Journal of Cancer Research and Clinical Oncology
https://doi.org/10.1007/s00432-019-03106-8

ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Tumour Treating Fields (TTFields) in combination with lomustine and temozolomide in patients with newly diagnosed glioblastoma

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Received: 3 November 2019 / Accepted: 7 December 2019

Abstract

Purpose In the EF-14 trial for newly diagnosed glioblastoma (ndGBM) patients addition of Tumour Treating Fields (TTFields) to temozolomide treatment resulted in a significantly improved overall survival (OS). In the NOA-09/CeTeG trial, combination of lomustine and temozolomide was superior to temozolomide monotherapy in patients with O6-methylguanine DNA methyltransferase (MGMT) promoter methylated (MGMTm) ndGBM. We evaluated combination of these two treatment modalities in patients with MGMTm ndGBM. There have been so far no data on the combination of these two efficient regimens.

Methods This bicentric retrospective analysis investigated 16 patients. Parameters evaluated included safety outcome as measured by Common Toxicity Criteria for Adverse Events (CTCAE), clinical outcomes, and compliance to treatment.

Results Hematologic adverse events CTCAE ≥ 3 were observed in seven, hepatotoxic adverse events of CTCAE ≥ 3 in four patients. Mild to moderate skin toxicity was detected in six patients. At data cutoff, patients demonstrated a median progression-free survival (PFS) of 20 months. The usage rate of TTFields showed a high median adherence (83%) to the therapy.

Conclusions This analysis provides first indication that the combination of TTFields/lomustine/temozolomide is safe and feasible. The observed survival outcomes might suggest potential beneficial effects.

Keywords Glioblastoma · TTfields · EF-14 · NOA-09 · Temozolomide · Lomustine

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Published online: 11 December 2019

Introduction

Since the introduction of the Stupp protocol in 2005 (Stupp et al. 2005), numerous phase 3 clinical trials were conducted to improve survival outcomes in newly diagnosed glioblastoma (GBM). However, since 2005, there have been only two randomised phase 3 trials, other than trials focusing on elderly patients, with significant positive survival outcome. One of these positive GBM trials is the EF-14, which demonstrated the efficacy of Tumour Treating Fields (TTFields) in the treatment of newly diagnosed GBM (ndGBM). Median overall survival (OS) and progression-free survival (PFS) were significantly extended when TTFields was added to temozolomide (TMZ) maintenance therapy compared to TMZ alone ($n=695$; OS: 20.9 versus 16.0 months [measured from randomisation], $p<0.001$; PFS: 6.7 versus 4.0 months, $p<0.001$). The OS benefit of TTFields was seen in all patient subgroups, irrespective of, e.g., O6-methylguanine DNA methyltransferase (MGMT) promoter methylation-status, age, clinical status, and gender. Subgroup analysis further showed that the median overall survival from randomisation in patients with MGMT promoter methylation was 31.6 versus 21.2 months. Notably, median time from diagnosis to randomisation was 3.8 months. In the EF-14 trial, patients were allowed to continue TTFields in combination with second-line therapies, such as lomustine (CCNU), at first tumour progression (Stupp et al. 2017).

In the recently published NOA-09/CeTeG trial, 141 patients with MGMT promoter methylated (MGMTm) ndGBM were randomised to receive either lomustine plus temozolomide (CCNU/TMZ) or TMZ alone. Results were reported based on a pre-specified modified intention-to-treat (mITT) analysis stratified for centre and RPA (recursive partitioning analysis) class. This trial demonstrated a significantly improved median OS (31.4 versus 48.1 months from diagnosis, $p=0.049$); however PFS was not improved in comparison to the control group (Herrlinger et al. 2019).

The results of the EF-14 and CeTeG trials provide a strong rationale for combining TTFields with CCNU/TMZ. Furthermore, preclinical data demonstrate the synergistic effects of combining TTFields with alkylating agents (Silginer et al. 2017). Here, we present the first results of a retrospective analysis of patients with MGMTm ndGBM treated with a triple combination of TTFields, and CCNU/TMZ after completion of radiochemotherapy. We report on the safety, feasibility, and initial efficacy results obtained from 16 patients receiving the triple combination.

