.2 months vs. 11.6 months, $p = 0.0167$), Fig. 1b. Multivariate Cox-regression analysis adjusting for age and preoperative KPS demonstrated that preoperative KPS ≥ 80 (HR 0.30, $p = 0.026$) and *PTEN* mutation (HR 0.23, $p = 0.003$) independently correlated with improved PPS in TTFields-treated patients (Table 2). In addition to prolonged median PPS, there was an increased median OS in TTFields-treated patients with *PTEN*-mutant compared to PTEN-WT rGBM (30.8 vs. 16.6 months, $p = 0.007$), Online Resource 3B.

TTFields therapy improves survival of patients with PTEN-mutant rGBM

To confirm our results, we evaluated the effects of TTFields treatment in patients with *PTEN*-mutant rGBM. Among the 149 patients with GBM included in this study, 70 (47%) harbored a *PTEN* mutation, while 79 (53%) were *PTEN*-WT.

We compared the PPS of patients with *PTEN*-mutant rGBM between those treated with TTFields and those who did not receive TTFields therapy. Our results show an increased PPS in patients with *PTEN*-mutant rGBM that received TTFields (n = 14, 22.2 months) compared to those who did not receive TTFields therapy (n = 56, 9.3 months), $p = 0.0053$, Fig. 1c. Multivariate analysis adjusting for the most established covariates of survival in GBM (age and KPS), as well as other therapies used at recurrence (bevacizumab, temozolomide, and TTFields), showed that TTFields therapy was independently associated with improved PPS in patients with *PTEN*-mutant IDH-WT rGBM, $p = 0.003$ (Table 3). Although patients with *PTEN*-mutant rGBM that received TTFields had an approximate doubling of the median OS (30.8 months) compared to those who did not receive TTFields therapy (16.8 months), the difference was not statically significant ($p = 0.054$, Online Resource 3C).

Importantly, the improved PPS and OS observed with TTFields treatment in patients with *PTEN*-mutant rGBM was not observed in the n = 79 patients with *PTEN*-WT rGBM. There

was no significant difference in median PPS between patients with *PTEN*-WT rGBM who received TTFields (n = 15, 11.6 months) and those who did not receive TTFields therapy (n = 64, 11.6 months), $p = 0.801$ (Fig. 1d). There was no significant difference in median OS between patients with *PTEN*-WT rGBM who received TTFields (n = 15, 16.6 months) and those who did not receive TTFields therapy (n = 64, 21.5 months), $p = 0.078$ (Online Resource 3D).

We also examined demographic and clinical characteristics that might explain the survival differences between patients with *PTEN*-mutant and *PTEN*-WT tumors treated with TTFields. One hundred percent (100%, n = 15) of patients with *PTEN*-WT rGBM treated with TTFields were simultaneously treated with salvage bevacizumab, which is higher than the 64% (n = 14) of patients with *PTEN*-mutant rGBM treated with TTFields ($p = 0.017$) that also received bevacizumab. However, no significant differences in TTFields usage percentage or any other clinical characteristics were observed between TTFields-treated patients with *PTEN*-mutant or *PTEN*-WT rGBM (Table 1).

The type of *PTEN* mutations and its biological effect were subsequently evaluated demonstrating 6 missense mutations, 4 nonsense mutations, 2 frameshift mutations, and 2 loss copy number alterations. From the 14 mutations; 7 are known to cause loss-of-function of the gene and 7 are likely to cause loss-of-function of the gene. Moreover, *PTEN* mutations reported in this study are considered pathogenic or likely pathogenic according to ClinVar and OncokB databases (Online Resource 5) [23, 24].

