ORIGINAL ARTICLE

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Real-world Outcomes of Second-line Irinotecan Plus Bevacizumab in Recurrent High-grade Gliomas: A Single-center Retrospective Study

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ABSTRACT

Objective: High-grade gliomas (HGGs), particularly glioblastoma, remain among the most aggressive primary central nervous system malignancies. Despite standard treatment consisting of maximal safe resection followed by radiotherapy with concurrent and adjuvant temozolomide, disease recurrence is nearly inevitable. Therapeutic options after progression remain limited, and the optimal management of recurrent HGGs continues to be debated. This study aimed to evaluate the real-world efficacy of second-line irinotecan plus bevacizumab in patients with recurrent HGGs.

Material and Methods: This retrospective single-center study included patients with recurrent HGGs treated at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital between January 2020 and December 2024. Demographic, clinical, pathological, treatment, and survival data were collected from institutional medical records. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Objective response rates (ORRs) were assessed according to radiological evaluations documented in routine clinical practice.

Results: A total of 55 patients were included. The median age was 50 years, and 76% of patients had glioblastoma. Following first-line chemoradiotherapy, 48 patients received adjuvant temozolomide, with a median PFS of 5.0 months. Fifty patients subsequently received second-line irinotecan plus bevacizumab, achieving an ORR of 46%. The median PFS associated with irinotecan plus bevacizumab was 8.8 months. At the final analysis, the median OS for the entire cohort was 23.4 months.

Conclusion: Second-line irinotecan plus bevacizumab demonstrated meaningful clinical activity in recurrent HGGs, yielding encouraging response rates and disease control in a real-world setting. These findings support the continued use of bevacizumab-based strategies for selected patients with recurrent disease.

Keywords: High-grade glioma; glioblastoma; bevacizumab; irinotecan; recurrent glioma; temozolomide; progression-free survival

INTRODUCTION

High-grade gliomas (HGGs) are among the most aggressive primary malignancies of the central nervous system and remain associated with poor clinical outcomes despite advances in surgical techniques, radiotherapy, molecular diagnostics, and systemic therapies. According to the 2021 World Health Organization (WHO) Classification of Tumors of the Central Nervous System, adult-type diffuse gliomas are classified as astrocytoma, isocitrate dehydrogenase (IDH)-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wildtype, with molecular features playing a central role in diagnosis and prognostication.[1] Among these entities, glioblastoma represents the most common and biologically aggressive subtype, accounting for approximately 45-50% of all malignant primary brain tumors in adults.[2]

The current standard-of-care for newly diagnosed glioblastoma consists of maximal safe surgical resection followed by radiotherapy with concurrent and adjuvant temozolomide, commonly referred to as the Stupp regimen.[3]

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This multimodal approach has significantly improved survival outcomes compared with radiotherapy alone and has remained the cornerstone of treatment for nearly two decades. Nevertheless, recurrence remains almost inevitable, with the majority of patients experiencing disease progression within the first year after completing initial therapy.[3,4] Consequently, recurrent HGGs continue to represent a major therapeutic challenge in neuro-oncology.

Management strategies for recurrent HGGs are considerably less well-defined than those used in the frontline setting. Treatment decisions are influenced by multiple factors, including patient age, performance status (PS), extent of prior treatment, tumor location, resectability, molecular characteristics, and patterns of recurrence.[5,6] Potential therapeutic options include repeat surgical resection, re-irradiation, alkylating agents such as lomustine, bevacizumab-containing regimens, regorafenib, enrollment in clinical trials, or best supportive care.[5-8] However, no universally accepted standard treatment exists following failure of temozolomide-based chemoradiotherapy.

