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Evaluation of the efficacy and tolerability of bevacizumab-based treatments in recurrent primary brain tumors: a multicenter real-world Turkish Oncology Group (TOG) study

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Abstract

Background Bevacizumab is widely used for recurrent high-grade glioma, but the real-world effectiveness of bevacizumab with or without irinotecan remains uncertain. We evaluated outcomes of bevacizumab-based regimens in a large multicenter Turkish cohort.

Methods In this retrospective study from 30 centers, adults with recurrent glioblastoma or other primary brain tumors treated with a bevacizumab-containing regimen at first or second progression were included. Patients received bevacizumab monotherapy, bevacizumab plus low-dose weekly irinotecan, or bevacizumab plus standard-dose irinotecan every 14 days. Tumor response, progression-free survival (PFS), overall survival (OS), and toxicity were assessed. Prognostic factors were analyzed using Cox regression.

Results A total of 437 patients were included; 78.0% had glioblastoma. Treatment consisted of bevacizumab monotherapy in 9.4%, bevacizumab plus weekly irinotecan in 8.5%, and bevacizumab plus irinotecan every 14 days in 82.2% of patients. The objective response rate was 41.6%, and the disease control rate was 80.1%. Median OS was 10.77, 7.37 and 9.77 months (log-rank $p = 0.024$), and median PFS was 5.77, 3.93 and 6.43 months ($p = 0.005$), respectively. On multivariable analysis, glioblastoma histology independently predicted shorter PFS and OS, whereas a higher number of treatment cycles and antiepileptic drug use were associated with longer PFS. For OS, the irinotecan–bevacizumab every-14-day regimen and a higher number of treatment cycles were associated with improved survival compared with bevacizumab monotherapy, while baseline corticosteroid use and discontinuation of bevacizumab-containing therapy were independent adverse prognostic factors.

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Conclusions In this large real-world cohort, bevacizumab-based therapy achieved meaningful disease control and survival in recurrent primary brain tumors. An irinotecan–bevacizumab regimen administered every 14 days was associated with superior OS at the expense of increased but manageable chemotherapy-related toxicity, supporting its use in appropriately selected patients.

Keywords Recurrent glioblastoma, Bevacizumab, Irinotecan, Anti-VEGF therapy

Introduction

Glioblastoma (GBM) represents the most prevalent and biologically aggressive primary brain tumor in adults, typically diagnosed around the fifth to sixth decade of life [1]. Standard management for newly diagnosed GBM involves maximal safe resection followed by radiotherapy administered concurrently with temozolomide, and then adjuvant temozolomide. Despite this multimodal strategy, recurrence remains the expected clinical course for most patients [2, 3]. Earlier analyses of recurrence patterns demonstrated that the majority of relapses occur locally—at or adjacent to the initial tumor site—while multifocal or distant progression is relatively uncommon, although such findings were shaped by earlier surgical and radiotherapy practices [4].

Reported median overall survival (OS) for GBM generally ranges between 14 and 16 months, with only 26–33% of patients alive at two years [2, 5]. Upon recurrence, treatment options become limited. Selected patients may benefit from repeat surgery or re-irradiation, particularly when recurrent tumors are small and performance status is favorable [6–8]. Given the absence of an established standard of care for recurrent GBM, multiple systemic strategies have been explored, and chemotherapy remains an important component of management [9]. Lomustine, either as monotherapy or in combination with procarbazine and vincristine (PCV), is commonly used [10]. Rechallenge with temozolomide is another option that may offer benefit in appropriately selected patients [11–13].

Angiogenesis plays a central role in the pathobiology of high-grade gliomas. Vascular endothelial growth factor (VEGF), a pivotal mediator of this process, is frequently overexpressed in these tumors and is associated with worsened prognosis [14–17]. With growing understanding of the significance of VEGF-driven pathways, bevacizumab— a humanized monoclonal antibody targeting VEGF—was integrated into clinical practice for recurrent GBM. Early clinical studies showed improvements in progression-free survival (PFS) and radiographic response rates with bevacizumab [18]. However, phase III trials were unable to demonstrate a corresponding OS benefit [19, 20].

In solid tumors, bevacizumab is often combined with cytotoxic chemotherapy [21]. In the largest randomized study evaluating lomustine alone versus lomustine plus bevacizumab, combination therapy improved the objective response rate and PFS but not OS [22]. Similarly, combinations of bevacizumab with carboplatin, vorinostat, temsirolimus, or sorafenib did not yield additional benefits over bevacizumab monotherapy [23–26].

Irinotecan, a topoisomerase I inhibitor with demonstrated efficacy across several malignancies, has the advantage of penetrating the blood–brain barrier [27–31]. In a phase II study, combining bevacizumab with irinotecan resulted in a six-month PFS of 46% and an objective response rate of 57% [32]. Another phase II trial comparing bevacizumab monotherapy with bevacizumab plus irinotecan found superior radiological response and PFS with the combination, although OS remained similar between groups [33]. These data suggest that adding irinotecan may improve disease control even if survival benefits are not consistently observed. Importantly, most available evidence arises from clinical trials, and real-world outcomes for bevacizumab-based regimens, with or without irinotecan, remain insufficiently characterized.

In this multicenter retrospective study, we aimed to assess the real-world effectiveness and tolerability of bevacizumab-based treatment regimens in patients with primary brain malignancies.

Materials and methods

Study design and patient population

This retrospective, multicenter study included adults diagnosed with recurrent primary brain malignancies who were treated with a bevacizumab-containing regimen between September 2010 and December 2023 across 30 oncology centers in Turkey. Eligible patients were ≥ 18 years of age, had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and had histologically confirmed glioblastoma, anaplastic astrocytoma, or oligodendroglioma based on surgical resection or biopsy. Bevacizumab-based therapy must have been administered at first or second recurrence.

Patients were excluded if they were pregnant or breastfeeding, had ECOG PS 3, a history of ischemic or hemorrhagic stroke, uncontrolled cardiovascular disease (including hypertension or heart failure), significant hepatic, renal, or hematologic dysfunction, or a second primary malignancy.

The study was approved by the Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: 48670771-514.10) and was

conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

Clinical and demographic variables—including age, sex, baseline ECOG PS, date of diagnosis, recurrence patterns, tumor histopathology, lesion location, use of corticosteroids, antiepileptic therapy, treatment regimen, number of administered cycles, treatment duration, and adverse events—were extracted from electronic medical records.

