The Oncologist®

Clinical Trial Results

TEMOBIC: Phase II Trial of Neoadjuvant Chemotherapy for Unresectable Anaplastic Gliomas: An ANOCEF Study

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Key Words. Chemotherapy • Glioma • ANOCEF • TEMOBIC • Phase II

Trial Information

- **ClinicalTrials.gov Identifier:** NCT04755023
- **Sponsor:** ANOCEF
- **Principal Investigator:** Olivier Chinot
- **IRB Approved:** Yes

Lessons Learned

- Treatment with temozolomide and BCNU was associated with substantial response and survival rates for patients with unresectable anaplastic glioma, suggesting potential therapeutic alternative for these patients.
- The optimal treatment for unresectable large anaplastic gliomas remains debated.

Abstract

Background. The optimal treatment for unresectable large anaplastic gliomas remains debated.

Methods. Adult patients with histologically proven unresectable anaplastic oligodendroglioma or mixed gliomas (World Health Organization [WHO] 2007) were eligible. Treatment consisted of BCNU (150 mg/m^2) and temozolomide (110 mg/m^2 for 5 days) every 6 weeks for six cycles before radiotherapy.

Results. Between December 2005 and December 2009, 55 patients (median age of 53.1 years; range, 20.5–70.2) were included. Forty percent of patients presented with wild-type *IDH1* gliomas, and 30% presented with methylated *MGMT* promoter. Median progression-free survival (PFS), centralized PFS, and overall survival (OS) were 16.6 (95% confidence interval [CI], 12.8–20.3), 15.4 (95% CI, 10.0–20.8), and 25.4 (95% CI, 17.5–33.2) months, respectively. Complete and partial responses under chemotherapy were observed for 28.3% and 17% of patients, respectively. Radiotherapy completion was achieved for 75% of patients. Preservation of functional status and self-care capability (Karnofsky performance status [KPS] ≥70) were preserved until disease progression for 69% of patients. Grade ≥ 3 toxicities were reported for 52% of patients, and three deaths were related to treatment. By multivariate analyses including age and KPS, *IDH* mutation was associated with better prognostic for both PFS and OS, whereas *MGMT* promoter methylation was associated with better OS.

Conclusion. The association of BCNU and temozolomide upfront is active for patients with unresectable anaplastic gliomas, but toxicity limits its use. ***The Oncologist*** 2021;26:647–e1304

Discussion

Our study found that the neoadjuvant use of a double alkylating agent combination (BCNU and temozolomide) is feasible and associated with interesting response rates and

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radiotherapy completion rate in this unresectable population. Half of patients responded to chemotherapy, both by investigator evaluation and blinded neuro-radiological centralized review (Table 1). Notably, we observed a high complete response rate of 28% (including 3 patients with IDH wild type), which compared favorably with the other complete response rate for unresectable anaplastic gliomas. Moreover, 75% of patients were able to complete radiotherapy, suggesting that this neoadjuvant treatment did not impair radiotherapy opportunity. On the contrary, our results suggest that neoadjuvant chemotherapy could allow some patients to benefit from irradiation despite large tumors initially not amenable to radiotherapy. We also observed encouraging median PFS and OS (Fig. 1), considering that half of the patients presented with *IDH* wide-type glioma, which confers a poor prognosis. Interestingly, this combination allowed the preservation of functional status and self-care capability with autonomy preservation (KPS ≥70) until disease progression for more than two-thirds of patients, reflecting an important component of quality of life for patients with brain tumors. The main toxicities of this combination were hematological, as expected regarding the toxicity profiles of these drugs. Adverse events were manageable, mainly with dose adaptation and hematological support. The occurrence of secondary leukemia or pulmonary fibrosis was already reported for the use of BCNU and temozolomide alone, requiring a close management and follow up of patients. Finally, we showed that *IDH* mutation and *MGMT* promoter status were significantly associated with patient prognosis after multivariate adjustment. The validation of these results in the population of patients with unresectable gliomas is very interesting, allowing the potential use of these markers for patient stratification in the next clinical trials dedicated to neoadjuvant treatment of anaplastic unresectable gliomas.