Tumor angiogenesis plays a pivotal role in glioma growth and progression. Glioblastomas are characterized by extensive neovascularization and overexpression of vascular endothelial growth factor (VEGF), which contributes to tumor proliferation, invasion, and treatment resistance.[9] Bevacizumab, a monoclonal antibody targeting VEGF-A, was therefore investigated as a potential therapeutic strategy in recurrent gliomas. Early-phase studies demonstrated promising radiographic response rates, improvements in peritumoral edema, and prolonged progression-free survival (PFS), leading to regulatory approval of bevacizumab for recurrent glioblastoma in several countries.[10,11]

Irinotecan, a topoisomerase I inhibitor, has also demonstrated activity against HGGs and has frequently been combined with bevacizumab based on potential synergistic effects.[12,13] Several prospective and retrospective studies have reported encouraging response rates and disease control with irinotecan plus bevacizumab for recurrent glioblastoma, although survival benefits have varied across studies.[10-13] Despite widespread clinical use, real-world evidence regarding the effectiveness of this combination remains limited, particularly outside clinical trial settings.

Furthermore, the evolving molecular classification of gliomas and the increasing heterogeneity of treatment approaches have highlighted the importance of institutional experience in understanding treatment outcomes in routine clinical practice. Real-world studies may provide clinically meaningful information regarding treatment effectiveness, tolerability, and survival outcomes among patient populations that are often underrepresented in prospective trials.

Therefore, the present study aimed to evaluate the real-world efficacy of second-line irinotecan plus bevacizumab in patients with recurrent HGGs treated at a tertiary referral center. We analyzed treatment response, PFS, and overall survival (OS) in a contemporary cohort managed in routine clinical practice.

MATERIAL AND METHODS

Study Design and Patient Population

This retrospective single-center study was conducted at University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital. Patients diagnosed with recurrent high-grade glioma who were treated between January 2020 and December 2024 were screened for eligibility. Histopathological diagnoses were established according to the WHO classification of central nervous system tumors.

Eligible patients were required to have:

1. Histologically confirmed high-grade glioma,
2. Receipt of first-line radiotherapy with or without concurrent and adjuvant temozolomide,
3. Radiologically confirmed disease progression
4. Availability of complete clinical and follow-up data.

Patients with insufficient medical records or incomplete follow-up information were excluded.

The study was conducted in accordance with the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (approval number: 2024-25, date: 07.11.2024).

Data Collection

Clinical data were retrospectively collected from electronic medical records. Variables included: age, sex, Eastern Cooperative Oncology Group-PS (ECOG-PS), comorbidities, family history of cancer, tumor histology, WHO grade, IDH mutation status, tumor size at diagnosis, extent of lobar involvement, number of lesions, surgical intervention, radiotherapy dose, treatment characteristics, radiological response, and survival outcomes.

Treatment Procedures

Patients underwent treatment according to institutional standards and at the physician's discretion. Initial management consisted of a maximal safe surgical resection or biopsy, followed by radiotherapy, with or without concurrent and adjuvant temozolomide. Following disease progression, second-line systemic treatment was administered. The majority of patients received irinotecan plus bevacizumab,

while alternative regimens were used in a limited number of cases. Subsequent therapies were administered according to clinical judgment and patient PS.

Outcome Measures

The primary objective of the study was to evaluate the efficacy of second-line irinotecan plus bevacizumab in recurrent HGGs.

PFS was defined as the interval between second-line treatment initiation and radiologically or clinically documented disease progression or death from any cause. OS was defined as the interval between initial diagnosis and death from any cause or last follow-up. Patients without documented events were censored on the date of last contact.

Radiological response assessments were performed according to routine institutional practice, using magnetic resonance imaging. Objective response rate (ORR) was defined as the proportion of patients achieving a complete or partial radiological response.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as median values with corresponding ranges or 95% confidence intervals (CIs), while categorical variables were presented as frequencies and percentages. Survival analyses were conducted using the Kaplan-Meier method. Median survival estimates were reported with 95% CIs. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 55 patients with recurrent HGGs were included in the study. The median follow-up duration was 36.1 months (95% CI: 29.5-42.7 months). The median age at diagnosis was 50 years (range, 41-56 years). Most patients were male (64%), had an ECOG-PS of 0-1 (89%), and had glioblastoma histology (76%). WHO grade 4 tumors were present in 91% of the study population, while IDH mutations were identified in 14% of patients. Additional baseline demographic and disease characteristics are summarized in Table 1.