Treatment selection was determined by treating physicians according to institutional practices, patient clinical status, tolerability considerations, and logistical factors rather than a standardized protocol. Patients were categorized into one of three bevacizumab-based treatment groups:

1. Bevacizumab monotherapy: 10 mg/kg administered every 14 days.
2. Bevacizumab combined with low-dose weekly irinotecan: 80 mg/m² on days 1, 8, and 15 of a 28-day cycle for patients not receiving enzyme-inducing antiepileptic drugs (EIAEDs; oxcarbazepine, carbamazepine, phenytoin, phenobarbital, primidone), and 200 mg/m² for those receiving EIAEDs, together with bevacizumab 10 mg/kg every 14 days.
3. Bevacizumab combined with standard-dose irinotecan: 125 mg/m² for patients not receiving EIAEDs and 340 mg/m² for EIAED users, with bevacizumab administered at 10 mg/kg every 14 days.

Treatment-related adverse events—including gastrointestinal, hematologic, and bevacizumab-associated toxicities (hemorrhage, thrombosis, hypertension, proteinuria) were systematically recorded.

Tumor response and survival outcomes

Radiological evaluation was performed every eight weeks. Radiologic responses were assessed locally by treating investigators at each participating center based on available imaging, reflecting routine clinical practice. Radiological response was evaluated according to the McDonald criteria due to the retrospective and multicenter nature of the study. Standardized longitudinal T2/FLAIR imaging, and centralized blinded image reassessment—required for reliable application of RANO criteria—were not consistently available across participating centers throughout the study period.

PFS was calculated from the initiation of bevacizumab-based therapy to documented radiographic or clinical progression. OS was defined as the time from treatment initiation to death from any cause or last follow-up.

Statistical analysis

Descriptive statistics were used to summarize baseline characteristics, with continuous variables reported as mean, standard deviation, and range, and categorical variables as frequencies and percentages. Group comparisons for continuous variables were performed using Student's t-test or the Mann–Whitney U test as appropriate. Categorical variables were compared using the chi-square test, with Monte Carlo simulation applied when necessary.

Survival distributions were estimated using the Kaplan–Meier method, and differences between groups were evaluated using the log-rank test. Prognostic factors were examined through Cox proportional hazards regression. Variables with a p value < 0.25 in univariate analyses were incorporated into a multivariable model using a forward stepwise approach. A two-sided p value < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 437 patients with recurrent primary brain malignancies were included in the analysis, comprising 264 men (60.4%) and 173 women (39.6%), with a median age at diagnosis of 53 years (range, 20–78). Glioblastoma represented the majority of cases (78.0%). At the initiation of bevacizumab-based therapy, ECOG performance status was 0 in 35.7% of patients, 1 in 41.2%, and 2 in 23.1%. Baseline corticosteroid use was documented in 270 patients (61.8%), and 329 (75.3%) were receiving antiepileptic medication.

Patients were treated with bevacizumab monotherapy (9.4%), bevacizumab combined with weekly irinotecan (8.5%), or bevacizumab combined with irinotecan administered every 14 days (82.2%). Patient and disease characteristics according to treatment group are presented in Table 1.

The overall response rate (complete or partial response) was 41.6%, while 80.1% of patients achieved disease control (complete response, partial response, or stable disease). Best radiologic response did not significantly differ across the three treatment groups ($p = 0.117$). The median follow-up duration was 7.9 months. At the time of last follow-up, 26.8% of the cohort remained alive, and 19.7% had not yet experienced progression while receiving bevacizumab-containing therapy.

Although unadjusted Kaplan–Meier analyses demonstrated statistically significant differences in both OS and PFS across treatment groups (log-rank $p = 0.024$ and $p = 0.005$, respectively). Median OS was 10.77 months