Table 1. Best investigator and centralized overall responses

	Localized, *n* (%)	Centralized, *n* (%)
Complete response	15 (28.3)	11 (21.2)
Partial response	9 (17.0)	10 (19.2)
Stable disease	10 (18.9)	9 (17.3)
Progression	19 (35.8)	22 (42.3)

Trial Information

Disease	Brain cancer – primary
Stage of Disease/Treatment	Neoadjuvant
Prior Therapy	None
Type of Study	Phase II, Single arm
Primary Endpoint	Overall response rate
Secondary Endpoints	Progression-free survival, overall survival, safety, other, centralized neuro-radiological response rate, functional status during treatment, predictive value of IDH, and MGMT alterations

Additional Details of Endpoints or Study Design

Patients aged ≥18 years with unresectable, newly diagnosed, histologically proven anaplastic oligodendroglioma or oligoastrocytoma (WHO 2007) were enrolled. For inclusion, prior surgery was limited to biopsy or partial surgery and KPS of >50 with stable or decreased dose of steroids during the 15 days before inclusion. Key exclusion criteria included non-measurable tumor, prior chemotherapy and/or radiotherapy, any severe or uncontrolled systemic disease or biological abnormalities, pregnancy or breast feeding, and coexisting malignancies.

The combination therapy of temozolomide and BCNU was administered up to six consecutive cycles before radiotherapy, or until disease progression, unacceptable toxicity, or withdrawal of consent. In case of progression, radiotherapy was administered without delay. Dose modifications were allowed and based on toxicity observed during prior treatment cycle.

Baseline assessments included physical and neurological examinations, assessments of KPS, cognitive evaluations by Mini-Mental State Examination, dose of steroids, complete blood counts and blood chemistry tests, and contrast-enhanced brain magnetic resonance imaging (MRI). Tumor histology was reviewed by independent committee (D.F.B., K.M.), and *IDH R132H* mutation, *ATRX* loss, and *MGMT* promoter methylation were assessed by immunohistochemistry. Clinical assessment and standard MRI were performed before each cycle during induction therapy, before and 1 month after radiation therapy, then every 3 months for 1 year, and then every 4 months. Tumor response was assessed using the response assessment in neuro-oncology criteria [1], taking into account the perpendicular diameters of the tumor in contrasted sequences and fluid-attenuated inversion recovery. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

The primary endpoint was the objective response rate after chemotherapy. The secondary endpoints were OS, PFS, tolerance of treatment, centralized neuro-radiological response rate, functional status during treatment, and predictive value of *IDH* and *MGMT* alterations. The sample size was based on the Simon methods in two phases assuming a minimal response rate of 30% and a maximal response rate of 50%. Using the Simon's min-max method, the sample size was estimated to 53 patients. All patients who received at least one dose of treatment were included in the analyses. OS was calculated from the date of surgery until death. PFS was defined as the time from surgery to the date of progression or death. The survival distributions were estimated by the Kaplan-Meier method. The log-rank test was used to compare OS and PFS according to prognostic factors. A Cox regression model was performed on the patients for whom *MGMT* promoter methylation and *IDH*

assessments were available, with age and KPS as covariates. All analyses were performed using SPSS software version 22. The α level was set at 0.05.	
Investigator's Analysis	Active and should be pursued further

Drug Information	
Temozolomide	
Generic Name	Temozolomide
Drug Type	Small molecule
Drug Class	Alkylating agent
Dose	110 mg/m^2
Route	oral (po)
Schedule of Administration	5 days every 6 weeks
BCNU	
Generic Name	BCNU
Drug Type	Small molecule
Drug Class	Alkylating agent
Dose	150 mg/m^2
Route	IV
Schedule of Administration	1 injection every 6 weeks

Patient Characteristics	
Number of Patients, Male	36
Number of Patients, Female	19
Stage	Anaplastic gliomas
Age	Median (range): 53.1 (20.5–70.2) years
Number of Prior Systemic Therapies	Median (range): 0
Performance status	The median postoperative Karnofsky performance status: 80 (range, 60–100)
Cancer Types or Histologic Subtypes	Anaplastic gliomas

Primary Assessment Method	
Title	Overall response rate
Number of Patients Screened	55
Number of Patients Enrolled	55
Number of Patients Evaluable for Toxicity	55
Number of Patients Evaluated for Efficacy	53
Evaluation Method	RANO
Response Assessment CR	*n* = 15 (28%)
Response Assessment PR	*n* = 9 (17%)
Response Assessment SD	*n* = 10 (19%)
Response Assessment PD	*n* = 19 (36%)
(Median) Duration Assessment PFS	16.6 Months, CI: 12.8–20.3
(Median) Duration Assessment OS	25.4 Months, CI: 17.5–33.2