Regarding tumor-related features, 56% of patients had tumors measuring ≥4 cm at diagnosis, whereas 34% demonstrated multilobar involvement. Most patients presented with a single lesion (89%) and underwent complete surgical resection (64%) as the initial intervention (Table 1).

Treatment Characteristics

Treatment characteristics are presented in Table 2. Following surgical management, 48 patients (87%) received standard chemoradiotherapy followed by adjuvant temozolomide, whereas 7 patients received chemoradiotherapy alone. Radiotherapy was administered at a dose of 6000 cGy to 69% of patients.

TABLE 1: Baseline patient and disease characteristics.

Characteristic	Patient number (n=55)	Percentage (%)
Age, years		
<50	25	45
≥50	30	55
Gender		
Male	35	64
Female	20	36
Familial history of cancer		
Yes	22	40
No	33	60
Comorbidity		
Yes	17	31
No	38	69
ECOG-PS		
0	15	27
1	34	62
2	6	11
Histology		
Glioblastoma	42	76
Astrocytoma	9	16
ODG	2	4
DMG	2	4
WHO grade		
3	5	9
4	50	91
IDH mutation		
Present	8	14
Absent	47	86
Initial tumor size, cm		
<4	24	44
≥4	31	56
Lobar involvement		
Unilobar	36	66
Multilobar	19	34
Lesion number		
1	49	89
2-3	7	11

DMG: Diffuse midline glioma; ECOG-PS: Eastern Cooperative Oncology Group performance status; IDH: Isocitrate dehydrogenase; ODG: Oligodendroglioma; WHO: World Health Organization.

TABLE 2: Treatment characteristics.		
Characteristic	**Patient number**	**Percentage**
Initial surgical intervention		
Biopsy only	12	22
Incomplete resection	8	14
Complete resection	35	64
First-line treatment		
CRT + TMZ	48	87
CRT only	7	13
Radiotherapy dosing, cGy		
6000	38	69
<6000	10	18
>6000	7	13
Objective response to TMZ		
Yes	16	29
No	32	58
NE (only CRT)	7	13
Re-resection		
Yes	17	31
No	38	69
Second-line treatment		
Irinotecan+beva	50	91
BCNU+beva	3	5
BCNU/CCNU+proc	1	2
CCNU	1	2
Objective response to second-line Irinotecan+beva treatment		
Yes	23	46
No	27	54
Third-line treatment		
None	42	76
BCNU	7	13
Regorafenib	3	5
Irinotecan+beva	1	2
TMZ	1	2
Carboplatin	1	2

Beva: Bevacizumab; BCNU: Carmustine; CCNU: Lomustine; CRT: Chemoradiotherapy; NE: Not evaluated, proc, procarbazine; TMZ: Temozolomide.

Among patients receiving adjuvant temozolomide, the median number of treatment cycles was 5 (range, 3-6 cycles). Objective radiological responses were observed in 16 patients (29%), whereas 32 patients (58%) experienced disease progression despite treatment. All patients ultimately developed recurrent disease requiring second-line therapy.

Second-line Treatment Outcomes

All patients received second-line systemic treatment after disease progression. Irinotecan plus bevacizumab was the predominant treatment regimen, administered to 50 patients (91%); alternative regimens were used in a limited number of cases (Table 2).

Among patients treated with second-line irinotecan plus bevacizumab, 23 achieved an objective response, corresponding to an ORR of 46%. The median number of administered cycles was 6 (range, 4-12 cycles). Fifteen patients, all of whom belonged to the irinotecan plus bevacizumab group, remained progression-free during or after second-line treatment.