Methods

Study design

For this analysis, the patient records between January 2017 through May 2019 (data cutoff) from two German brain tumour centres (Division of Clinical Neurooncology, Department of Neurology, University Hospital Essen and Division of Clinical Neurooncology, Department of Neurology, University of Bonn Medical Centre) were screened for patients who met the following eligibility criteria:

- histologically confirmed diagnosis of ndGBM,
- MGMTm,
- treatment with TTFields and CCNU/TMZ following completion of radiochemotherapy.

Data were obtained as part of routine clinical assessments. These included reviewing patients' medical reports, case files, and laboratory results. Approval for this analysis was obtained from the respective institutional review boards.

Follow-up extended through May 2019 and included the assessment of tumour recurrence by magnetic resonance imaging (MRI) in accordance with the Response Assessment of Neuro-Oncology (RANO) criteria (Wen et al. 2017), survival outcomes (PFS and OS), treatment compliance, and adverse events as measured by Common Toxicity Criteria for Adverse Events (CTCAE) version 5. MRI of the brain for the assessment of treatment response was performed at the investigators' discretion at a time interval of eight up to 12 weeks. In the event of suspected pseudoprogression, we performed positron-emission-tomography or follow-up MRI as per RANO criteria. The extent of resection was based on contrast-enhanced T1-weighted MRI performed within 72 h. Complete resection was defined as absence of radiographic evidence for contrast-enhancing tumour. Otherwise partial resection was defined. Chemotherapy with CCNU and TMZ was administered according to the protocol of the recently published NOA-09/CeTeG trial (Herrlinger et al. 2019). Six patients, however, were treated with TMZ only concomitant to radiotherapy, starting with the combination of TMZ and CCNU after completion of radiotherapy.

At baseline, before the onset of triple therapy, and at the time of recurrence, MRI-based tumour growth patterns were determined as previously published (Kebir et al. 2019) based on T1-weighted MRI scans before and after injection of a gadolinium-based contrast agent and T2-weighted fluid-attenuated inversion recovery (FLAIR) scans. The following growth patterns were determined:

- local: one contiguous contrast-enhancing (CE) lesion site,

- multifocal: at least two non-contiguous CE lesion sites with intervening areas of normal brain signals,
- distant (assessment is done only at recurrence): one single new CE or non-CE lesion, occurring beyond a 3 cm radius from the primary tumour margin and being non-contiguous to it,
- diffuse: when the signal on FLAIR images extended diffusely at least 2 cm beyond the CE area. In the event of multiple lesions, any lesion meeting the definition of diffuse was sufficient for the pattern to be categorised as diffuse,
- non-diffuse: lesions not meeting the definition of diffuse were classified as non-diffuse.

Hematoxylin-eosin staining was used to detect putative TTFields related histomorphological effects on a cellular basis in one patient, in whom repeat surgery was performed following TTFields plus CCNU/TMZ treatment.

Technical support with the TTFields device (Optune®) was provided to the patients under the surveillance of a local technical instructor from the device manufacturer. Treatment compliance reports collected at 4-week intervals served to ascertain TTFields treatment adherence, defined as the total TTFields usage time from therapy start until data cutoff.

Statistics

Patients' characteristics were presented descriptively in a tabular format. RPA was applied to represent a composite of prognostic markers, as has been published (Bell et al. 2017). To estimate the survival function from lifetime data we used the Kaplan-Meier estimator. For PFS, the event of interest was the time from primary diagnosis until the next MRI indicating recurrence. For OS evaluation, the event of interest was the time from primary diagnosis until death from any cause. Patients who had not died at the time of analysis (May 1, 2019) were censored. For data visualisation R (version 3.3.1; The R Foundation for Statistical Computing) was employed. There was no missing data.

