Received: 24 October 2025 | Revised: 23 March 2026 | Accepted: 1 April 2026

DOI: 10.1002/epi4.70274

Epilepsia Open® Open Access

ORIGINAL ARTICLE

Perampanel as add-on in high-grade glioma–related epilepsy: Seizure control and QoL in a prospective, multicenter, real-world 6-month follow-up study

Matteo Impellizzeri[1] | **Paolo Paone**[1] | **Giada Pauletto**[2] | **Annacarmen Nilo**[2] | **Simone Beretta**[3,4] | **Andrea Salmaggi**[5] | **Stefano Consoli**[5] | **Stefano Quadri**[1]

[1]SC Neurology ASST Papa Giovanni XXIII, Bergamo, Italy

[2]Head-Neck and Neurosciences Department, S. Maria Della Misericordia University Hospital, Udine, Italy

[3]Department of Medicine and Surgery, University of Milano-Bicocca, Milano-Bicocca, Italy

[4]Department of Neurology, Fondazione IRCCS San Gerardo Dei Tintori, Monza, Italy

[5]Neurology Unit, Presidio A, Manzoni ASST, Lecco, Italy

Correspondence
Paolo Paone, SC Neurology ASST Papa Giovanni XXIII, Bergamo, Italy.
Email: ppaone@asst-pg23.it

Abstract

Objective: High-grade astrocytomas, including glioblastomas, are aggressive brain tumors with poor prognosis and a 5-year survival below 7%. Seizures affect up to 75% of glioma patients, especially in low-grade tumors but also in high-grade cases. Elevated extracellular glutamate in peritumoral tissue—due to tumor release, impaired uptake, and metabolic changes like D-2-hydroxyglutarate in IDH1-mutated tumors—contributes to neuronal hyperexcitability and tumor progression via AMPA and NMDA receptors' activation. Perampanel (PER), a selective noncompetitive AMPA receptor antagonist, targets this pathway, potentially reducing seizures and tumor growth. Clinical data on the use of perampanel in brain tumor-related epilepsy, particularly in patients with high-grade gliomas, are still limited.

Methods: This prospective multicenter observational study included 14 patients with brain tumor-related epilepsy (BTRE) from four Italian neuro-oncology centers. Patients received PER and were followed for 6 months. Seizure frequency, adverse events, quality of life (QoL), and survival were evaluated as real-world effectiveness outcomes.

Results: Seizure frequency decreased from 12.5 to 3 seizures/month at 6 months ($p = 0.0023$). Responder rate (≥50% seizure reduction) was 78.6%, with 57.1% seizure-free. Adverse events were mild; two patients discontinued PER treatment. QoL analyses showed improvement in communication and appetite even if not statistically significant. Survival analyses revealed no significant associations with clinical variables. Sensitivity analyses supported the consistency of results.

Significance: This real-world study suggests that PER may be effective and well tolerated in BTRE. While findings are exploratory, they provide useful clinical insight and highlight the need for larger studies to confirm efficacy, QoL effects, and the influence of molecular factors.

Plain Language Summary: Patients with aggressive brain tumors often develop seizures that are difficult to control. In this study, perampanel reduced the number of seizures and did not worsen quality of life, being generally well tolerated. Patient survival was mainly determined by the tumor itself. Larger studies are needed to confirm the drug's effectiveness in reducing seizures, improving quality of life, evaluating survival, and monitoring side effects.

KEYWORDS

astrocytoma, epilepsy, glioblastoma, Perampanel, seizures

1 | INTRODUCTION

High-grade gliomas (HGGs), particularly glioblastomas, rank among the most aggressive tumors of the central nervous system. These neoplasms carry a significant burden of morbidity and mortality, with a 5-year relative survival rate of only 6.8%, which varies depending on the patient's age at diagnosis and sex.[1] Among the various clinical manifestations associated with gliomas, seizures are notably common. While brain tumors account for only 6–10% of all epilepsy cases, up to 75% of patients with gliomas, especially those with low-grade gliomas (LGGs), experience seizures as an initial manifestation.[2] Even in HGGs, the incidence of epilepsy remains clinically meaningful. A growing body of evidence has revealed that tumor progression and epileptogenesis share common pathophysiological pathways in which glutamate, the principal excitatory neurotransmitter in the central nervous system, plays a central role.[3–5] In peritumoral tissue, extracellular concentrations of glutamate have been reported to be up to 100 times higher than those found in healthy brain tissue. This accumulation is the result of multiple mechanisms. Tumor cells actively release glutamate via the cystine/glutamate antiporter system (xCT), while the glutamate transporter GLT-1 (also known as EAAT2), which is primarily responsible for synaptic glutamate uptake, is markedly downregulated in gliomas. Additionally, hypoxic conditions within the tumor microenvironment induce overexpression of hypoxia-inducible factor 1-alpha (HIF-1α), which in turn promotes the expression of branched-chain amino acid transaminase 1 (BCAT1), an enzyme involved in glutamate synthesis through amino acid metabolism. In IDH1-mutated gliomas, the production of D-2-hydroxyglutarate (D-2HG), a structural analog of glutamate, has been implicated both in increased radiosensitivity and epileptogenic potential, due to its ability to mimic or interfere with glutamate receptor signaling. Beyond its effects on neuronal hyperexcitability, excessive glutamate also serves as a signaling molecule for tumor and glial cells, contributing to tumor proliferation, migration, and invasion. These effects are mediated through activation of glutamatergic receptors, including ionotropic subtypes (AMPA, NMDA, and kainate receptors) as well as metabotropic glutamate receptors (mGluRs). More recently, functional glioneuronal synapses have been identified as a novel mechanism of glioma–neuron communication, further amplifying the glutamatergic cross-talk within the tumor microenvironment.[6,7] In this pathological context, perampanel (PER), a noncompetitive AMPA receptor antagonist, emerges as a potentially valuable therapeutic option for tumor-related epilepsy. By targeting AMPA receptors, perampanel disrupts the glutamate-dependent signaling circuit, exerting a dual effect: a direct anti-seizure action via inhibition of excitatory neurotransmission and an indirect antitumor effect through inhibition of cell migration and limitation of the tumor microenvironment's expansion.[8] Several preclinical studies have demonstrated perampanel's

Key points

- Perampanel significantly reduced seizure frequency in patients with brain tumor-related epilepsy associated with high-grade gliomas.
- 78.6% of patients achieved ≥50% seizure reduction and 57.1% became seizure-free at 6 months.
- Perampanel was generally well tolerated, with mostly mild adverse events and only two treatment discontinuations.
- No significant associations were found between clinical variables and survival in this small exploratory cohort.
- These real-world findings support the feasibility of perampanel in BTRE and highlight the need for larger multicenter studies.