Adverse Events							
All Cycles							
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Platelet count decreased	15%	35%	16%	13%	22%	0%	85%
White blood cell decreased	62%	20%	7%	9%	2%	0%	38%
Neutrophil count decreased	49%	16%	11%	15%	9%	0%	51%
Lymphopenia	42%	24%	20%	15%	0%	0%	58%
Anemia	44%	38%	13%	5%	0%	0%	56%
Aplasia	98%	0%	0%	0%	2%	0%	2%
Septic shock	98%	0%	0%	0%	0%	2%	2%
Leukemia	98%	0%	0%	0%	0%	2%	2%
Nausea	75%	16%	5%	4%	0%	0%	25%
Vomiting	85%	7%	5%	2%	0%	0%	15%
Anorexia	93%	7%	0%	0%	0%	0%	7%
Constipation	78%	13%	9%	0%	0%	0%	22%
Diarrhea	95%	5%	0%	0%	0%	0%	5%
Gastrointestinal pain (epigastraligia)	96%	4%	0%	0%	0%	0%	4%
Abdominal pain	98%	2%	0%	0%	0%	0%	2%
Hepatic cytolysis	85%	7%	4%	4%	0%	0%	15%
Cholestasis	98%	0%	0%	0%	2%	0%	2%
Dyspnea (shortness of breath)	98%	2%	0%	0%	0%	0%	2%
Pneumopathy	89%	0%	9%	2%	0%	0%	11%
Pulmonary fibrosis	98%	0%	0%	0%	0%	2%	2%
Thoracic pain	98%	0%	2%	0%	0%	0%	2%
Hypokalemia	96%	4%	0%	0%	0%	0%	4%
Deep Vein thrombosis	93%	0%	4%	2%	2%	0%	7%
Asthenia	47%	25%	24%	4%	0%	0%	53%
Dermatitis	91%	5%	4%	0%	0%	0%	9%
Stomatitis	98%	2%	0%	0%	0%	0%	2%
Epistaxis	98%	0%	2%	0%	0%	0%	2%
Mucositis oral	98%	0%	2%	0%	0%	0%	2%
Pruritus	98%	2%	0%	0%	0%	0%	2%
Cutaneous infection	98%	0%	2%	0%	0%	0%	2%
Dental pain	98%	2%	0%	0%	0%	0%	2%
Edema: face	98%	2%	0%	0%	0%	0%	2%
Myalgia	98%	2%	0%	0%	0%	0%	2%
Arthralgia	95%	2%	4%	0%	0%	0%	5%
Renal lithiasis	98%	0%	2%	0%	0%	0%	2%
Urinary tract infection	98%	2%	0%	0%	0%	0%	2%
Cephalalgia	87%	0%	9%	4%	0%	0%	13%
Seizure	91%	2%	4%	4%	0%	0%	9%
Peripheral neuropathy	95%	5%	0%	0%	0%	0%	5%
Vagal discomfort	98%	0%	2%	0%	0%	0%	2%
Decreased testosterone	98%	2%	0%	0%	0%	0%	2%

Number of toxicities observed during all cycles, regardless of attribution.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events (leading to death)		
Name	**Grade**	**Attribution**
Pulmonary fibrosis	5	Probable
Leukemia	5	Definite
Septic shock	5	Definite

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's Assessment	Active and should be pursued further

In the present study, we analyzed the feasibility of neoadjuvant combination of double alkylating agents for unresectable anaplastic astrocytomas. Currently, standard of care for anaplastic oligodendroglioma is the procarbazine-CCNU-vincristine (PCV) schedule, preceded or followed by radiotherapy [2, 3]. For *IDH*-mutated anaplastic gliomas, both radiotherapy-PCV or radiotherapy with concomitant and adjuvant temozolomide (the Stupp protocol) [4] are proposed. *IDH* wild-type anaplastic astrocytomas are now mainly considered as grade IV gliomas, based on the recent c-IMPACT recommendations [5], with a very close prognosis to that of *IDH* wild-type glioblastoma. The Stupp protocol is commonly proposed to these patients. However, in the clinical trials, the groups of patients with unresectable disease were in the minority and the relevance of these schedules was questioned for these specific patients, particularly when upfront radiotherapy was considered to be difficult to achieve Moreover, the PCV schedule remains debated in some indications: if clinical evidence coming from phase III trials define PCV as standard of care for oligodenroglioma, temozolomide or the combination of BCNU-temozolomide appears to be logistically simpler and may be also effective.