Table 1 Baseline characteristics of the patients

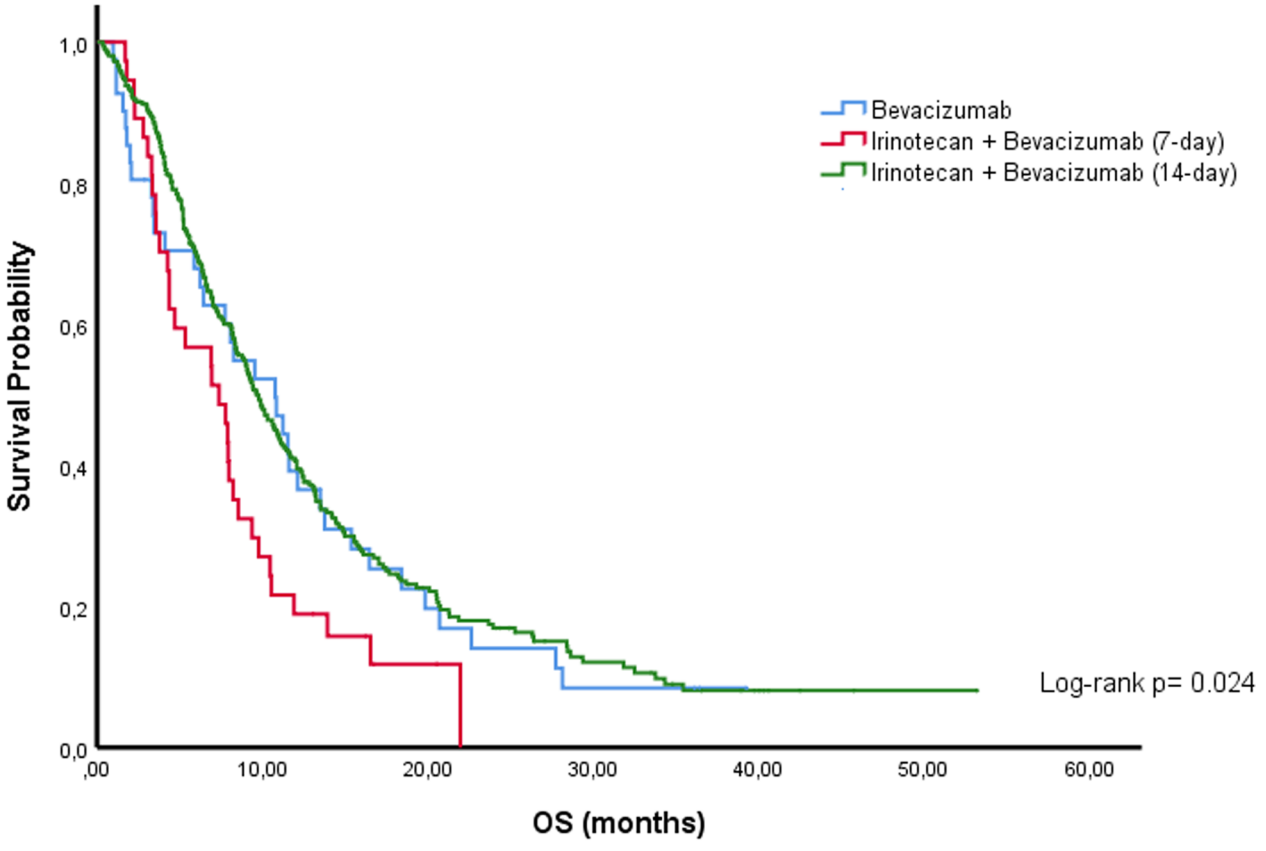
Characteristics		Total		Beva		Irino-Beva-7		Irino-Beva-14		*P*
		n	%	*n*	%	*n*	%	*n*	%	
Gender	Male	264	60.4	21	51.2	20	54.1	223	62.1	0.285
	Female	173	39.6	20	48.8	17	45.9	136	37.9	
Age (years)	Median (Min-Max)	53(20–78)		52 (20–75)		53 (18–69)		53 (20–78)		0.784
HT	No	363	83.1	37	90.2	36	97.3	290	80.8	0.017
	Yes	74	16.9	4	9.8	1	2.7	69	19.2	
DM	No	389	89.0	38	92.7	35	94.6	316	88.0	0.441
	Yes	48	11.0	3	7.3	2	5.4	43	12.0	
Location	Frontal	146	33.4	17	41.5	16	43.2	113	31.5	*0.001*
	Occipital	58	13.3	0	0.0	0	0.0	58	16.2	
	Temporal	135	30.9	15	36.6	13	35.1	107	29.8	
	Parietal	65	14.9	4	9.8	3	8.1	58	16.2	
	Other	33	7.6	5	12.2	5	13.5	23	6.4	
Pathology	Oligodendroglioma	34	7.8	2	4.9	1	2.7	31	8.6	0.068
	Astrocytoma	62	14.2	4	9.8	1	2.7	57	15.9	
	GBM	341	78.0	35	85.4	35	94.6	271	75.5	
Prior Adjuvant Therapy	RT	24	5.5	3	7.3	1	2.7	20	5.6	< 0.001
	CRT	105	24.0	22	53.7	31	83.8	52	14.5	
	CRT + RT	275	62.9	14	34.1	5	13.5	256	71.3	
	RT + ChT	16	3.7	2	4.9	0	0	14	3.9	
Recurrence Surgery	Yes	112	25.6	5	12.2	2	5.4	105	29.2	0.001
	No	325	74.4	36	87.8	35	94.6	254	70.8	
Grade	2	34	7.8	1	2.4	0	0.0	33	9.2	*0.048*
	3	61	14.0	5	12.2	2	5.4	54	15.0	
	4	342	78.3	35	85.4	35	94.6	272	75.8	
IDH-1	Negative	242	55.4	22	53.7	29	78.4	191	53.2	*0.011*
	Positive	56	12.8	5	12.2	6	16.2	45	12.5	
	Unknown	139	31.8	14	34.1	2	5.4	123	34.3	
1p19q	Negative	118	27.0	3	7.3	4	10.8	111	30.9	*0.001*
	Positive	14	3.2	1	2.4	2	5.4	11	3.1	
	Unknown	305	69.8	37	90.2	31	83.8	237	66.0	
Antiepileptic Prophylaxis	No	108	24.7	21	51.2	27	73.0	60	16.7	*< 0.001*
	Yes	329	75.3	20	48.8	10	27.0	299	83.3	
Steroid Use	No	167	38.2	15	36.6	30	81.1	122	34.0	*< 0.001*
	Yes	270	61.8	26	63.4	7	18.9	237	66.0	
Number of cycles	Median (Min-Max)			10 (1–48)		7 (1–27)		8 (1–48)		0.408
Treatment discontinuation	No	355	81.2	36	87.8	36	97.3	283	78.8	*0.012*
	Yes	82	18.8	5	12.2	1	2.7	76	21.2	
Treatment interruption	No	317	72.5	33	80.5	35	94.6	249	69.4	*0.002*
	Yes	120	27.5	8	19.5	2	5.4	110	30.6	
Best Response	CR	6	1.4	0	0.0	1	2.7	5	1.4	0.117
	PR	176	40.3	13	31.7	9	24.3	154	42.9	
	SD	168	38.4	18	43.9	16	43.2	134	37.3	
	PD	87	19.9	10	24.4	11	29.7	66	18.4	
Progression with Bevacizumab	No	86	19.7	4	9.8	2	5.4	80	22.3	*0.012*
	Yes	351	80.3	37	90.2	35	94.6	279	77.7	
Last follow up	Alive	117	26.8	6	14.6	4	10.8	107	29.8	*0.008*
	Dead	320	73.2	35	85.4	33	89.2	252	70.2	

ChT Chemotherapy, *CR* Complete Response, *CRT* Chemoradiotherapy, *DM* Diabetes Mellitus, *GBM* Glioblastoma Multiforme, *HT* Hypertension, *PD* Progressive Disease, *PR* Partial Response, *RT* Radiotherapy, *SD* Stable Disease

for bevacizumab monotherapy, 7.37 months for weekly irinotecan plus bevacizumab, and 9.77 months for the every-14-day irinotecan combination. Median PFS values were 5.77, 3.93, and 6.43 months, respectively (Figs. 1 and 2). In an exploratory analysis restricted to patients with known IDH status, no significant association with overall survival was observed ($p = 0.44$; Supplementary Fig. 1).