antiproliferative properties in glioblastoma cell lines, including synergistic activity when combined with temozolomide.[9] In animal models, perampanel has shown not only robust anti-seizure efficacy but also a tangible reduction in tumor activity.[10] However, despite these promising results, clinical data remain limited. Available studies are largely retrospective, uncontrolled, and based on small, heterogeneous patient cohorts, limiting their external validity.[9,11,12] Among them, the PERADET study represents the largest clinical cohort published to date, comprising 36 patients. It reported a 12-month response rate—defined as ≥50% reduction in seizure frequency—of approximately 90%, with a seizure freedom rate of 30%, outcomes that compare favorably with those of other anti-seizure medications (ASMs) in similar populations.[13] Given the poor prognosis of patients with HGGs and brain tumor-related epilepsy (BTRE), the clinical impact of uncontrolled seizures, and the biological rationale supporting AMPA receptor antagonism, further research into perampanel's role is both timely and necessary. The present study aims at contributing to this field by providing real-world data from a multicenter cohort involving four Italian neuro-oncology centers, with the goal of assessing the clinical efficacy and tolerability of perampanel in the treatment of BTRE. In fact, studies specifically addressing epilepsy treatment in HGGs are limited, considering the lower incidence of epilepsy in these patients and their shorter survival. For these reasons, the management of epilepsy in HGGs patients should be differentiated from that of subjects affected by LGGs, in order to ensure a rapid efficacy and a better tolerability of ASMs.

2 | METHODS

2.1 | Study design and ethics

A prospective, multicenter observational study was planned to investigate clinical efficacy and tolerability of perampanel in patients with HGGs, in accordance with the STROBE guidelines for observational studies.[14] All patients formally provided informed consent to participate in the study, which was approved by the Ethics Committee of Papa Giovanni XXIII Hospital (approval number 046/23, dated 05/06/2023). Patients were recruited from the Neurology Department of Papa Giovanni XXIII Hospital (Bergamo), the Neurology Department of IRCCS San Gerardo dei Tintori (Monza), the Head–Neck and Neurosciences Department of "Santa Maria della Misericordia" University Hospital (Udine), and the Neurology Unit of Alessandro Manzoni Hospital (Lecco). As none of the authors are native English speakers, AI tools were used to support the proofreading and language editing of the manuscript.

2.2 | Sample size estimate

This study was conceived as an exploratory pilot investigation conducted within the framework of an interim analysis and aimed at hypothesis generation. Therefore, no formal sample size calculation based on statistical power was performed. The target sample size was defined pragmatically, based on the number of eligible patients who could be realistically recruited during the study period, considering the rarity of high-grade glioma–related epilepsy and the restrictive inclusion criteria. Previous observational studies[11,15] provided a clinical context for the expected magnitude of perampanel effects; however, their heterogeneous patient populations and different study designs precluded their use for formal sample size estimation in the present study. Accordingly, all quantitative analyses should be interpreted as exploratory. The study was not powered to detect small or moderate effects or to support definitive conclusions regarding efficacy or prognostic factors. Instead, the primary aim was to assess feasibility, safety, and potential early signals in previously unexplored domains, in order to inform the design of future adequately powered studies.

2.3 | Sample characteristics

Eligible patients were adults (age >18 years) with a diagnosis of HGG or glioblastoma (diffuse adult astrocytoma, IDH-mutated, grade 3 or 4 or glioblastoma, IDH1 wt) and BTRE, who had experienced at least three seizures within the previous 6 weeks despite first-line anti-seizure therapy. All eligible patients received a histological and molecular diagnosis of high-grade glioma or glioblastoma according to the WHO 2021[16] classification and the AIOM (Italian Association of Medical Oncology) 2023 guidelines.[17] For all tumors of glial origin, the molecular profile was assessed, including IDH mutation status, 1p/19q codeletion, and homozygous deletion of CDKN2A/2B. In addition, for diffuse IDH-wild-type astrocytomas, the absence of EGFR amplification, TERT promoter mutation, and combined gain of chromosome 7 and loss of chromosome 10 were confirmed. The diagnosis of tumor-related epilepsy was based on the ILAE 2014 definition,[18] supplemented by the 2015 guidelines of the American Academy of Neurology. Accordingly, epilepsy was diagnosed in patients who experienced even a single seizure in the presence of a congruent structural brain lesion. Exclusion criteria included nonepileptic paroxysmic events, pregnancy or potential

pregnancy within the 2 months prior to enrollment, a history of alcohol or substance abuse, moderate and/or severe hepatic or renal insufficiency, and active hematologic disorders.

2.4 | Procedures, objectives, and outcomes

The enrollment period spanned from October 2023 to January 2025. The observational follow-up was halted on June 30, 2025, in order to obtain preliminary data corresponding to the completion of 6 months of treatment for the last enrolled patient. All visits were in person. Participating physicians enrolled patients referred to the epilepsy clinic who met the study's inclusion and exclusion criteria. Collected data included demographics (name, birthdate, sex, enrollment date); epilepsy history (onset date, seizure type, concomitant medications); tumor-related clinical data (histology, molecular profile, grade, surgeries, chemotherapy and radiotherapy dates, corticosteroid use); epilepsy-related clinical data (monthly seizure frequency from diaries and neurological exams); and investigations (most recent EEG, MRI, and CT). At 6- and 12-month follow-ups, additional data were recorded on epilepsy (seizure frequency, neurological exams, ASM dose changes, adverse events), tumor treatment updates, imaging results, and disease status per RANO criteria.[19] Seizure frequency was calculated based on the number of events occurring in the 30 days prior to the initiation of perampanel therapy (T0) and in the 30 days preceding the 6-month evaluation (T1). Perampanel was titrated every 14 days, starting from 2 mg/day, according to prescribing information. During follow-up, two patients discontinued treatment early due to adverse events (one at 13 days and one at 91 days from enrollment). For the 6-month efficacy analysis, patients were required to have at least one complete 30-day post-baseline observation period, consistent with the definition of monthly seizure frequency. Patients with <30 days of follow-up could not contribute interpretable seizure data and were therefore excluded. Conversely, patients who died or discontinued treatment after ≥30 days were retained in the efficacy dataset, and their last available seizure observations within the 6-month window were used. As a result, 13 patients were included in the 6-month efficacy analysis. After the 6-month follow-up, two additional patients died (one at 256 days and one at 279 days from enrollment). At the cut-off date of June 30, 2025, four patients had not yet reached 12 months of follow-up, while three patients had completed the 12-month evaluation (T2) (Figure 1). The prospective study was authorized for a maximum follow-up of 18 months; however, this report discusses preliminary data related to the first 6 months. The primary end point was the change in monthly seizure frequency (seizures/month, S/M) between T0 and T1 and responder rates, defined as a ≥ 50% reduction in seizure frequency (50% responder rate). Quality of life (QoL) data were also collected using the QLQ-C30[20] and QLQ-BN20[21] scales at both T1 and T2, and fatal events of deceased patients were recorded. Adverse events (AEs) were reported by patients, using their diary. Patients were instructed to promptly contact their clinician at the onset of any AE. Finally, AEs were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, Cancer Therapy Evaluation Program, 2003), and assessed using the Adverse Events Profile.[22]