The median PFS associated with second-line irinotecan plus bevacizumab was 8.8 months (95% CI: 5.1-12.4 months) (Figure 1).

Survival Outcomes

Among the 48 patients who received adjuvant temozolomide following chemoradiotherapy, the median PFS was 5.0 months (95% CI: 3.2-6.8 months) (Figure 2).

At the time of the final analysis, 35 deaths had occurred. The median OS for the entire cohort was 23.4 months (95% CI: 15.5-31.3 months) (Figure 3).

Third-line therapy was administered to 13 patients. One patient achieved an objective response, whereas disease progression occurred in 11 patients despite treatment.

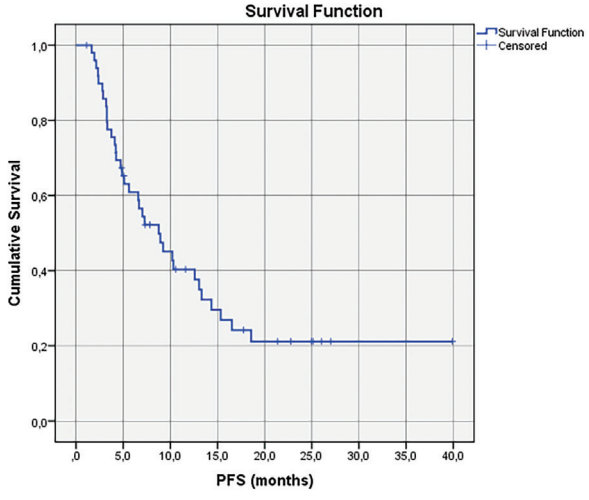

FIGURE 1: PFS plot of patients who had received second-line irinotecan plus bevacizumab.

PFS: Progression-free survival

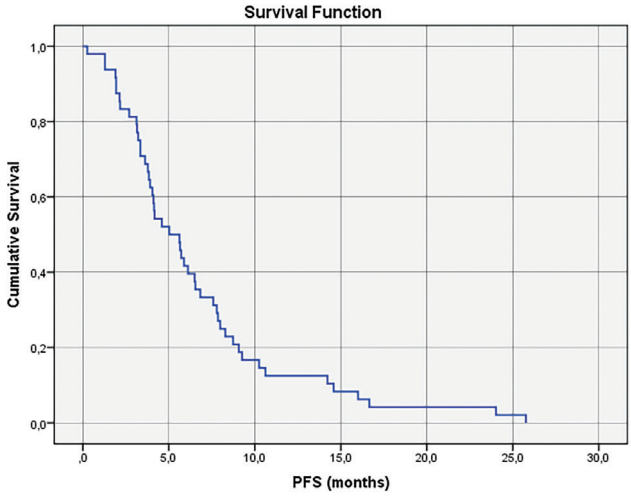

FIGURE 2: PFS plot of patients who had received temozolomide following chemoradiotherapy.

PFS: Progression-free survival

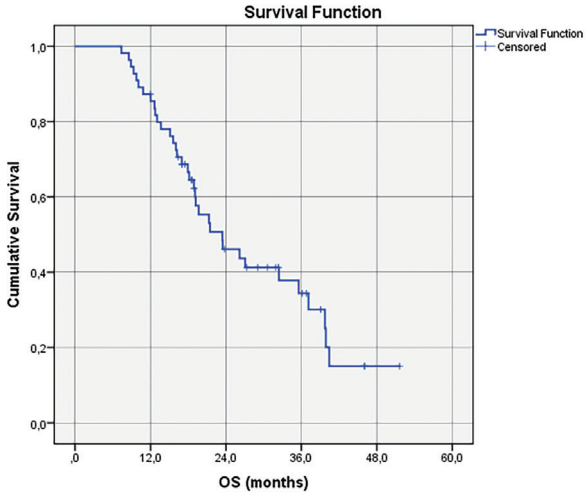

FIGURE 3: OS plot of all patients.