Discussion

The results of this study suggest that the effects of TTFields are influenced by tumor-related factors, particularly, the *PTEN* mutation status. Our study reveals, for the first time, a molecular biology predictor of responsiveness to TTFields therapy, i.e., that compared to *PTEN*-WT, *PTEN*-mutant GBM IDH-WT patients have an almost-doubling of median PPS due to TTFields at the time of recurrence (11.6 months vs. 22.2 months, respectively, $p = 0.0167$). More importantly, we did not observe differences in TTFields compliance, which is a known factor that influences TTFields efficacy [25], between patients with *PTEN*-mutant and *PTEN*-WT rGBM. Additionally, we found that TTFields-treated patients with KPS ≥ 80 derived a PPS benefit, which has been demonstrated in several GBM studies prior to the advent of TTFields therapy [26–28]. Importantly, large studies have demonstrated that *PTEN* mutations do not confer an outcome benefit in GBM IDH-WT [19–21]. Accordingly, we did not observed survival differences in either OS (*PTEN*-WT 21.5 vs. *PTEN*-mutant 16.8-months, $p = 0.062$) or PPS (*PTEN*-WT 11.6 vs. *PTEN*-mutant 9.3-months, $p = 0.296$) in patients not treated with TTFields.

The improved survival observed in patients with *PTEN*-mutant GBM might indicate a relationship between the mechanism of action of TTFields and *PTEN*'s cellular function. *PTEN,* a gene found in chromosome 10, is commonly mutated in human cancers including ~ 50% of GBM IDH-WT tumors [19–21]. Given the frequent loss-of-function of *PTEN* in cancers and its function (inhibition of PI3K pathway), *PTEN* is recognized as a bona fide tumor suppressor gene [29]. *PTEN* is involved in maintaining mitotic spindle

architecture and promoting chromosome alignment and segregation [29]. These functions overlap with the postulated mechanism of action of TTFields, which involves induction of abnormal spindle formation and subsequent mitotic arrest or delay [30, 31]. Even though the mechanism is not yet fully elaborated, it is believed that TTFields cause an improper attachment of chromosomes to the spindle fibers [3, 32, 33]. Loss of *PTEN* function causes disruption of proper spindle assembly and chromosome segregation, which results in mitotic catastrophe [29, 34, 35]. Therefore, it is possible that the effects of TTFields therapy, which can inhibit the polymerization of microtubules and the assembly of the mitotic spindle apparatus, would be enhanced by loss-of-function mutations in *PTEN*.

Future directions

In vitro experiments using *PTEN*-mutant and *PTEN*-WT cell lines will facilitate the evaluation of TTFields' effects on the mitotic spindle and mitotic division. Similarly, studies with animal models using *PTEN*-WT and *PTEN*-mutant tumor models could shed light into the mechanism of action of TTFields and the possible sensitizing effects of *PTEN* mutations. Finally, a prospective study evaluating the effects of TTFields on GBM patient survival in the context of the tumor's genomic alterations (including *PTEN* mutation status) will be critical to confirm our results.

Limitations

Some limitations of our study include its retrospective nature and the potential for selection bias, as not all patients with rGBM in our institution had information available on the mutations present in the tumor. Also, the effects of concurrent systemic chemotherapies cannot be entirely segregated from the effects of TTFields. However, as Table 1 shows, the only significant difference in concurrent therapy use with TTFields at recurrence was more frequent salvage bevacizumab use in the *PTEN*-WT compared to the *PTEN*-mutant cohort. Other limitations of our study are the relatively small sample size of TTFields-treated patients and unknown MGMT promoter methylation status for most patients. Lastly, mutation analysis was performed in tissue from the initial resection. However, recent studies have shown that GBM may evolve stochastically from early driver events that are shared both at presentation and recurrence. Therefore, differences in genetic alterations between initial and recurrent tumors are not expected in critical oncogenic drivers like *PTEN* [36].