2.5 | Statistical analysis

Normality of continuous variables was assessed using the Shapiro–Wilk test. Baseline seizure frequency showed a significantly skewed distribution (Shapiro–Wilk $p < 0.01$); therefore, a logarithmic transformation ($\log[X+1]$) was applied to reduce skewness. After log-transformation, the distribution was compatible with normality (Shapiro–Wilk $p > 0.05$), allowing the use of parametric tests in the main analyses. For descriptive and clinical contextualization purposes only,

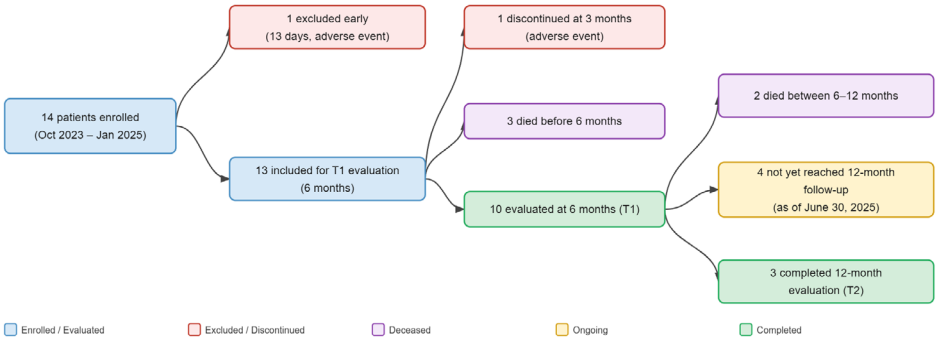

FIGURE 1 Flow-chart enrollment.

a ≥ 50% reduction in monthly seizure frequency was also reported as a conventional responder threshold, in accordance with epilepsy and BTRE literature. This dichotomized measure was not used for inferential testing and was included solely to facilitate comparability with previously published studies. In accordance with recommended practice for skewed variables, descriptive statistics are reported as median and interquartile range (IQR), whereas inferential analyses were performed on log-transformed values. The change in monthly seizure frequency between baseline (T0) and 6 months (T1) was analyzed using a paired *t*-test applied to log-transformed seizure data, with results reported as mean differences and 95% confidence intervals. Clinical response rates (≥50% reduction in seizures) and categorical variables were reported as frequencies and percentages. To assess the significance of the effects of age and epilepsy duration on improvement, a bootstrap analysis with 1000 replications was performed, which is useful for evaluating the stability of *p*-values in the context of a small sample size.[23] Age and epilepsy duration were included as clinically relevant potential confounders known to influence seizure burden and treatment response in BTRE. Their relevance was evaluated across exploratory models incorporating tumor-related variables (histology, location, IDH status), demographic variables (age, sex), and epilepsy-related variables (duration defined either as onset-to-baseline or onset-to-PER initiation). A bootstrap procedure (1000 replications) was used to assess the stability of *p*-values and the robustness of effect estimates, confirming the consistent association of age and epilepsy duration with clinical improvement. We also verified the detected clinical effect with Cohen's Effect Size analysis.[24] Survival analysis was conducted using a Cox proportional hazards regression model, and Hazard ratios were reported together with their 95% confidence intervals, including age, epilepsy duration at T0, tumor type, seizure type, and neurological deficits as covariates. Covariates included in the final Cox model were selected through a two-step process: (i) exploratory Cox models grouping demographic, tumor-related, and epilepsy-related variables were first tested independently; (ii) variables showing a trend toward significance or strong clinical plausibility were retained in order to avoid overfitting while preserving control for potential confounders. Model robustness was further evaluated using a bootstrap procedure with 1000 replications, which confirmed the stability of the estimated effects—particularly, for epilepsy duration. Additionally, survival curves for different clinical subgroups were estimated using the Kaplan–Meier method, and compared via the log-rank test to evaluate significant differences. Subgroups were chosen based on clinical relevance (seizure type, treatment response, histology, tumor location, laterality, grade, and IDH status), reflecting categories commonly used in BTRE research to describe prognostic differences. Given the limited sample size, these subgroups analyses were considered exploratory and descriptive, aimed at visualizing potential trends without influencing the primary conclusions derived from the Cox models. To explore potential predictors of AEs, all baseline (T0) demographic, tumor-related, and epilepsy-related variables were tested for association with the percentage of AEs reported during follow-up. Odds ratios were calculated with corresponding 95% confidence intervals and continuous variables were analyzed using correlation tests (Pearson or Spearman according to distribution), while categorical variables were compared using *t*-tests or nonparametric equivalents. This analysis was prespecified as exploratory and aimed at identifying potential clinical factors associated with tolerability. Variables not showing significant association were reported in the Results section. Quality of life (QoL) outcomes, measured with the QLQ-C30 and QLQ-BN20 instruments, were compared between T0 and T1 (and T2, when available), using parametric or nonparametric tests, depending on data distribution. Differences are reported as means, SDs, and confidence intervals. Bootstrap methods were also applied to QoL outcomes to test the robustness of the results. Statistical analyses were performed using R Studio (R Software, version 4.4.1).