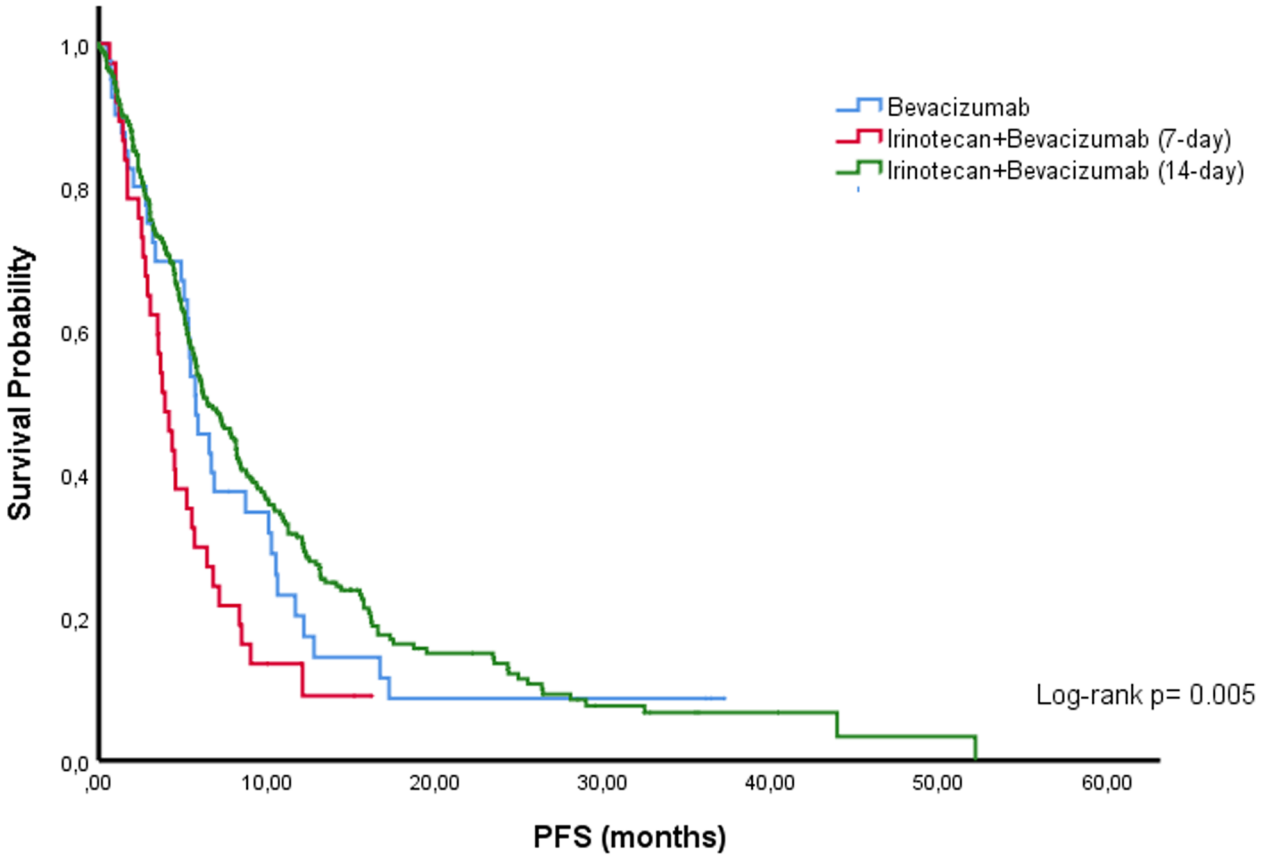
Univariate and multivariate predictors of PFS are summarized in Table 2. In univariate analysis, pathology ($p = 0.001$), tumor grade ($p = 0.002$), treatment regimen ($p = 0.035$), number of administered cycles ($p < 0.001$), corticosteroid use ($p < 0.001$), and discontinuation of bevacizumab-containing therapy ($p = 0.001$) were significantly associated with PFS. In the multivariable model, glioblastoma histology independently predicted shorter PFS compared with oligodendroglioma (HR 1.87; 95% CI, 1.16–2.99; $p = 0.009$). A greater number of treatment cycles was associated with longer PFS (HR 0.89 per cycle; 95% CI, 0.87–0.90; $p < 0.001$). Antiepileptic drug use was independently associated with longer PFS (HR 0.72; 95% CI, 0.56–0.94; $p = 0.016$), whereas corticosteroid use remained an independent adverse factor (HR 1.50; 95% CI, 1.18–1.90; $p = 0.001$).

Analyses of OS are presented in Table 3. Pathology ($p = 0.001$), tumor grade ($p = 0.001$), treatment regimen ($p = 0.031$), number of cycles ($p < 0.001$), and corticosteroid use ($p < 0.001$) were significant in univariate analysis. In multivariable analyses, glioblastoma histology was again associated with inferior OS compared with oligodendroglioma (HR 2.14; 95% CI, 1.28–3.59; $p = 0.004$). The irinotecan–bevacizumab regimen administered every 14 days showed a survival advantage over



Group	0	6	12	18	24
Bevacizumab	41	27	15	9	5
Irinotecan+Bevacizumab (7-day)	37	21	7	2	0
Irinotecan+Bevacizumab (14-day)	359	221	109	52	31

Fig. 1 Overall survival according to treatment regimens. Kaplan–Meier curves illustrating OS across treatment groups. Median OS was 10.77 months (95% CI, 6.97–14.56) for bevacizumab, 7.37 months (95% CI, 4.31–10.43) for irinotecan plus bevacizumab administered every 7 days, and 9.77 months (95% CI, 8.70–10.83) for irinotecan plus bevacizumab administered every 14 days (log-rank $p = 0.024$). Numbers at risk are shown below the x-axis



Group	0	6	12	18	24
Bevacizumab	41	17	6	3	3
Irinotecan+Bevacizumab (7-day)	37	11	3	0	0
Irinotecan-Bevacizumab (14-day)	359	146	66	26	19

Fig. 2 Progression-free survival according to treatment regimens. Kaplan–Meier curves illustrating PFS across treatment groups. Median PFS was 5.77 months (95% CI, 4.38–7.15) for bevacizumab, 3.93 months (95% CI, 2.94–4.93) for irinotecan plus bevacizumab administered every 7 days, and 6.43 months (95% CI, 5.23–7.64) for irinotecan plus bevacizumab administered every 14 days (log-rank $p = 0.005$). Numbers at risk are shown below the x-axis

bevacizumab monotherapy (HR 0.68; 95% CI, 0.47–0.97; $p = 0.038$), whereas the weekly irinotecan schedule did not. A higher number of treatment cycles remained strongly associated with improved OS (HR 0.87 per cycle; 95% CI, 0.85–0.89; $p < 0.001$). Baseline corticosteroid use (HR 1.38; 95% CI, 1.07–1.77; $p = 0.010$) and discontinuation of bevacizumab-containing therapy (HR 1.42; 95% CI, 1.06–1.90; $p = 0.017$) were significant adverse prognostic factors.