Results

At data cutoff, 16 patients (medians: age, years, 50 [27–70]; Karnofsky performance status score (KPS), percent, 90 [60–100]) were treated and analysed: GBM isocitrate dehydrogenase (IDH) mutant ($n=4$), IDH wildtype ($n=12$). From the IDH mutant GBM patients in two analysis of 1p/19q revealed a non-codeletion status and in the two other patients ATRX analysis revealed a loss of expression, indicating astrocytic lineage. Patients with complete resection ($n=7$), partial resection ($n=8$) as well as biopsy only ($n=1$) were included in the analysis. Amongst these patients, seven were female (44%). Six patients were classified RPA class III, eight patients RPA class IV and two patients RPA class V. At data cutoff, median treatment duration of the triple therapy was 11 weeks (range 3–36 weeks), median treatment duration of TTFields therapy was 32 weeks (range 3–140 weeks). TTFields was initiated after a median interval of 19 weeks (range 12–33 weeks) after primary diagnosis. Analysis of the usage rate of TTFields therapy demonstrated a high median adherence to the therapy (83%; range 45–99%). Ten of 16 patients are still on TTFields therapy at the time of data cutoff. Basic patients' characteristics are summarised in Table 1.

CTCAE grade 3 or 4 hematotoxicity was observed in seven patients (43%), CTCAE grade 3 or 4 hepatotoxicity (predominantly combined elevation of transaminases and gamma-glutamyltransferase) was observed in four patients (25%). No further non-hematologic/non-hepatologic toxicity of CTCAE grade 3 or higher was observed, except for infection with influenza A virus (CTCAE 3) that emerged in one patient. Medical device site reactions (low-grade skin reactions) were detected in six patients (37%). In patients who received triple therapy for at least eight weeks (12/16) CTCAE grade 3 or 4 hematotoxicity was observed in five patients (41%), CTCAE grade 3 or 4 hepatotoxicity was observed in three patients (25%), low-grade skin reactions were detected in six patients (50%). An overview of the toxicity observed in this study and a comparison with the corresponding toxicity in the EF-14 trial and the NOA-09/CeTeG trial is shown in Table 2.

Table 1 Patients' characteristics

	All ($n=16$)
Age, median (range)	50 (27–70)
Sex, % (n)	
Female	44 (7)
Male	66 (9)
KPS, %, median (range)	90 (60–100)
IDH status, % (n)	
Wildtype	75 (12)
Mutation	25 (4)
Surgery, % (n)	
Complete resection	44 (7)
Partial resection	50 (8)
Biopsy	6 (1)
TTFields therapy, weeks, median (range)	32 (3–140)
Triple therapy, weeks, median (range)	11 (3–36)
Time from diagnosis to start of TTFields, weeks, median (range)	19 (12–33)
Usage rate of TTFields, %, median (range)	83 (45–99)

IDH isocitrate dehydrogenase, *KPS* karnofsky performance status score

Table 2 Comparison of toxicity in the EF-14 trial, the NOA-09/CeTeG trial and the combination of TTFields/lomustine/temozolomide

Toxicity	NOA-09/CeTeG	EF-14	Combination (%)	Combination[a] (%)
Skin reaction CTCAE 1/2	n.a.	52%	37	50
Hepatotoxicity CTCAE 3/4	6%	n.a.	25	25
Hematotoxicity CTCAE 3/4	36%	13%	43	41

CTCAE common toxicity criteria for adverse events, *n.a.* data not available

[a]Triple therapy for at least 8 weeks

At data cutoff, survival analysis of the 16 patients revealed a median PFS of 20 months from diagnosis; median OS has not yet been reached. The corresponding Kaplan-Meier curves are displayed in Fig. 1.

Tumour progression under TTFields therapy was detected in five patients. Notably, in one patient, there was a tendency towards larger tumour cells at recurrence compared to the primary tumour. However, multinucleated giant cells were absent (Fig. 2). Further MRI analysis of the precise progression pattern showed distant (with respect to the primary brain lesion) tumour recurrence in one patient (20%). The tumour progression patterns of the five analysed patients are depicted in Fig. 3.