3 | RESULTS

The study included 14 patients with BTRE, all diagnosed with either glioblastoma ($n = 7$) or HGGs ($n = 7$). The mean age at enrollment was 53.3 years (SD = 15.4). They were six females and eight males, with a median duration of epilepsy (ONSETE: the number of days between the first documented seizure onset and the baseline study visit) of 328 days (IQR 87, 8-1013) and days of seizure before PER therapy (TPER: the number of days between seizure onset and the initiation of add-on perampanel therapy) 301 (IQR 67–895) (Table 1). The median seizure frequency at baseline was 12.5 seizures per month (IQR 4-37.5). Perampanel treatment was initiated at a dose of 2 mg/day and titrated to a maintenance dose of 4 mg/day for eight patients, 6 mg/day for three patients, and 8 mg/day for two patients, added to existing ASM regimens. Only one patient remained on a stable dose of 2 mg/day. Dose reduction due to AEs was required in two patients, who were both titrated to 4 mg/day of perampanel. Two patients had their AEs doses reduced, and both underwent a PER titration to

TABLE 1 Baseline characteristics of the recruited patients are presented as mean ± standard deviation (SD) for continuous variables, and as frequency (*f*) with percentage (%) for categorical variables.

Variable	Value (median[IQR] or mean ± SD) *N* = 14
Females (*n*, %)	6 (42.9)
Age (y, mean ± SD)	53.3 ± 15.4
ONSETE (d, median [IQR])	301 [67–1099]
TPER (d, median [IQR])	301 [59–1169]
Seizure frequency at baseline (*n*, median [IQR])	10 [4–40]
Memory deficit (*n*, %)	4 (28.6)
Cognitive deficit (*n*, %)	5 (35.7)
Motor signs (*n*, %)	6 (42.9)
Sensory deficit (*n*, %)	6 (42.9)
Chemiotherapy + radiotherapy (*n*, %)	8 (57.1)
Only bradiotherapy (*n*, %)	1 (7.1)

Note: *N* indicates the total number of patients.

Abbreviations: d, days; *f*, frequency; *n*, number; SD, standard deviation; y, years.

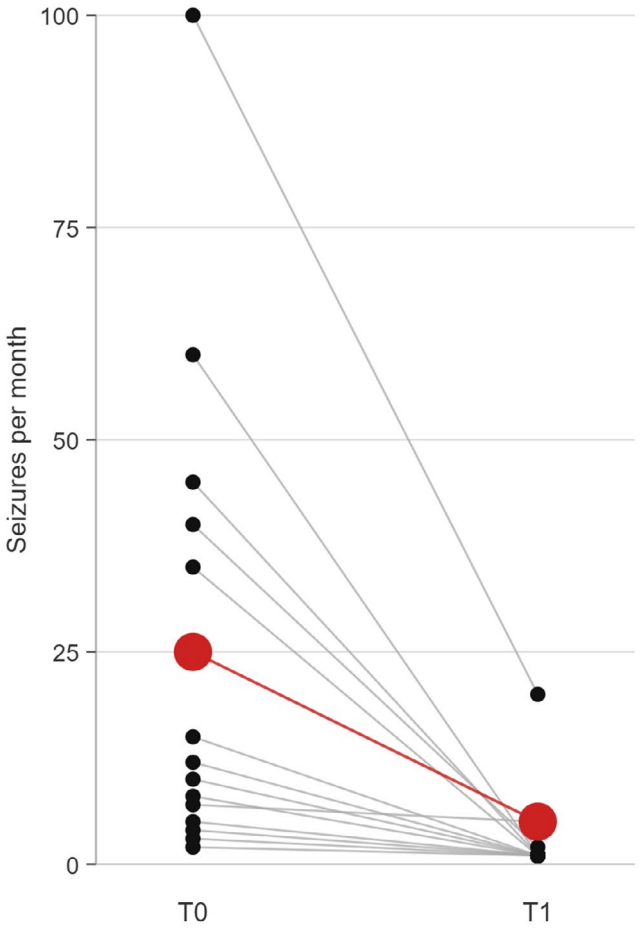

FIGURE 2 Boxplots comparing the monthly seizure frequency at baseline (T0) and at 6 months (T1) after perampanel treatment (left panel). Individual patient trajectories showing seizure frequency reduction from T0 to T1 (right panel). Blue and green dots indicate individual seizure counts at T0 and T1, respectively, with gray lines connecting paired measurements. Diamonds represent the mean seizure frequency at each time point.

4 mg/day. Although descriptive statistics are reported as median and IQR, due to the skewed distribution of baseline seizure frequency, the corresponding standard deviation (SD = 28.5) remained lower than that observed in a previous heterogeneous cohort.[11] This finding is consistent with the expected reduction in variability associated with a more homogeneous population of HGGs and glioblastomas. At the time of evaluation, eight patients had undergone chemotherapy and radiotherapy and only one underwent radiotherapy alone. During the 6 months of follow-up, no additional oncological therapies were started. Only one patient underwent second surgery. The complete characteristics of each patient have been included in Data S2, in the additional materials.

3.1 | Seizure (primary endpoint)

After the introduction of PER, the markedly skewed distribution of baseline seizure frequency required reporting descriptive statistics as median and IQR. The median monthly seizure frequency decreased from 12.5 (IQR 4–37.5) at baseline to 3 (IQR 0–7) at 6 months. After log-transformation to correct for the strong right-skew of seizure counts, seizure frequency showed a statistically significant reduction from T0 to T1 (paired *t*-test: $t = -5.14$, df = 12, $p = 0.00023$). The mean log-difference was −2.03 (SD = 1.43), with a 95% CI ranging from −2.90 to −1.17. Eleven patients (78.6%) achieved ≥50% seizure reduction, while eight patients (57.1%) became seizure-free (Figure 2). At 12 months, seizure data were available for three patients, all seizure-free. No significant correlations were found between seizure reduction and age, sex, epilepsy duration, or any other demographic variables. To assess whether age or epilepsy duration acted as potential confounders, a bootstrap analysis with 1000 replications was performed. The bootstrap *p*-values showed high variability and no consistent evidence of association (age: mean $p = 0.48$, 95% CI: 0.002–0.97; epilepsy duration: mean $p = 0.49$, 95% CI: 0.003–0.97), indicating that the data are insufficient to draw reliable conclusions.