In this context, based on the potential chemosensitivity of oligodendrogliomas and oligo-astrocytomas, the TEMOBIC trial was initiated to propose an efficient neoadjuvant doublet of alkylating agents for unresectable patients (Fig. 2; Table 2). Alkylating combination is strongly supported by preclinical data suggesting a significant synergy between these molecules [6] leading to their evaluation for patients with glioblastoma (GBM) in preliminary clinical trials [7]. In 2005, Barrié et al. reported the results of a phase II trial evaluating the association of BCNU and temozolomide for newly diagnosed unresectable GBM [8]. They showed an interesting response rate of more than 40%, including two complete responses and encouraging median progression-free survival (PFS) and overall survival (OS) of 7.4 and 12.7 months, respectively. Despite patient heterogeneity observed after reclassification according to the 2016 WHO classification, which could not be anticipated at the time of the inclusion, the results of our trial confirmed the potential activity of combining BCNU and temozolomide for neoadjuvant treatment of unresectable anaplastic gliomas. Indeed, half of our patients responded to this chemotherapy schedule and 28% presented with a complete response (Figs. 3, 4, 6; Table 1). Moreover, the high response rate allowed us to complete the radiotherapy for more than 75% of patients, with encouraging patient overall survival. These results compared favorably with those for unresectable anaplastic or grade IV gliomas previously reported in the literature [9–11]. Moreover, the interest of this combination was increased by the recent phase III trial CeTeg/NOA-09 reporting the superiority of the combination of temozolomide and belustine versus temozolomide alone in association with radiotherapy for newly diagnosed GBM with methylated *MGMT* promoter [12]. This study reported a significant improvement in patient overall survival. The safety profile of this schedule was comparable to the one we observed in our study (Table 3), as well as with those previously reported, although three deaths were observed in our study in contrast to the NOA9 trial. Importantly, the authors showed that the combination did not impair patient quality of life or cognitive functions, reinforcing the interest in this combination. These results are in line with the functional status preservation that we observed for our patients.

Interestingly, we confirmed the prognostic impact of *MGMT* promoter methylation that was associated with better overall survival, but we also showed a significantprognostic impact for *IDH* mutation: patients with IDH-mutated gliomas presented with better PFS and OS (Fig. 5; Tables 4, 5). Nevertheless, the role of *IDH* mutation in the therapeutic strategy of anaplastic gliomas is still debated. Although its prognostic impact has been validated in the PCV clinical trials [13] as well as in our study, its predictive value remains to be demonstrated.

The association of temozolomide and BCNU given upfront was associated with interesting response and survival rates for patients with unresectable anaplastic glioma. This schedule could be an interesting therapeutic alternative for these patients.

Acknowledgments

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Disclosures

The authors indicated no financial relationships.

References

1. Wen PY, Macdonald DR, Reardon DA et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28:1963–1972.

2. van den Bent MJ, Brandes AA, Taphoorn MJB et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 2013;31:344–350.

3. Cairncross G, Wang M, Shaw E et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31:337–343.

4. Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–996.

5. Louis DN, Wesseling P, Aldape K et al. cIMPACT-NOW update 6: New entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol 2020;30: 844–856.

6. Plowman J, Waud WR, Koutsoukos AD et al. Preclinical antitumor activity of temozolomide in mice: efficacy against human brain tumor xenografts and synergism with 1,3-bis(2-chloroethyl)-1-nitrosourea. Cancer Res 1994;54: 3793–3799.

7. Schold SC, Kuhn JG, Chang SM et al. A phase I trial of 1,3-bis(2-chloroethyl)-1-nitrosourea plus temozolomide: A North American Brain Tumor Consortium study. Neuro Oncol 2000;2:34–39.

8. Barrié M, Couprie C, Dufour H et al. Temozolomide in combination with BCNU before and after radiotherapy in patients with inoperable newly diagnosed glioblastoma multiforme. Ann Oncol Off 2005;16:1177–1184.

9. Chang SM, Prados MD, Yung WKA et al. Phase II study of neoadjuvant 1, 3-bis (2-chloroethyl)-1-nitrosourea and temozolomide for newly diagnosed anaplastic glioma: A North American Brain Tumor Consortium Trial. Cancer 2004;100:1712–1716.

10. Chauffert B, Feuvret L, Bonnetain F et al. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: Final results of the TEMAVIR study from ANOCEF†. Ann Oncol 2014; 25:1442–1447.

11. Peters KB, Lou E, Desjardins A et al. Phase II trial of upfront bevacizumab, irinotecan, and temozolomide for unresectable glioblastoma. ***The Oncologist*** 2015;20:727–728.