OS: Overall survival

DISCUSSION

In this retrospective real-world study, we evaluated the outcomes of second-line irinotecan plus bevacizumab in patients with recurrent HGGs who were treated at a tertiary referral center. The principal findings of our analysis were a 46% ORR, a median PFS of 8.8 months with irinotecan plus bevacizumab, and a median OS of 23.4 months for the entire cohort. These findings suggest that bevacizumab-based therapy continues to provide meaningful clinical benefit in selected patients with recurrent HGGs.

Despite substantial advances in neuro-oncology, recurrence remains nearly universal among patients with HGGs. Following the establishment of the Stupp regimen as the standard frontline treatment, recurrent disease has emerged as the major cause of treatment failure and mortality.[3,4,7] Therapeutic options after progression remain limited, and no universally accepted standard of care has been established.[5,6]

The antiangiogenic rationale for bevacizumab is particularly compelling in glioblastoma because VEGF overexpression is a hallmark of tumor biology and contributes to angiogenesis, edema formation, and tumor progression.[9] Several clinical studies have investigated bevacizumab alone or in combination with irinotecan in patients with recurrent glioblastoma.

One of the landmark studies evaluating bevacizumab-based treatment was conducted by Friedman et al.[10], who reported ORRs of 28.2% with bevacizumab monotherapy and 37.8% with bevacizumab plus irinotecan, with median PFSs of approximately 4-5 months. Similarly, Vredenburgh et al.[13] reported response rates approaching 57% and median PFS of approximately 6 months in patients with recurrent glioblastoma treated with bevacizumab-containing regimens.

Our observed ORR of 50% compares favorably with these historical studies and may reflect careful patient selection, advances in supportive care, and improvements in radiological monitoring. Furthermore, the median PFS of 8.8 months observed in our cohort appears numerically longer than that reported in several pivotal bevacizumab studies.[10,12,13] Although cross-study comparisons should be interpreted cautiously, our findings support the continued effectiveness of bevacizumab-based strategies in routine clinical practice.

More recently, alternative therapeutic approaches have been explored in recurrent glioblastoma. The REGOMA trial demonstrated improved OS with regorafenib compared with lomustine, establishing regorafenib as an important treatment option in recurrent disease.[14] Nevertheless, bevacizumab-based therapy remains widely used due to its ability to achieve rapid symptom control, reduce corticosteroid requirements, improve radiographic responses, and maintain quality of life in appropriately selected patients.[10,15,16]

The median OS of 23.4 months, observed in our study, is generally consistent with outcomes reported in contemporary high-grade glioma cohorts receiving multimodal treatment.[17-19] Importantly, most patients in our cohort had glioblastoma histology and WHO grade 4 disease, representing a population with an inherently poor prognosis. Therefore, the survival outcomes observed in our study further support the potential clinical value of bevacizumab-containing salvage therapy.

Study Limitations

Several limitations should be acknowledged. First, the retrospective nature of the study introduces the possibility of selection bias and unmeasured confounding factors. Second, the sample size was relatively small and was drawn from a single institution, potentially limiting generalizability. Third, molecular information beyond IDH status was unavailable for a substantial proportion of patients, precluding detailed molecular subgroup analyses. The absence of a control group receiving alternative second-line therapies limits direct comparisons of treatment efficacy.

Despite these limitations, our study reflects real-world clinical practice and provides contemporary evidence regarding the effectiveness of irinotecan plus bevacizumab in recurrent HGGs. Given the scarcity of prospective randomized data in this setting, such institutional experiences remain clinically relevant.