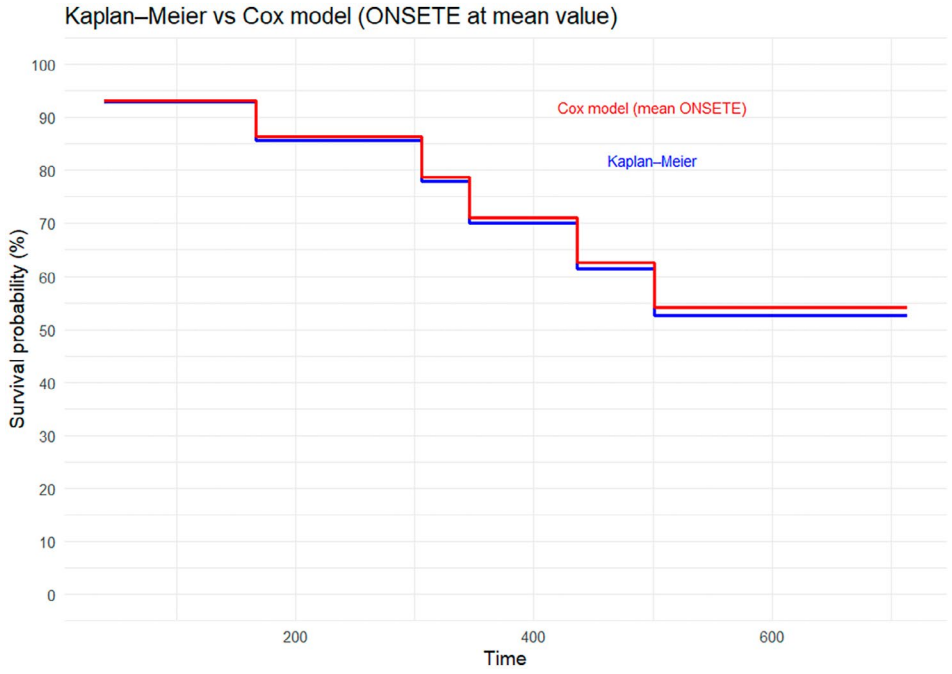

FIGURE 3 Overall survival estimated with the Kaplan–Meier curve and the survival curve predicted by the Cox model adjusted for ONSETE, calculated at the mean values of the covariates. The curves are overlaid for visual comparison of survival trends over time.

3.2 | Adverse events

Among the 14 patients, AEs recorded included somnolence, irritability, obtundation, asthenia and drowsiness, and headache, with the majority (nine patients—64.2%) reporting no AEs (Data S2). Only two patients discontinued treatment due to AEs, indicating that the PER was generally well tolerated. The percentage of patients experiencing AEs was higher in the IDH1-mutated group compared with the IDH1-WT group (OR: 0.09 95% CI: [0.001–1.55] $p = 0.09$). No other T0 variables correlated with the percentage of AEs. However, the wide intervals and the results of the bootstrap sensitivity analysis suggest uncertainty in the estimate, due to the small sample size. Overall, all patients successfully titrated the ASM regimen, supporting the feasibility of treatment despite some adverse effects.

3.3 | Survival

A Cox proportional hazards model adjusted for age, ONSETE, maximum daily dose of therapy, and TPER was used to assess the impact of these covariates on overall patient survival. Results showed no significant effect of age (HR = 1.05 CI: 95% 0.94–1.16, $p = 0.23$), maximum daily dose of PER (HR = 1.03 CI: 95% 0.93–1.08, $p = 0.43$), or TPER (HR = 0.96 CI: 95% 0.91–1.03, $p = 0.35$). Survival was subsequently modeled using a Cox proportional hazards analysis with ONSETE (time from the onset of epileptic seizures) as the covariate alone (Figure 3). The estimated coefficient for ONSETE was −0.00337 (hazard ratio = 0.997, 95% CI: 0.992–1.001), with a significant likelihood ratio test ($p = 0.01$). To assess the robustness of this estimate, a bootstrap analysis with 1000 replications was performed. The mean bootstrap coefficient was −0.0149, with a 95% confidence interval ranging from −0.234 to −0.0013. Kaplan–Meier analysis revealed no significant differences in survival between responders and nonresponders to treatment ($p = 0.88$). Furthermore, tumor type, seizure type, and the presence of neurological deficits were not significant covariates. Survival curves for various clinical subgroups (crisis type, treatment response, histology, tumor location, laterality, grade, and IDH status) were estimated using the Kaplan–Meier method and compared by log-rank tests, which showed no significant differences between groups.

3.4 | QoL

The differences in selected QLQ-C30 and QLQ-BN20 domains between baseline and follow-up (T1) did not reach statistical significance (all $p > 0.05$). The domains communication deficits (CD), loss of appetite (AP), and pain (PA) had p-values of 0.09, 0.17, and 0.18, respectively (Figure 4). Bootstrap analyses for CD and AP yielded mean bootstrap p-values below 0.15, whereas the PA domain showed a

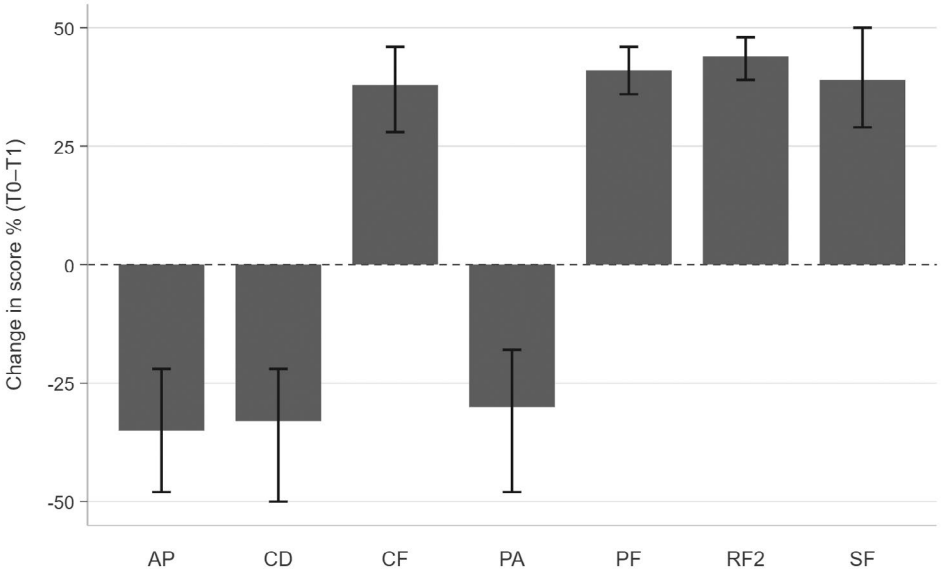

FIGURE 4 Percentage change in QoL items with *p*-value between T0 and T1 ≤ 0.20.

high bootstrap *p*-value. These results indicate variability in the estimates and do not allow reliable conclusions in this small sample.