Regarding safety outcomes, gastrointestinal events, diarrhea, and hematologic toxicities were more frequently observed in patients receiving irinotecan every 14 days ($p < 0.05$). The incidence of proteinuria, thrombosis, and hemorrhage was low and did not significantly differ between treatment groups. Detailed adverse event distributions and severity grades are provided in Table 4.

Discussion

In this large multicenter retrospective cohort of 437 patients with recurrent primary brain tumors, predominantly glioblastoma, we evaluated the efficacy and tolerability of bevacizumab-based regimens in routine clinical practice. Bevacizumab-containing therapy achieved a high disease control rate (80.1%) and a clinically meaningful median OS of approximately 7–11 months across treatment groups. The irinotecan plus bevacizumab every-14-day regimen was associated with improved OS compared with bevacizumab monotherapy in multivariable analysis, whereas the weekly irinotecan schedule did not confer a clear survival advantage. Steroid exposure and discontinuation of bevacizumab were independently associated with poorer survival, while a higher number of treatment cycles and antiepileptic drug use were linked

Table 2 Univariate and multivariate analyses for progression free survival

Characteristics		Univariate analysis			Multivariate analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
Age	Years	1.01	0.99–1.02	0.083	1.18	0.93–1.50	0.158
Gender	Female vs. Male	0.92	0.74–1.14	0.464			
HT	Yes vs. No	1.05	0.79–1.40	0.719			
DM	Yes vs. No	1.12	0.80–1.57	0.502			
Location	Frontal			0.532			
	Occipital	0.99	0.71–1.38	0.966			
	Temporal	1.07	0.82–1.39	0.594			
	Parietal	0.86	0.61–1.21	0.389			
	Other	0.77	0.50–1.18	0.242			
Pathology	Oligodendroglioma			0.001			0.023
	Astrocytoma	1.71	1.01–2.29	0.046	1.54	0.90–2.65	0.114
	Glioblastoma multiforme	2.29	1.43–3.66	0.000	1.87	1.16–2.99	0.009
Grade	Grade 2			0.002			0.639
	Grade 3	1.34	0.80–2.26	0.263	1.27	0.68–2.35	0.445
	Grade 4	1.95	1.24–3.05	0.004	2.13	0.27–16.78	0.473
IDH	Negative			0.259			
	Positive	0.87	0.62–1.23	0.445			
	Unknown	1.15	0.91–1.44	0.226			
1p19q	Negative			0.372			
	Positive	1.08	0.59–1.97	0.800			
	Unknown	1.18	0.93–1.51	0.162			
Treatment Regimens	Bevacizumab			0.035			0.047
	Irinotekan + Bevacizumab/7	1.54	0.96–2.45	0.069	1.37	0.84–2.23	0.202
	Irinotekan + Bevacizumab/14	0.96	0.68–1.36	0.846	0.84	0.59–1.21	0.371
Number of cycles		0.89	0.87–0.90	0.000	0.89	0.87–0.90	< 0.001
Antiepileptic use	Yes vs. No	0.80	0.63–1.01	0.071	0.72	0.56–0.94	0.016
Steroid use	Yes vs. No	1.62	1.29–2.03	0.000	1.50	1.18–1.90	0.001
Bevacizumab discontinuation	Yes vs. No	1.51	1.17–1.95	0.001	0.95	0.71–1.28	0.748
Bevacizumab interruption	Yes vs. No	0.94	0.74–1.19	0.620			

DM Diabetes Mellitus, *HR* Hazard Ratio, *HT* Hypertension

to prolonged progression-free survival (PFS). These findings provide real-world evidence supporting the use of bevacizumab-based combinations at first or second recurrence in selected patients.

The prognosis of recurrent glioblastoma remains poor, with most series reporting median OS of 6–9 months despite various salvage therapies [3, 9, 10]. In the landmark Stupp regimen for newly diagnosed GBM, median OS was 14–16 months with concurrent chemoradiotherapy followed by adjuvant temozolomide, and two-year survival did not exceed one-third of patients [4]. Consistent with these observations, the majority of patients in our cohort experienced recurrence within a relatively short interval after standard chemoradiotherapy, and subsequent outcomes remained poor despite anti-angiogenic treatment.

Median OS values of 10.77, 7.37, and 9.77 months in the bevacizumab monotherapy, weekly irinotecan–bevacizumab, and every-14-day irinotecan–bevacizumab groups, respectively, are broadly in line with prior reports of bevacizumab use in recurrent GBM [18, 19, 34]. In particular, our findings echo the outcomes of real-world cohorts in which bevacizumab, alone or in combination with lomustine, yielded median OS of approximately 8–10 months in heavily pretreated patients [19, 20]. Taken together, these comparisons suggest that the survival achieved in our multicenter "real-world" population is consistent with, and in some cases slightly better than, results from more selected clinical trial populations.

Bevacizumab was incorporated into recurrent GBM management based on its anti-VEGF activity and consistent radiographic and PFS improvements in phase II studies [14–18], although later phase III trials failed to show an OS advantage [19, 20]. Irinotecan, which penetrates the blood–brain barrier and has documented activity in malignant glioma [27–31], has therefore been explored as a combination partner. Early studies reported higher response rates and 6-month PFS with the combination than with chemotherapy alone [32], while Friedman et al. demonstrated improved response and PFS—but not OS—with bevacizumab plus irinotecan compared with bevacizumab alone [33]. Our real-world