Discussion

This pilot study suggests that the combined treatment of TTFields and CCNU/TMZ is feasible and safe in patients with MGMTm ndGBM. This study further shows a preliminary signal that the combined treatment could have an additional survival benefit.

The rate of mild to moderate skin irritations was 37% (all patients) or 50% (patients with triple combination therapy for at least eight weeks) in our study and data was comparable to that in the EF-14 trial (Stupp et al. 2017). As reflected by a high median TTFields patient compliance rate (83%), the combined treatment (TTFields plus CCNU/TMZ) was associated with high adherence. The median usage rate of TTFields was well above the threshold of 75%, a minimum usage rate that has been demonstrated—in a recently published subgroup analysis of the EF-14 trial—to be required to predict—independently from canonical prognostic factors—benefit from TTFields with regard to OS (Toms et al. 2019).

The rate of high-grade (CTCAE 3 or 4) hematotoxicity was similar to that in the NOA-09/CeTeG trial. The impact of the higher rate of high-grade (CTCAE 3 or 4) hepatotoxicity in our study in comparison to that in the NOA-09/CeTeG trial is limited by the fact that in one patient the detected high-grade hepatotoxicity was based on an isolated elevation of gamma-glutamyltransferase only with no discernible reason for hepatic ailment; a fact, which is

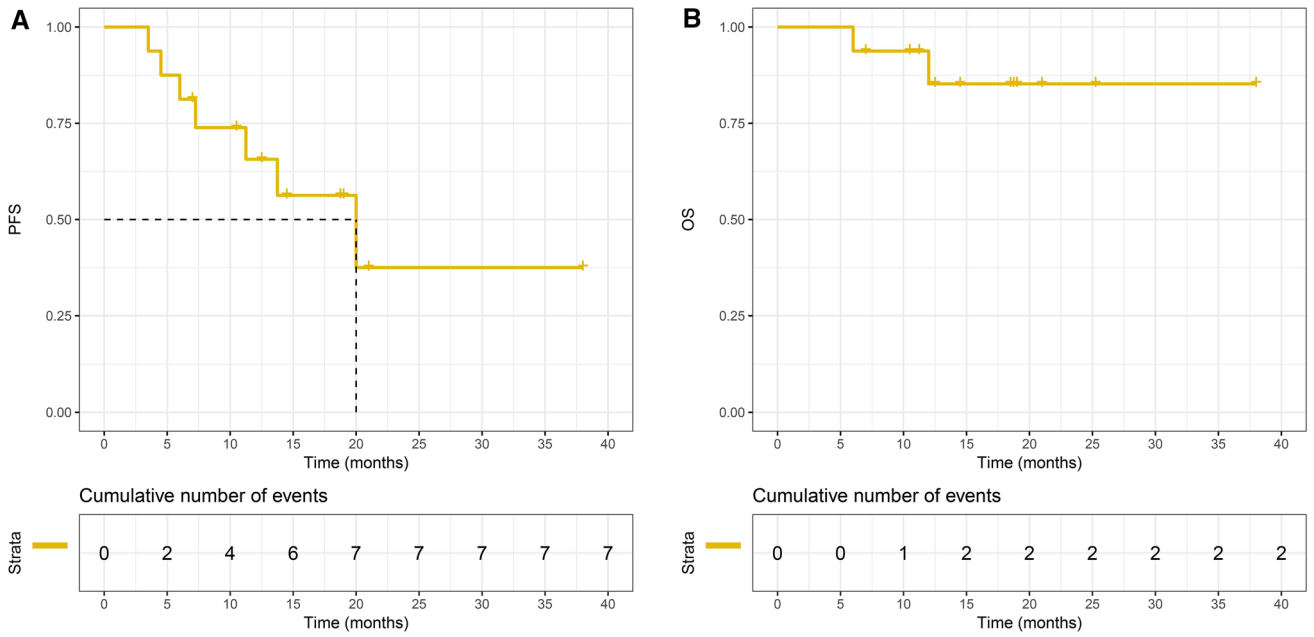

Fig. 1 Kaplan-Meier curves with integrated panels indicating the corresponding cumulative event numbers concerning the combination of TTFields/CCNU/TMZ. *OS* overall survival, *PFS* progression-free survival