4 | DISCUSSION

Perampanel is an AMPA receptor antagonist used in the treatment of epilepsy associated with brain tumors. Clinical studies have demonstrated its efficacy in seizure control, with a significant reduction in seizure frequency in many patients. However, the incidence of AEs varies across studies. For example, in one observational study, 30.6% of patients reported AEs, including anxiety, aggression, dizziness, and fatigue, although none discontinued treatment due to these effects.[13] Although our study did not directly measure 2-HG levels or NMDA receptor activity, previous literature suggests that the IDH1 mutation leads to the production of D-2-hydroxyglutarate (2-HG), an oncometabolite structurally similar to glutamate. 2-HG could theoretically act as an agonist at NMDA receptors, potentially promoting neuronal hyperexcitability and increasing the risk of seizure generation.[25] Perampanel, by contrast, antagonizes AMPA receptors, helping to dampen excitatory neurotransmission and restore synaptic balance. Experimental models have shown that PER may also enhance synaptic plasticity and reduce neuronal excitability.[26] Despite its therapeutic benefits, PER is associated with a risk of AEs in some patients, including somnolence, irritability, and headache. The co-presence of 2-HG with its glutamatergic agonist activity could theoretically modulate patients' sensitivity to AMPA antagonism, thus influencing both efficacy and AEs susceptibility.[27] Our findings demonstrate that following the introduction of PER, the markedly skewed distribution of seizure counts required reporting medians rather than means; accordingly, seizure frequency decreased from a median of 12.5 seizures/month at baseline to 3 at 6 months, with a responder rate of 78.6% and seizure freedom achieved in 57.1% of patients. These effects would appear to indicate an anticonvulsant response to PER in our BTRE cohort, consistent with results reported in previous observational studies. A study by Coppola et al.[13] showed high efficacy of PER in BTRE, with responder rates around 90% and a favorable tolerability profile. Similarly, a recent systematic review reported responder rates ranging from 75% to 95% at 6–12 months, with seizure freedom observed in up to 94% of cases.[28] All AEs observed in our study were grade 1 or 2, and a possible correlation with IDH1 mutation was noted. The patients who discontinued treatment due to AEs were both IDH1-mutated. A previous study[28] reported a significant reduction in seizure frequency, particularly in patients with IDH1 mutations treated with perampanel. Regarding the lack of association between age or epilepsy duration and seizure reduction, some studies in non-BTRE epilepsy populations have suggested that younger age and shorter epilepsy duration may be associated with better treatment response.[29] However, in case of BTRE, this association remains poorly defined, as highlighted by recent studies that emphasize the complexity of identifying reliable predictive factors in these patients, as well as the intricate pathophysiological mechanisms underlying BTRE itself. These factors continue to challenge the identification of clear treatment response predictors.[25,30] In our cohort, Cox regression adjusted for age, ONSETE, maximum daily dose of PER, and TPER yielded no significant effect of any of the covariates on overall survival from seizure onset, although the trend

for ONSETE suggests a possible protective association. Similarly, tumor type, seizure type, and neurological deficits are prognostically inconclusive, and subgroup analyses by histology, tumor location, laterality, grade, and IDH status revealed no distinct survival patterns. Although there is evidence that seizures may be associated with longer survival in patients with HGGs,[31] the specific relationship between seizure duration and survival remains unclear. The role of glutamate and epileptogenic brain regions is a promising area of research that could offer new therapeutic perspectives. These findings are consistent with the ambiguous role of epilepsy as a prognostic marker in glioblastoma and other brain tumors: while some studies report improved survival in patients with seizures at presentation,[32,33] others find no clear independent effect.[34] The recent systematic review and meta-analysis[28] also highlights this controversy, showing a pooled HR of ~0.73 in favor of seizures, but with considerable heterogeneity. Our data suggest that, in a small prospectively followed BTRE cohort, seizure control alone may not substantially affect survival, underscoring that tumor biology and oncological therapies likely remain the dominant determinants of patient outcome. The analysis of selected QLQ-C30 and QLQ-BN20 domains did not reveal statistically significant changes between baseline and follow-up (T1), with all p-values exceeding 0.05. In specific domains, such as communication deficits (CD) and appetite loss (AP), numerical improvements were observed ($p = 0.09$ and $p = 0.10$, respectively); however, these differences did not reach statistical significance. Given the exploratory and potentially underpowered nature of the analysis, these findings should be considered hypothesis-generating and require confirmation in larger studies. These findings were reinforced by bootstrap analysis, which yielded p-values below 0.15 for both domains, suggesting a consistent signal of improvement. These trends are particularly noteworthy, considering the known impact of communication deficits and appetite loss on the overall well-being of patients with brain tumors. Communication deficits have been associated with decreased social functioning and emotional distress,[34] while appetite loss is commonly linked to disease burden and treatment-related AEs, with implications for nutritional status and physical functioning.[3,35] These exploratory trends, while preliminary, warrant further investigation in larger cohorts to confirm whether seizure control may influence patient-perceived well-being.

4.1 | Study limitations

An important limitation of this study is the relatively small sample size. Although 14 patients were initially enrolled, outcome analysis at the 6-month follow-up was conducted on 13 patients, as one withdrew from the study at a very early stage. Based on preliminary data, a sample of 14 patients would have been sufficient to achieve 80% statistical power to detect a significant difference in seizure frequency. However, the loss of one patient reduced the effective power to approximately 71%, slightly below the conventional 80% threshold, indicating a modest risk of type II error. Nevertheless, the reduction in seizure frequency from baseline (mean 25.2 ± 28.5 seizures/month) to the 6-month follow-up (mean 2.4 ± 5.5 seizures/month) was statistically significant. The effect size calculated using Cohen's d was large ($d = 0.78$), suggesting a clinically relevant impact of the treatment. The standard deviation of the difference in seizure frequency (29.6) reflects substantial inter-patient variability. To avoid misinterpretation, we clarify that the value 29.6 refers exclusively to the within-patient change from baseline to 6 months and is not directly comparable to baseline SDs reported in external studies. This variability is a common challenge when investigating primary endpoints in small cohorts. Moreover, the evaluation of survival outcomes, AEs, and QoL would benefit from a larger patient population to enhance statistical robustness and detect more subtle effects. While bootstrap analyses provided some support for the stability of observed effects, the low power and small cohort size limit definitive conclusions. These limitations underscore the need for larger, multicenter prospective studies to validate these findings and clarify the potential influence of clinical variables, including IDH mutation status, on both efficacy and safety profiles of perampanel in BTRE.