Table 3 Univariate and multivariate analyses for overall survival

Characteristics		Univariate Analysis			Multivariate Analysis		
		HR	95% CI	*p*	HR	95% CI	*p*
Age	Years	1.01	0.99–1.01	0.165			
Gender	Female vs. Male	0.94	0.75–1.18	0.619			
HT	Yes vs. No	1.14	0.85–1.53	0.381			
DM	Yes vs. No	1.18	0.84–1.68	0.336			
Location	Frontal			0.119			
	Occipital	0.87	0.61–1.25	0.464			
	Temporal	1.06	0.81–1.33	0.633			
	Parietal	0.80	0.56–1.14	0.229			
	Other	0.60	0.37–0.96	0.035			
Pathology	Oligodendroglioma			0.001			0.007
	Astrocytoma	1.65	0.93–2.95	0.087	1.67	0.92–3.02	0.087
	Glioblastoma multiforme	2.41	1.45-4.00	0.001	2.14	1.28–3.59	0.004
Grade	Grade 2			0.001			0.377
	Grade 3	1.07	0.62–1.87	0.801	1.23	0.69–2.19	0.478
	Grade 4	1.80	1.14–2.85	0.012	1.02	0.51–1.47	0.185
IDH	Negative			0.351			
	Positive	0.87	0.61–1.25	0.471			
	Unknown	1.13	0.89–1.43	0.309			
1p19q	Negative			0.238			
	Positive	1.21	0.65–2.22	0.543			
	Unknown	1.25	0.96–1.62	0.090			
Treatment Regimens	Bevacizumab			0.031			0.012
	Irinotecan + Bevacizumab/7	1.52	0.94–2.45	0.085	1.08	0.66–1.78	0.744
	Irinotecan + Bevacizumab/14	0.93	0.65–1.33	0.702	0.68	0.47–0.97	0.038
Number of cycles		0.88	0.86–0.89	< 0.001	0.87	0.85–0.89	< 0.001
Antiepileptic use	Yes vs. No	0.81	0.64–1.04	0.106	0.86	0.66–1.13	0.292
Steroid use	Yes vs. No	1.59	1.26–2.02	0.000	1.38	1.07–1.77	0.010
Bevacizumab discontinuation	Yes vs. No	1.20	0.92–1.58	0.170	1.42	1.06–1.90	0.017
Bevacizumab interruption	Yes vs. No	0.82	0.64–1.06	0.137			

DM Diabetes Mellitus, *HR* Hazard Ratio, *HT* Hypertension

data align with these findings and additionally suggest a schedule-dependent effect: although radiologic response rates were similar across regimens, the every-14-day irinotecan–bevacizumab schedule was independently associated with longer OS, whereas the weekly regimen was not. Clinically, these results support the 14-day combination as a feasible option for appropriate patients, while bevacizumab monotherapy remains suitable for those with limited tolerance for cytotoxic therapy.

Histology remained a major prognostic factor: GBM was independently associated with significantly shorter PFS and OS compared with oligodendroglioma, consistent with its more aggressive biology [1, 2, 4]. The observed association between a higher number of treatment cycles and improved outcomes should be interpreted with caution. This finding most likely reflects a survivor effect, whereby patients with more favorable disease biology or better clinical condition are able to continue therapy for longer durations, rather than a direct causal benefit of treatment duration itself. Nevertheless, the independent association between treatment discontinuation and worse overall survival suggests that, among clinically stable patients, premature cessation of bevacizumab-based therapy may adversely affect outcomes. Similar associations have been reported in other retrospective real-world studies and highlight the inherent limitations of non-randomized analyses [19, 20].

Concomitant medications also influenced outcomes. Baseline steroid use was an independent adverse prognostic factor for both PFS and OS, likely reflecting more advanced disease, greater tumor burden, or poorer performance status, as well as the deleterious immunosuppressive and metabolic effects of glucocorticoids [35]. In contrast, antiepileptic drug use was associated with longer PFS, though not OS, in multivariate analysis. The association between antiepileptic drug use and longer PFS should also be interpreted in the context of underlying tumor biology. Seizure presentation is more frequently observed in lower-grade or less aggressive gliomas and has been associated with more favorable outcomes in prior studies. Therefore, the observed relationship between antiepileptic drug use and PFS in

Table 4 Adverse events of bevacizumab with or without Irinotecan

		Total		Bevacizumab		Irino-beva-7		Irino-beva-14		*p*
		n	%	*n*	%	*n*	%	*n*	%	
GIS AE	No	242	55.4	33	80.5	32	86.5	177	49.3	*0.001*
	Grade 1	147	33.6	7	17.1	4	10.8	136	37.9	
	Grade 2	45	10.3	1	2.4	1	2.7	43	12.0	
	Grade 3	3	0.7	0	0.0	0	0.0	3	0.8	
Nausea	No	335	76.7	39	95.1	32	86.5	264	73.5	0.061
	Grade 1	78	17.8	2	4.9	4	10.8	72	20.1	
	Grade 2	20	4.6	0	0.0	1	2.7	19	5.3	
	Grade 3	4	0.9	0	0.0	0	0.0	4	1.1	
Diarrhea	No	340	77.8	40	97.6	36	97.3	264	73.5	*0.001*
	Grade 1	63	14.4	1	2.4	1	2.7	61	17.0	
	Grade 2	27	6.2	0	0.0	0	0.0	27	7.5	
	Grade 3	7	1.6	0	0.0	0	0.0	7	1.9	
Hematological AE	No	309	70.7	34	82.9	35	94.6	240	66.9	*0.005*
	Grade 1	105	24.0	5	12.2	1	2.7	99	27.6	
	Grade 2	18	4.1	2	4.9	1	2.7	15	4.2	
	Grade 3	4	0.9	0	0.0	0	0.0	4	1.1	
	Grade 4	1	0.2	0	0.0	0	0.0	1	0.3	
Neutropenia	No	332	76.0	38	92.7	33	89.2	261	72.7	0.174
	Grade 1	71	16.2	3	7.3	3	8.1	65	18.1	
	Grade 2	17	3.9	0	0.0	0	0.0	17	4.7	
	Grade 3	11	2.5	0	0.0	1	2.7	10	2.8	
	Grade 4	6	1.4	0	0.0	0	0.0	6	1.7	
Thrombocytopenia	No	342	78.3	35	85.4	35	94.6	272	75.8	0.287
	Grade 1	68	15.6	6	14.6	1	2.7	61	17.0	
	Grade 2	12	2.7	0	0.0	1	2.7	11	3.1	
	Grade 3	9	2.1	0	0.0	0	0.0	9	2.5	
	Grade 4	6	1.4	0	0.0	0	0.0	6	1.7	
Febrile Neutropenia	No	400	91.5	41	100.0	35	94.6	324	90.3	0.268
	1	33	7.6	0	0.0	2	5.4	31	8.6	
	2	4	0.9	0	0.0	0	0.0	4	1.1	
Hypertension	No	359	82.2	41	100.0	31	83.8	287	79.9	*0.032*
	Grade 1	62	14.2	0	0.0	6	16.2	56	15.6	
	Grade 2	13	3.0	0	0.0	0	0.0	13	3.6	
	Grade 3	3	0.7	0	0.0	0	0.0	3	0.8	
Proteinuria	No	409	93.6	38	92.7	32	86.5	339	94.4	0.057
	Grade 1	21	4.8	1	2.4	4	10.8	16	4.5	
	Grade 2	6	1.4	1	2.4	1	2.7	4	1.1	
	Grade 3	1	0.2	1	2.4	0	0.0	0	0.0	
Thrombosis	No	406	92.9	40	97.6	35	94.6	331	92.2	0.510
	Yes	31	7.1	1	2.4	2	5.4	28	7.8	
Hemorrhage	No	420	96.1	38	92.7	37	100.0	345	96.1	0.245
	Yes	17	3.9	3	7.3	0	0.0	14	3.9	