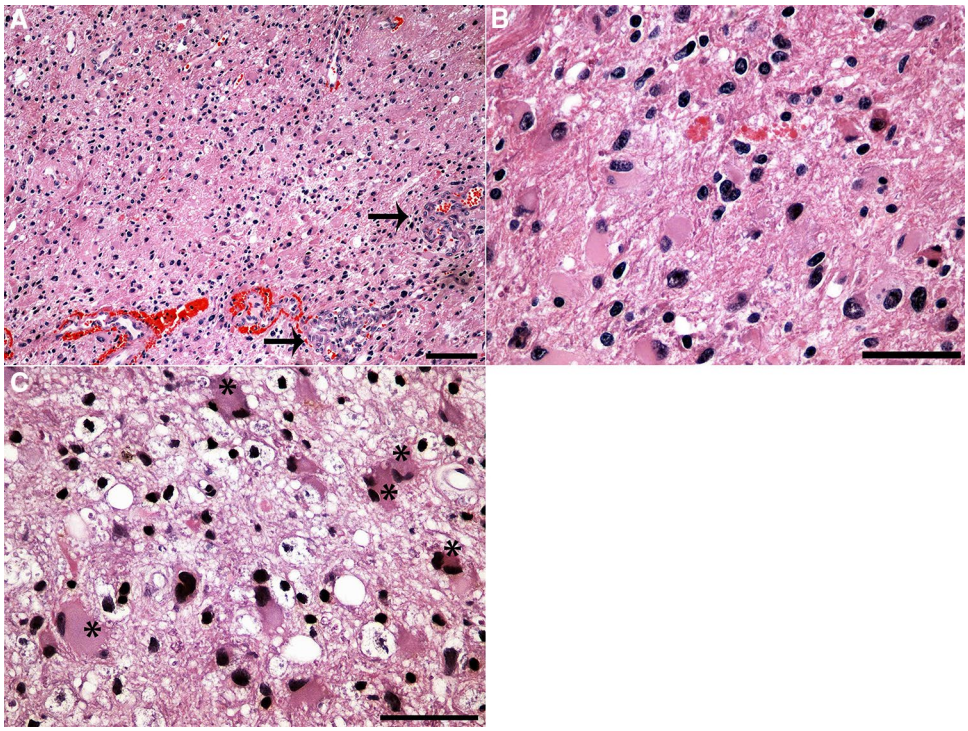

Fig. 2 Hematoxylin-eosin staining of the primary tumour revealed a diffusely infiltrating astrocytic tumour with high cellularity accompanied by glomeruloid vascular proliferation (arrows) and mitoses leading to the diagnosis of glioblastoma (**a**). A higher magnification (depicted in **b**) highlights the pleomorphism of the tumour cells. Nonetheless, multinucleated cells were rare **b**. Tumour cells of the recurrent tumour tended to be bigger in size and to show some more bi- or multinucleated cells (asterisks); however, true multinucleated giant cells were absent **c**. Scale bar in **a** represents 100 µm, scale bars in **b** and **c** represent 50 µm