5 | CONCLUSIONS

The results of this prospective pilot study demonstrate the feasibility of perampanel use in a real-world BTRE setting and provide preliminary information on its safety profile. A reduction in seizure frequency was observed at 6 months, with a high proportion of responders and seizure-free patients. However, due to the small sample size and the skewed distribution of seizure counts, given the exploratory design and limited sample size, efficacy outcomes should be interpreted cautiously and considered preliminary. AEs were mostly mild, and only two patients discontinued treatment, supporting the overall tolerability of the drug in this cohort. No statistically significant changes were detected in quality-of-life domains and the study was not powered to detect differences in these secondary outcomes. Survival analyses did not identify significant prognostic effects of PER-related or clinical variables. Within the limits of the sample size, survival outcomes appeared to be mainly influenced by tumor-related factors rather than PER exposure. Larger,

multicenter studies with adequate power are needed to confirm these observations, clarify the potential influence of molecular markers such as IDH-1 mutation, and better define the clinical role of PER in seizure control, QoL, and patient-centered outcomes.

6 | CLINICAL RELEVANCE OR FUTURE DIRECTIONS

This prospective multicenter study provides real-world data on the efficacy and safety of perampanel in treating seizures associated with HGGs. The significant seizure reduction observed in a homogeneous, albeit small, sample represents an important contribution compared with previous often heterogeneous studies. Statistical analysis, including bootstrap analysis, supports the reliability of trends toward innovative findings, such as the association between seizure duration and survival, and the impact of IDH-1 mutations on AEs. These findings may open new avenues for future translational research aimed at better understanding glutamatergic mechanisms in glioma and optimizing the treatment of tumor-related personalized management of tumor-related epilepsy, confirming perampanel's value in everyday clinical practice.

AUTHOR CONTRIBUTIONS

MI: Participated in the study design, contributed to data acquisition, and was involved in both the drafting and critical revision of the manuscript. PP: Contributed to the study conception, data acquisition and analysis, interpretation of results, and was involved in drafting and final revision of the manuscript. GP: Assisted in study design and data collection, and contributed to both drafting and revising the manuscript. AN: Supported data collection and organization, and contributed to drafting and critically revising the manuscript. AB: Contributed to clinical data collection and was involved in drafting and reviewing the manuscript. AS: Participated in data acquisition and contributed to the drafting and revision of the manuscript. SC: Contributed to scientific supervision, manuscript drafting, and critical revision for intellectual content. SQ: Participated in the study conception and provided overall supervision, contributing to both manuscript drafting and its final revision. All authors approved the final version of the manuscript and take full responsibility for every aspect of the work.

ACKNOWLEDGMENTS

The authors sincerely thank all the patients who generously contributed by sharing their data, making this study possible and advancing scientific knowledge in this field. Open access publishing facilitated by Aziende Socio Sanitarie Territoriale Papa Giovanni XXIII, as part of the Wiley - SBBL agreement.

FUNDING INFORMATION

No funding, grants, or other support was received for the conception, preparation, or conduct of this manuscript.

CONFLICT OF INTEREST STATEMENT

All the authors have received no financial or other support from any organization for the work submitted. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the study are available in CSV format, while the R Studio scripts used for the statistical analyses are provided in a PDF file. Both files are stored in a dedicated repository shared with the publisher. Additional Supporting Information, if of interest, can be requested by contacting ppaone@asst-pg23.it.

CONSENT

All patients signed informed consent prior to enrollment in the perampanel drug program. Patient enrollment was possible after the protocol and accompanying documents were approved by the Ethics Committee of the ASST Papa Giovanni XXIII in Bergamo, subsequently authorized by the Italian Medicines Agency.

ORCID

Matteo Impellizzeri https://orcid.org/0000-0002-8861-5303
Paolo Paone https://orcid.org/0000-0002-1505-746X
Giada Pauletto https://orcid.org/0000-0002-8875-6640
Annacarmen Nilo https://orcid.org/0000-0001-9827-8059
Simone Beretta https://orcid.org/0000-0002-9417-2748
Andrea Salmaggi https://orcid.org/0000-0001-6925-3434
Stefano Consoli https://orcid.org/0000-0003-2523-4578
Stefano Quadri https://orcid.org/0000-0001-9696-6878

REFERENCES

1. Wen PY, Weller M, Lee EQ, Touat M. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. Neuro Oncol. 2025;27:2751–88.
2. Prakash O, Lukiw WJ, Peruzzi F, Reiss K, Musto AE. Gliomas and seizures. Med hypotheses. 2012;79(5):622–6. https://doi.org/10.1016/j.mehy.2012.07.037