Conclusions

Compared to patients with *PTEN*-WT GBM, those with *PTEN*-mutant GBM derived a significantly improved survival benefit when treated with TTFields at recurrence. Understanding the molecular mechanisms underpinning and predicting the differences in response to TTFields therapy could help elucidate the mechanisms of action of TTFields, thereby identifying those patients that will benefit the most from this therapeutic option.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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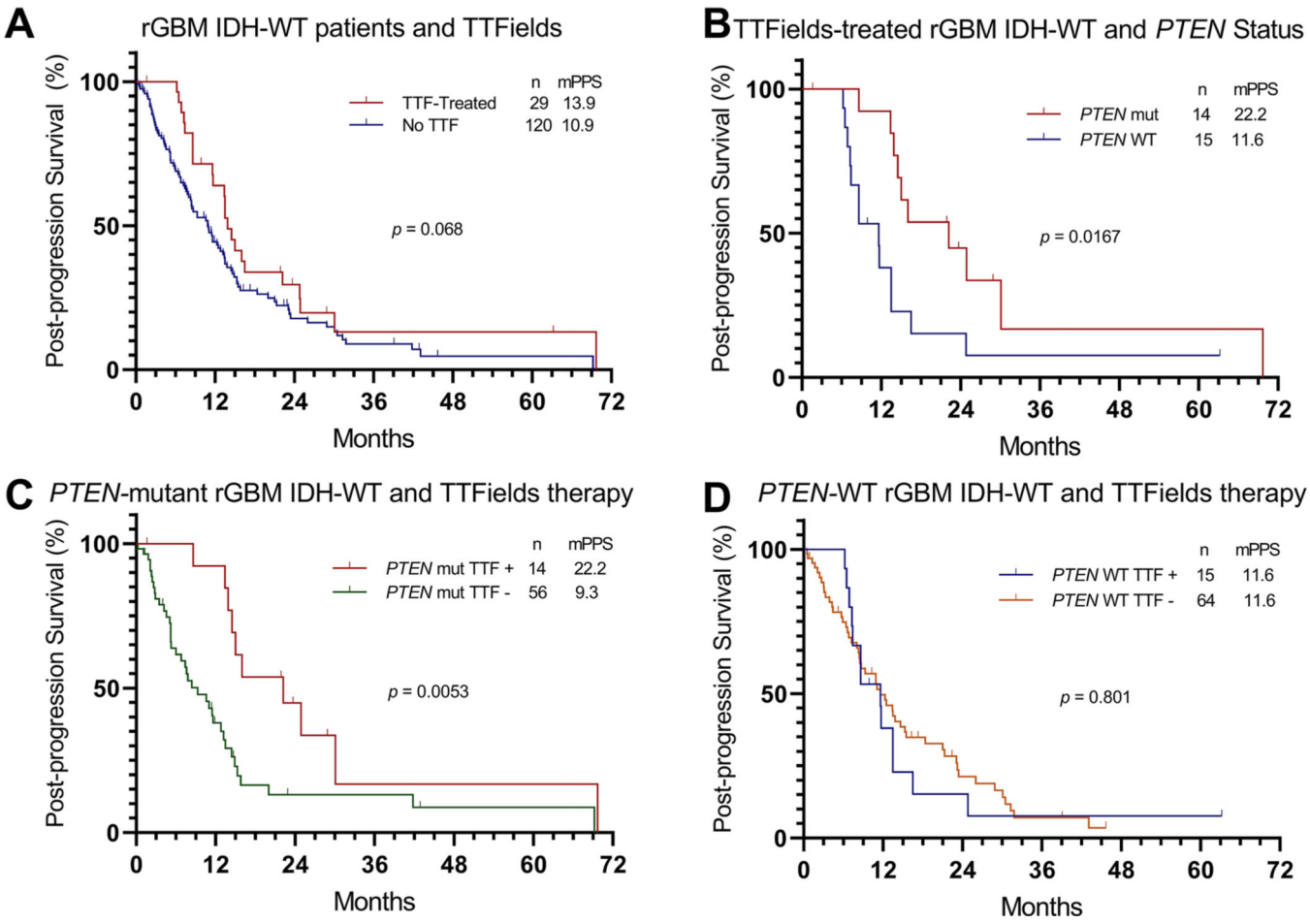

Fig. 1.