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4

AE Adverse Event, *GIS* Gastrointestinal System

our cohort may partly reflect tumor grade and biological behavior rather than a direct therapeutic effect of antiepileptic agents. This interpretation is further supported by the lack of a corresponding independent association with overall survival. Some antiepileptic drugs, such as valproic acid, have been suggested to possess histone deacetylase–inhibitory properties and potential antitumor activity, although this remains controversial [36, 37].

Although molecular markers such as IDH mutation are well-established prognostic factors in newly diagnosed gliomas, IDH status was not independently associated with overall survival in our multivariate model. This finding may reflect the recurrent disease setting,

where tumor evolution, treatment resistance, and clinical factors increasingly shape outcomes. Additionally, the incomplete availability of molecular data may have reduced the statistical power to detect subtle prognostic effects [38].

The safety profile observed in our cohort confirms that bevacizumab-based therapy is generally well tolerated in routine practice. Gastrointestinal toxicity, diarrhea, and hematologic adverse events were more frequent in irinotecan-containing arms—especially the every-14-day regimen—but were predominantly low grade and manageable with supportive care, in line with the known toxicity profile of topoisomerase I inhibitors [27–31]. Hypertension, a classical bevacizumab-related toxicity, was more frequent in irinotecan-containing regimens, whereas proteinuria, thrombosis, and hemorrhage occurred at relatively low rates and were broadly similar across groups, without an excess of life-threatening vascular events. These findings are consistent with previous bevacizumab trials in recurrent glioma [19, 20, 32, 33] and support the feasibility of sustained bevacizumab exposure, alone or in combination with irinotecan, in appropriately selected patients.

The principal strengths of this study are its large sample size, multicenter design, and reflection of real-world clinical practice, which together enhance the generalizability of the findings. However, some limitations should be acknowledged. The retrospective and non-randomized design introduces potential selection bias and residual confounding, and the relatively small numbers in the bevacizumab monotherapy and weekly irinotecan groups reduce the power of between-group comparisons. Response assessment was based on McDonald criteria rather than RANO due to the retrospective multicenter setting and heterogeneity/incompleteness of imaging which may have influenced radiological response classification. Incomplete molecular profiling—particularly the absence of comprehensive MGMT promoter methylation and IDH/1p19q data—limits the ability to perform biomarker-based analyses. Detailed information regarding prior treatment pathways, including extent of surgery and salvage therapies, was not uniformly available and may have contributed to residual confounding between treatment groups. Additionally, detailed data on antiepileptic drug type were unavailable, limiting drug-specific analyses.

Conclusion

In this large real-world cohort, bevacizumab-based therapy provided meaningful disease control in recurrent primary brain tumors. While unadjusted survival analyses showed differences in OS among treatment regimens, these differences were attenuated after multivariable adjustment, resulting in comparable median OS estimates across regimens. Multivariable analyses suggested that treatment continuity, reduced corticosteroid exposure, and in some patients an every-14-day irinotecan–bevacizumab schedule were associated with better survival. These findings support tailored use of bevacizumab-containing regimens and underscore the need for prospective studies to confirm the optimal regimen and schedule.

Supplementary Information

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Supplementary Material 1: Figure S1: Overall survival according to IDH-mutation.

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Authors' contributions
ZSİ, ŞS, AS, MMA: Conceptualization, data curation, formal analysis, investigation, writing—original draft, and writing—review and editing. ŞC, MB, SK, MKE, EZ, EÇY, EK, NŞ, FPT, ÖA, ÖÖ, S IŞ, FY, AG, STü, GK, MG, LÖ, AA, FK, TS, DDE, FT, ND, ÖD, STr, HMT, KE, EÇ, MMA: Data curation, investigation, and editing. ZSİ, ŞS, AS, KE, EÇ, MMA: Formal analysis and writing—review and editing. ŞS, AS, KE, EÇ, MMA: Supervision, project administration, and validation. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Data availability
The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (approval number: 48670771-514.10). The requirement for informed consent was waived due to the retrospective and anonymized nature of the data. All study procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.

Consent for publication
All authors agree to publish.

Competing interests
The authors declare no competing interests.