3. Lange F, Hörnschemeyer J, Kirschstein T. Glutamatergic mechanisms in glioblastoma and tumor- associated epilepsy. Cells. 2021;10(5):1226. https://doi.org/10.3390/cells10051226
4. Aronica E, Ciusani E, Coppola A, Costa C, Russo E, Salmaggi A, et al. Epilepsy and brain tumors: two sides of the same coin. J Neurol Sci. 2023;15(446):120584. https://doi.org/10.1016/j.jns.2023.120584
5. Michelucci R, Pauletto G, Silvani A, Pasini E, Ius T, Martinoni M, et al. Tumor-related epilepsy in glioma: a multidisciplinary overview.; Italian multidisciplinary Group for Tumor Epilepsy. Epilepsia. 2025;66:3621–41. https://doi.org/10.1111/epi.18523
6. Lange F, Weßlau K, Porath K, Hörnschemeyer MF, Bergner C, Krause BJ, et al. AMPA receptor antagonist perampanel affects glioblastoma cell growth and glutamate release in vitro. PLoS One. 2019;14(2):e0211644. https://doi.org/10.1371/journal.pone.0211644
7. Salmaggi A, Corno C, Maschio M, Donzelli S, D'Urso A, Perego P, et al. Synergistic effect of perampanel and temozolomide in human glioma cell lines. J Pers Med. 2021;11(5):390. https://doi.org/10.3390/jpm11050390
8. Venkatesh HS, Morishita W, Geraghty AC, Silverbush D, Gillespie SM, Arzt M, et al. Electrical and synaptic integration of glioma into neural circuits. Nature. 2019;573(7775):539–45. https://doi.org/10.1038/s41586-019-1563-y
9. Tabaee P, Pasini F, Fanella G, Cereda G, Mainini G, DiFrancesco J, et al. Perampanel in brain tumor-related epilepsy: a systematic review. Brain Sci. 2023;13(2):326. https://doi.org/10.3390/brainsci13020326
10. Nishide T, Yamamuro S, Sano E, Aida Y, Nara K, Yazawa G, et al. Synergistic effect of perampanel with temozolomide on glioblastoma cells in vivo. Heliyon Mar. 2025;11:e43167. https://doi.org/10.1016/j.heliyon.2025.e43167
11. Maschio M, Zarabla A, Maialetti A, Giannarelli D, Koudriavtseva T, Villani V, et al. Perampanel in brain tumor-related epilepsy: observational pilot study. Brain Behav. 2020;10(6):e01612. https://doi.org/10.1002/brb3.1612
12. Gilliam FG, Fessler AJ, Baker G, Vahle V, Carter J, Attarian H. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. Neurology. 2004;62(1):23–7. https://doi.org/10.1212/wnl.62.1.23
13. Coppola A, Zarabla A, Maialetti A, Villani V, Koudriavtseva T, Russo E, et al. Perampanel confirms to Be effective and well-tolerated as an add-on treatment in patients with brain tumor-related epilepsy (PERADET study). Front Neurol. 2020;25(11):592.
14. von E, Altman DG, Egger M, Pocock S, Gøtzsche P, Vandenbroucke J. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet. 2007;370(9596):1453–7. https://doi.org/10.1016/S0140-6736(07)61602-X
15. Vecht CJ, Kerkhof M, Duran-Pena A. Seizure prognosis in brain tumors: new insights and evidence-based management. Oncologist. 2014;19(7):751–9. https://doi.org/10.1634/theoncologist.2014-0060
16. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neuro Oncol. 2021;23(8):1231–51.
17. https://www.aiom.it/linee-guida-aiom-2023-neoplasie-cerebrali/
18. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82. https://doi.org/10.1111/epi.12550
19. Wen PY, van den Bent M, Youssef G, Cloughesy TF, Ellingson BM, Weller M, et al. RANO 2.0: update to the response assessment in neuro-oncology criteria for high- and low-grade gliomas in adults. J Clin Oncol. 2023;41(33):5187–99. https://doi.org/10.1200/JCO.23.01059
20. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76. https://doi.org/10.1093/jnci/85.5.365
21. Taphoorn MJ, Claassens L, Aaronson NK, Coens C, Mauer M, Osoba D, et al. Bottomley a; EORTC quality of life group, and brain cancer, NCIC and radiotherapy groups. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. Eur J Cancer. 2010;46(6):1033–40. https://doi.org/10.1016/j.ejca.2010.01.012
22. Baker GA, Frances P, Middleton E. Initial development, reliability, and validity of a patient-based adverse events scale. Epilepsia. 1994;35(suppl 7):80.
23. Thomas EV. Use of the bias-corrected parametric bootstrap in sensitivity testing/analysis to construct confidence bounds with accurate levels of coverage. J Qual Technol. 2023;55:4. https://doi.org/10.1080/00224065.2023.2185558
24. Cohen J. Statistical power analysis for the behavioral sciences. Routledge; 1988. United Kingdom Editions published by ACADEMIC PRESS, INC. (London) LTD. https://doi.org10/4324/9780203771587
25. Avila EK, Tobochnik S, Inati SK, Koekkoek JAF, McKhann GM, Riviello JJ, et al. Brain tumor-related epilepsy management: a Society for Neuro-oncology (SNO) consensus review on current management. Neuro Oncol. 2024;26(1):7–24.
26. Chen H, Judkins J, Thomas C, Wu M, Khoury L, Benjamin CG, et al. Mutant IDH1 and seizures in patients with glioma. Neurology. 2017;88(19):1805–13. https://doi.org/10.1212/WNL.0000000000003911
27. Bellingacci L, Tallarico M, Mancini A, Megaro A, De Caro C, Citraro R, et al. Non-competitive AMPA glutamate receptors antagonism by perampanel as a strategy to counteract hippocampal hyper-excitability and cognitive deficits in cerebral amyloidosis. Neuropharmacology. 2023;225:109373. https://doi.org/10.1016/j.neuropharm.2022.109373
28. Rossi J, Cavallieri F, MC B. Efficacy and tolerability of Perampanel in brain tumor-related epilepsy: A Systematic Review. Biomedicine. 2023;11(3):651. https://doi.org/10.3390/biomedicines11030651
29. Bjellvi J, Olsson I, Malmgren K, Wilbe RK. Epilepsy duration and seizure outcome in epilepsy surgery: a systematic review and meta-analysis. Neurology. 2019;93(2):e159–e166. https://doi.org/10.1212/WNL.0000000000007753
30. Zhang X, Zheng L, Duan J, Li Z, Tang Y. Clinical characteristics of brain tumor related epilepsy and factors influencing the

identification of epilepsy-associated tumors. Acta Epileptologic. 2020;2:25. https://doi.org/10.1186/s42494-020-00034-w
31. Rilinger RG, Guo L, Sharma A, Volovetz J, Thompson NR, Grabowski M, et al. Tumor-related epilepsy in high-grade glioma: a large series survival analysis. J Neurooncol. 2024;170(1):153–60. https://doi.org/10.1007/s11060-024-04787-z
32. Berendsen S, Kroonen J, Seute T, Snijders TJ, Broekman ML, Spliet WGM, et al. Prognostic relevance of epilepsy at presentation in glioblastoma patients. Neuro Oncol. 2016;18(5):700–6.
33. Toledo M, Sarria Estrada S, Quintana M, Maldonado X, Martinez Ricarte F, Rodon J, et al. Prognostic implications of epilepsy in glioblastomas. Clin Neurol Neurosurg. 2015;139:166–71. https://doi.org/10.1016/j.clineuro.2015.10.002
34. Dobran M, Nasi D, Chiriatti S, Gladi M, Somma LD, Iacoangeli M, et al. Prognostic factors in glioblastoma: is there a role for epilepsy? Neurol med Chir (Tokyo). 2018;58:110–5. https://doi.org/10.2176/nmc.oa.2017-0167
35. Heimans JJ, Taphoorn MJ. Impact of brain tumour treatment on quality of life. J Neurol. 2002;249(8):955–60. https://doi.org/10.1007/s00415-002-0839-5

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Impellizzeri M, Paone P, Pauletto G, Nilo A, Beretta S, Salmaggi A, et al. Perampanel as add-on in high-grade glioma–related epilepsy: Seizure control and QoL in a prospective, multicenter, real-world 6-month follow-up study. Epilepsia Open. 2026;00:1–12. https://doi.org/10.1002/epi4.70274