Post-progression survival (PPS) differences in response to tumor treating fields (TTFields) treatment of recurrent glioblastoma (rGBM) isocitrate dehydrogenase wild-type (IDH-WT). **a** PPS of recurrent GBM IDH-WT by TTFields therapy **b** PPS of recurrent GBM IDH-WT patients treated with TTFields by PTEN status. **c** PPS of PTEN-mutant rGBM IDH-WT by TTFields therapy. **d** PPS of PTEN-WT rGBM IDH-WT by TTFields therapy. *TTF* TTFields.

Table 1

Characteristics of tumor treating fields (TTFields)-treated patients with recurrent glioblastoma (rGBM) IDH-WT and *PTEN* mutation status (n = 29)

Characteristics, N (%)	**TTFields-treated patients N = (29)**	***PTEN* wild-type N = 15**	***PTEN* mutant N = 14**	***p*-value**
Age, median (IQR)	58 (52–63)	61 (54–64)	58 (51–60)	0.457
Male	19 (66)	10 (67)	9 (64)	1.000
White/Caucasian	26 (90)	12 (80)	14 (100)	0.224
Pre-operative KPS ≥ 80	11 (38)	7 (47)	4 (29)	0.450
Gross total resection	9 (31)	5 (33)	4 (29)	1.000
Chemoradiotherapy with TMZ	28 (97)	14 (93)	14 (100)	1.000
Second resection	12 (41)	6 (40)	6 (43)	1.000
Salvage TMZ	19 (66)	10 (67)	9 (64)	1.000
Salvage bevacizumab	24 (83)	15 (100)	9 (64)	**0.017**
Salvage SRS	8 (28)	3 (20)	5 (36)	0.427
TTFields usage percentage, median (IQR) *	59 (39–76)	59 (37–74)	64 (44–78)	0.600

Significant *p*-values are bolded

TMZ temozolomide, *KPS* Karnofsky Performance Status, *SRS* stereotactic radiosurgery, *WT* wildtype, *IQR* interquartile range, *N* number

* 10 patients did not have available information (4 *PTEN* wildtype and 6 *PTEN* mutant)

Table 2

Multivariate analysis of post-progression survival of patients with recurrent glioblastoma (rGBM) IDH-WT treated with tumor treating fields (TTFields) (n = 29)

Variables	HR (CI 95%)	*p*-value
Age (years)	0.95 (0.90–1.01)	0.128
Preoperative KPS ≥ 80	0.30 (0.11–0.87)	**0.026**
PTEN mutation	0.23 (0.09–0.63)	**0.003**

Significant *p*-values are bolded

Multivariate analysis was performed using a Cox regression model *HR* hazard ratio, *CI* confidence interval, *KPS* Karnofsky Performance Status, *WT* wildtype

Table 3

Multivariable analysis of post-progression survival of patients with *PTEN*-mutant recurrent glioblastoma (rGBM) IDH-WT (N = 70)

Variables	HR (CI 95%)	*p*-value
Age (years)	1.00 (0.98–1.03)	0.778
Male	0.77 (0.42–1.42)	0.404
Preoperative KPS ≥ 80	0.59 (0.30–1.17)	0.130
Non-GTR	1.72 (0.85–3.48)	0.134
Salvage TMZ	0.84 (0.43–1.65)	0.610
Salvage bevacizumab	0.91 (0.48–1.73)	0.775
Salvage TTFields	0.29 (0.12–0.66)	**0.003**

Significant *p*-values are bolded

Multivariate analysis was performed using a Cox regression model

TTFields tumor treating fields, *KPS* Karnofsky Performance Status, *GTR* Gr oss-total resection *TMZ* temozolomide, *HR* hazard ratio, *CI* confidence interval, *WT* wildtype