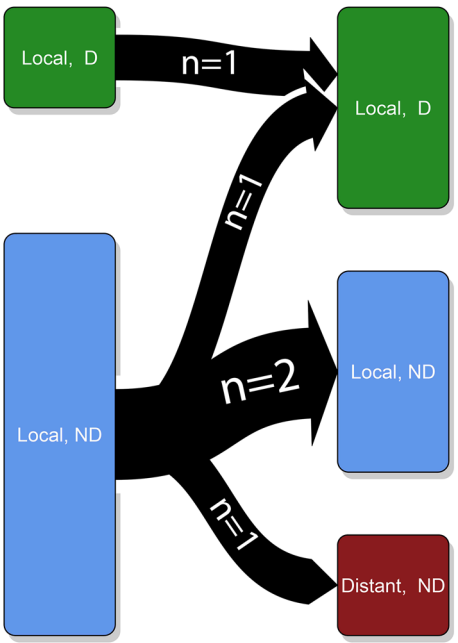

Fig. 3 Progression pattern of patients with tumour recurrence under TTFields therapy. *D* diffuse, *ND* not diffuse

considered not to be related to the addition of TTFields to CCNU/TMZ chemotherapy.

According to the NOA-09/CeTeG trial younger patients (≤ 70 years) were treated with TMZ and CCNU plus TTFields (Herrlinger et al. 2019). There is no data on treating elderly patients with TMZ and CCNU; however, a higher toxicity rate would be probable. In accordance with the results of the EF-14 trial with elderly patients being integrated in this trial addition of TTFields to TMZ and CCNU in elderly patients should not provoke relevant increase in frequency of systemic toxicity (Stupp et al. 2017). This fact is a substantial benefit of TTFields compared to other currently much sought-after treatment concepts such as combination of poly(ADP-ribose) polymerase (PARP) inhibitors plus alkylating agents associated with relevantly increased frequency of systemic toxicity (Middleton et al. 2015).

In our analysis, patients treated with the combination of TTFields and CCNU/TMZ demonstrated an encouraging preliminary median PFS of 20 months which is well within the 95% confidence interval of the PFS in the CeTeG trial (Herrlinger et al. 2019). The median OS was not yet reached at the time of data cutoff.

Analysis of the progression pattern of patients with tumour recurrence under TTFields therapy showed a distant (primary brain lesion) tumour growth in one patient out of five. This fact suggests potential synergistic effects of the combination of systemic therapy with a local active therapy such as TTFields as performed in this pilot trial.

A previously published report indicated that TTFields might induce the emergence of giant cells at tumour recurrence (Turner et al. 2014). In one patient with recurrence under TTFields plus CCNU/TMZ who underwent repeat surgery, there was a tendency towards the development of giant cells on histomorphologic appearance. Of note,

there was only one patient overall in our study cohort, who received repeat surgery at recurrence. This finding suggests that additional studies may be valuable to evaluate reasons for any potentially altered histomorphology.

There are several limitations in our analysis that should be addressed in further studies. Patient accrual is mainly confounded by the retrospective nature of the performed analysis. A longer follow-up time, larger sample size and validation in a prospective setting are needed to verify these preliminary survival and safety results. On the other hand it has to be mentioned that patients were recruited consecutively from two German cancer centres. Furthermore, a more homogenous patient population would be essential for validation of results. The investigated patient cohort included patients with IDH mutant GBM that make up about a quarter of patients while in the CeTeG trial, IDH mutant patients were about 6% only. However, it has to be mentioned that PFS of IDH wildtype patients only was also 20 months from diagnosis. Also, the onset of TTFields therapy and the duration of triple therapy (TTFields/CCNU/TMZ) was heterogeneous amongst patients.

In summary, the results of this bicentric analysis provide first indications that combining two positive trial concepts, EF-14 and NOA-09/CeTeG, is probably feasible and safe. It is tempting to speculate that this combination could potentially result in a promising survival benefit for patients with MGMTm ndGBM. Owing to the above mentioned shortcomings we cannot draw a reliable conclusion on a putative efficacy of the triple treatment (TTFields/CCNU/TMZ).