CONCLUSION

Second-line irinotecan plus bevacizumab demonstrated clinically meaningful antitumor activity in patients with recurrent HGGs, achieving an ORR of 46% and a median PFS of 8.8 months. The observed survival outcomes are favorable compared with those reported in previously published studies and support the continued use of bevacizumab-based treatment strategies in appropriately selected patients. Prospective multicenter studies incorporating contemporary molecular classification systems are warranted to further define the optimal role of irinotecan plus bevacizumab in recurrent HGGs.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital Clinical Research Ethics Committee (approval number: 2024-25, date: 07.11.2024).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Footnotes

Authorship Contributions

Concept: A.Ö., G.U.E., Design: A.Ö., G.U.E., Data Collection or Processing: A.Ö., G.U.E., Analysis or Interpretation: A.Ö., G.U.E., Literature Search: A.Ö., Writing: A.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncol. 2021;23(8):1231-1251. [Crossref] [PubMed] [PMC]
2. Ostrom QT, Price M, Ryan K, et al. CBTRUS statistical report: pediatric brain tumor foundation childhood and adolescent primary brain and other central nervous system tumors diagnosed in the United States in 2014-2018. Neuro Oncol. 2022;24(Suppl 3):iii1-iii38. [Crossref] [PubMed] [PMC]
3. Stupp R, Mason WP, van den Bent MJ, et al.; European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups; National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987-996. [Crossref] [PubMed]
4. Stupp R, Hegi ME, Mason WP, et al.; European Organisation for Research and Treatment of Cancer Brain Tumour and Radiation Oncology Groups; National Cancer Institute of Canada Clinical Trials Group. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459-466. [Crossref] [PubMed]
5. Weller M, van den Bent M, Preusser M, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021;18(3):170-186. Erratum in: Nat Rev Clin Oncol. 2022;19(5):357-358. [Crossref] [PubMed] [PMC]
6. Wen PY, Weller M, Lee EQ, et al. 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. 2020;22(8):1073-1113. [Crossref] [PubMed] [PMC]
7. van den Bent MJ, Ghisai SA, Wick W, et al. Concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma (CATNON; EORTC study 26053-22054): final and exploratory analyses of a randomised, open-label, phase 3 trial. Lancet Oncol. 2026;27(1):45-56. [Crossref] [PubMed]
8. Weller M, van den Bent M, Hopkins K, et al.; European Association for Neuro-Oncology (EANO) Task Force on Malignant Glioma. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. Lancet Oncol. 2014;15(9):e395-e403. Erratum in: Lancet Oncol. 2014;15(13):e587. Erratum in: Lancet Oncol. 2014;15(13):e587. [Crossref] [PubMed]
9. Nowacka A, Śniegocki M, Smuczyński W, Bożiłow D, Ziółkowska E. Angiogenesis in glioblastoma-treatment approaches. Cells. 2025;14(6):407. [Crossref] [PubMed] [PMC]
10. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009;27(28):4733-4740. [Crossref] [PubMed]
11. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27(5):740-745. [Crossref] [PubMed] [PMC]
12. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Phase II trial of bevacizumab and irinotecan in recurrent malignant glioma. Clin Cancer Res. 2007;13(4):1253-1259. [Crossref] [PubMed]
13. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol. 2007;25(30):4722-4729. [Crossref] [PubMed]
14. Lombardi G, De Salvo GL, Brandes AA, et al. Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial. Lancet Oncol. 2019;20(1):110-119. [Crossref] [PubMed]

15. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014;15(9):943-953. [Crossref] [PubMed]
16. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med. 2017;377(20):1954-1963. [Crossref] [PubMed]
17. Champeaux Depond C, Bauchet L, Elhairech D, et al. Survival after newly-diagnosed high-grade glioma surgery: what can we learn from the french national healthcare database? Brain Tumor Res Treat. 2024;12(3):162-171. [Crossref] [PubMed] [PMC]
18. Noiphithak R, Veerasarn K. Clinical predictors for survival and treatment outcome of high-grade glioma in Prasat Neurological Institute. Asian J Neurosurg. 2017;12(1):28-33. [Crossref] [PubMed] [PMC]
19. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance temozolomide vs maintenance temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. JAMA. 2017;318(23):2306-2316. Erratum in: JAMA. 2018;319(17):1824. [Crossref] [PubMed] [PMC]