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References

1. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the united States in 2012–2016. Neuro Oncol. 2019;21(Suppl 5):v1–100.
2. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96.
3. Filippini G, Falcone C, Boiardi A, Broggi G, Bruzzone MG, Caldiroli D, et al. Prognostic factors for survival in 676 consecutive patients with newly diagnosed primary glioblastoma. Neuro Oncol. 2008;10(1):79–87.
4. Roy S, Lahiri D, Maji T, Biswas J. Recurrent glioblastoma: where we stand. South Asian J Cancer. 2015;4(4):163–73.
5. Gilbert MR, Wang M, Aldape KD, Stupp R, Hegi ME, Jaeckle KA, et al. Dose-dense Temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol. 2013;31:4085–91.
6. Lee J, Ahn SS, Chang JH, Suh CO. Hypofractionated re-irradiation after maximal surgical resection for recurrent glioblastoma: therapeutic adequacy and prognosticators of survival. Yonsei Med J. 2018;59(2):194–201.
7. Azoulay M, Santos F, Shenouda G, Petrecca K, Oweida A, Guiot MC, et al. Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme: results from a single institution. J Neurooncol. 2017;132(3):419–26.
8. Wirsching HG, Tonn JC, Tabatabai G, Senft C, Hau P, Sabel MC, et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma: results from the DIRECTOR trial. Eur J Neurol. 2016;23:921–2.
9. Thon N, Kreth S, Kreth FW. Personalized treatment strategies in glioblastoma: MGMT promoter methylation status. Onco Targets Ther. 2013;6:1363–72.
10. Niyazi M, Siefert A, Schwarz SB, Ganswindt U, Kreth FW, Tonn JC, et al. Therapeutic options for recurrent malignant glioma. Radiother Oncol. 2011;98(1):1–14.
11. Perry JR, Rizek P, Cashman R, Morrison M, Morrison T. Temozolomide Rechallenge in recurrent malignant glioma using a continuous Temozolomide schedule: the rescue approach. Cancer. 2008;113(8):2152–7.
12. Perry JR, Bélanger K, Mason WP, Fulton D, Kavan P, Easaw J, et al. Phase II trial of continuous dose-intense Temozolomide in recurrent malignant glioma (RESCUE study). J Clin Oncol. 2010;28(12):2051–7.
13. Wick A, Pascher C, Wick W, Jauch T, Weller M, Bogdahn U, et al. Rechallenge with Temozolomide in patients with recurrent gliomas. J Neurol. 2009;256(5):734–41.
14. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. Nat Med. 2003;9:669–76.
15. Godard S, Getz G, Delorenzi M, Farmer P, Kobayashi H, Desmedt C, et al. Classification of human astrocytic gliomas on the basis of gene expression: a correlated group of genes with angiogenic activity emerges as a strong predictor of subtypes. Cancer Res. 2003;63:6613–25.
16. Lamszus K, Ulbricht U, Matschke J, Brockmann MA, Fillbrandt R, Westphal M. Levels of soluble vascular endothelial growth factor receptor-1 in astrocytic tumors and its relation to malignancy, vascularity, and VEGF-A. Clin Cancer Res. 2003;9:1399–405.
17. Jain HV, Nor JE, Jackson TL. Modeling the VEGF-Bcl-2-CXCL8 pathway in intratumoral angiogenesis. Bull Math Biol. 2008;70:89–117.
18. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist. 2009;14:1131–8.
19. McBain C, Lawrie TA, Rogozińska E, Kernohan A, Robinson T, Jefferies S. Treatment options for progression or recurrence of glioblastoma: a network meta-analysis. Cochrane Database Syst Rev. 2021;5(1):CD013579. https://doi.org/10.1002/14651858.CD013579.pub2.
20. Heiland DH, Masalha W, Franco P, Machein MR, Weyerbrock A. Progression-free and overall survival in recurrent glioblastoma treated with last-line bevacizumab versus bevacizumab/lomustine. J Neurooncol. 2016;126:567–75.
21. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350:2335–42.
22. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med. 2017;377(20):1954–63.
23. Field KM, Simes J, Nowak AK, Cher L, Wheeler H, Hovey EJ, et al. Randomized phase 2 study of carboplatin and bevacizumab in recurrent glioblastoma. Neuro Oncol. 2015;17(11):1504–13.
24. Lassen U, Sorensen M, Gaziel TB, Hasselbalch B, Poulsen HS. Phase II study of bevacizumab and Temsirolimus combination therapy for recurrent glioblastoma multiforme. Anticancer Res. 2013;33(4):1657–60.
25. Galanis E, Anderson SK, Lafky JM, Uhm JH, Giannini C, Kumar SK, et al. Phase II study of bevacizumab in combination with Sorafenib in recurrent glioblastoma (N0776): a North central cancer treatment group trial. Clin Cancer Res. 2013;19(17):4816–23.
26. Puduvalli VK, Wu J, Yuan Y, Armstrong TS, Vera E, Wu J, et al. A bayesian adaptive randomized phase II multicenter trial of bevacizumab with or without Vorinostat in adults with recurrent glioblastoma. Neuro Oncol. 2020;22(10):1505–15.
27. Cloughesy TF, Filka E, Kuhn J, Nelson G, Lamborn KR, Prados MD, et al. Two studies evaluating Irinotecan treatment for recurrent malignant glioma using an every-3-week regimen. Cancer. 2003;97:2381–6.
28. Chamberlain MC. Salvage chemotherapy with CPT-11 for recurrent glioblastoma multiforme. J Neurooncol. 2002;56:183–8.
29. Prados MD, Lamborn K, Yung WK, Chang S, Gilbert MR, Fine HA, et al. A phase II trial of Irinotecan (CPT-11) in recurrent malignant glioma: a North American brain tumor consortium study. Neuro Oncol. 2006;8:189–93.
30. Friedman HS, Petros WP, Friedman AH, Keir ST, Houghton PJ, Douglas JG, et al. Irinotecan therapy in adults with recurrent or progressive malignant glioma. J Clin Oncol. 1999;17:1516–25.

31. Batchelor TT, Gilbert MR, Supko JG, Carson KA, Nabors LB, Grossman SA, et al. Phase II study of weekly Irinotecan in adults with recurrent malignant glioma: final report of NABTT 97 – 11. Neuro Oncol. 2004;6:21–7.
32. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus Irinotecan in recurrent glioblastoma multiforme. J Clin Oncol. 2007;25:4722–9.
33. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, et al. Bevacizumab alone and in combination with Irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733–40.
34. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy–temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014;370(8):709–22.
35. Pitter KL, Tamagno I, Alikhanyan K, Hosni-Ahmed A, Pattwell SS, Donnola S, et al. Corticosteroids compromise survival in glioblastoma. Brain. 2016;139(5):1458–71.
36. Patel MA, Bimali M, Li C, Kesaria A, Xia F. Effect of anticonvulsants on survival among patients with GBM undergoing radiation: a SEER-Medicare analysis. J Clin Neurosci. 2022;106:32–6.
37. Happold C, Gorlia T, Chinot O, Gilbert MR, Nabors LB, Wick W, et al. Does valproic acid or Levetiracetam improve survival in glioblastoma? A pooled analysis of prospective clinical trials. J Clin Oncol. 2016;34(7):731–9.
38. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360(8):765–73. https://doi.org/10.1056/NEJMoa0808710.

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