Author contributions Conceptualisation: Lazaros Lazaridis, Sied Kebir, and Martin Glas. Methodology: Lazaros Lazaridis, Sied Kebir, and Martin Glas. Formal analysis and investigation: Lazaros Lazaridis, Niklas Schäfer, Sarah Teuber-Hanselmann, Tobias Blau, Sied Kebir, and Martin Glas. Writing-original draft preparation: Lazaros Lazaridis, Sied Kebir, and Martin Glas. Writing-review and editing: Lazaros Lazaridis, Niklas Schäfer, Sarah Teuber-Hanselmann, Tobias Blau, Teresa Schmidt, Christoph Oster, Johannes Weller, Theophilos Tzaridis, Daniela Pierscianek, Kathy Keyvani, Christoph Kleinschnitz, Martin Stuschke, Björn Scheffler, Cornelius Deuschl, Ulrich Sure, Ulrich Herrlinger, Sied Kebir, and Martin Glas. Supervision: Sied Kebir, Martin Glas.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest L. Lazaridis received speaker honorarium and travel support from Novocure. N. Schäfer reports personal fees and other support from Roche. T. Schmidt received travel support from Novocure. U. Herrlinger reports grants from German Federal Ministry of Education and Research, grants and personal fees from Roche, personal fees and non-financial support from Medac, personal fees and non-financial support from Bristol-Myers Squibb, personal fees from Novocure, personal fees from Novartis, personal fees from Daichii-Sankyo, personal fees from Noxxon, personal fees from Abbvie, personal fees from Bayer, and personal fees from Jansen. S. Kebir received honoraria and travel support from Novocure. M. Glas reports personal fees and other from Novartis, personal fees and other from Daiichi Sankyo, personal fees and other from Novocure, personal fees and other from Medac, personal fees and other from Merck, personal fees and other from Kyowa Kirin, personal fees and other from Bayer, personal fees and other from Jansen-Cilag, personal fees and other from Abbvie. All remaining authors have declared no conflicts of interest.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (ethics committee University Duisburg-Essen; reference number: 18-8428-BO) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study (retrospective and anonymous analysis) formal consent is not required.

References

Bell EH et al (2017) Molecular-based recursive partitioning analysis model for glioblastoma in the temozolomide era: a correlative analysis based on NRG oncology RTOG 0525. JAMA Oncol 3:784–792. https://doi.org/10.1001/jamaoncol.2016.6020

Herrlinger U et al (2019) Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): a randomised, open-label, phase 3 trial. Lancet 393:678–688. https://doi.org/10.1016/S0140-6736(18)31791-4

Kebir S et al (2019) Regorafenib in patients with recurrent high-grade astrocytoma. J Cancer Res Clin Oncol 145:1037–1042. https://doi.org/10.1007/s00432-019-02868-5

Middleton MR et al (2015) Randomized phase II study evaluating veliparib (ABT-888) with temozolomide in patients with metastatic melanoma. Ann Oncol 26:2173–2179. https://doi.org/10.1093/annonc/mdv308

Silginer M, Weller M, Stupp R, Roth P (2017) Biological activity of tumor-treating fields in preclinical glioma models. Cell Death Dis 8:e2753. https://doi.org/10.1038/cddis.2017.171

Stupp R et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. https://doi.org/10.1056/NEJMoa043330

Stupp R et al (2017) Effect of Tumor-Treating Fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA 318:2306–2316. https://doi.org/10.1001/jama.2017.18718

Toms SA, Kim CY, Nicholas G, Ram Z (2019) Increased compliance with tumor treating fields therapy is prognostic for improved survival in the treatment of glioblastoma: a subgroup analysis of the EF-14 phase III trial. J Neurooncol 141:467–473. https://doi.org/10.1007/s11060-018-03057-z

Turner SG, Gergel T, Wu H, Lacroix M, Toms SA (2014) The effect of field strength on glioblastoma multiforme response in patients treated with the NovoTTF-100A system. World J Surg Oncol 12:162. https://doi.org/10.1186/1477-7819-12-162

Wen PY, Chang SM, Van den Bent MJ, Vogelbaum MA, Macdonald DR, Lee EQ (2017) Response assessment in neuro-oncology clinical trials. J Clin Oncol 35:2439–2449. https://doi.org/10.1200/JCO.2017.72.7511