12. Herrlinger U, Tzaridis T, Mack F et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA-09): A randomised, open-label, phase 3 trial. Lancet 2019;393:678–688.

13. Dubbink HJ, Atmodimedjo PN, Kros JM et al. Molecular classification of anaplastic oligodendroglioma using next-generation sequencing: A report of the prospective randomized EORTC Brain Tumor Group 26951 phase III trial. Neuro Oncol 2016;18:388–400.

Figures and Tables

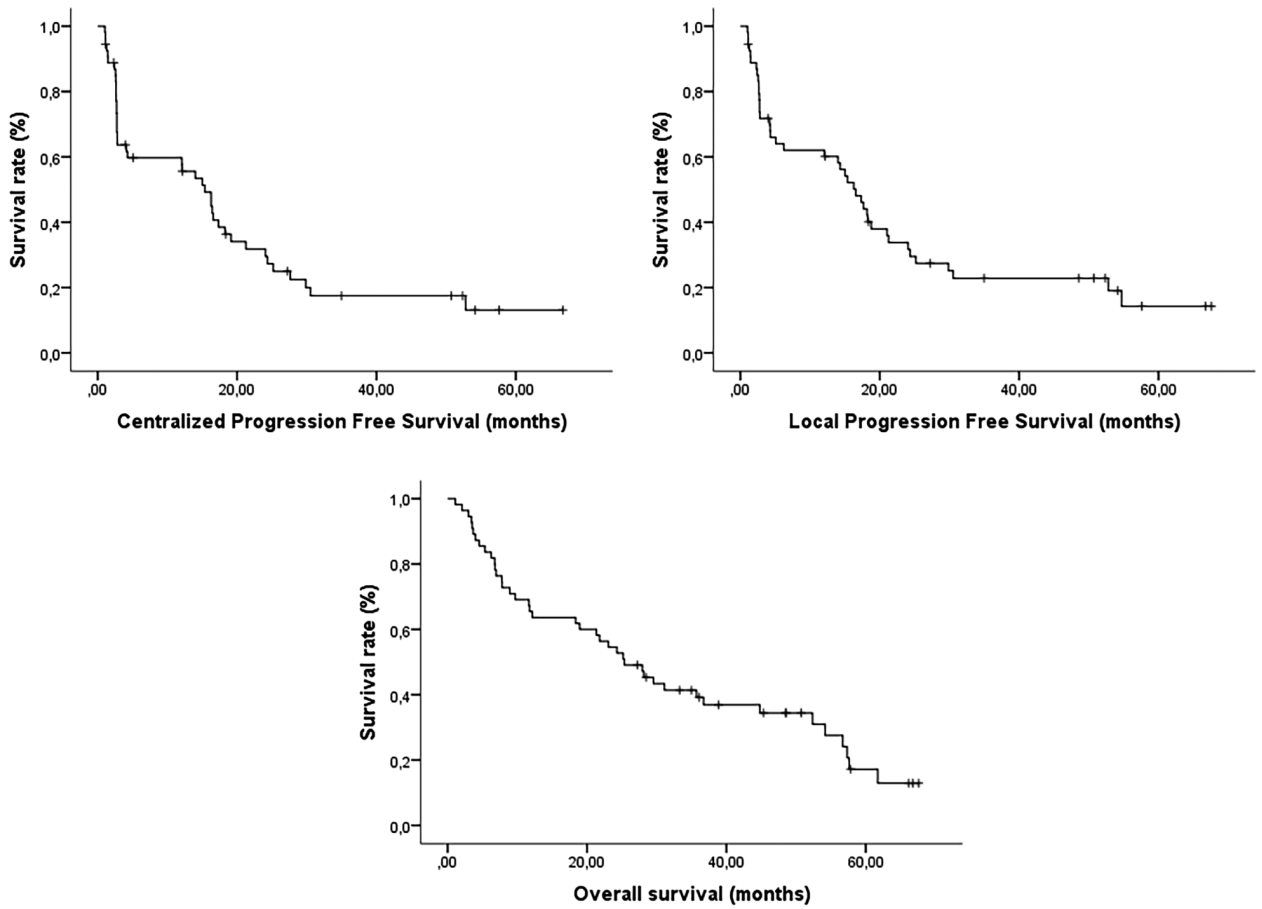

Figure 1. Progression-free survival **(A)**, centralized progression-free survival **(B)**, and overall survival **(C)** curves.

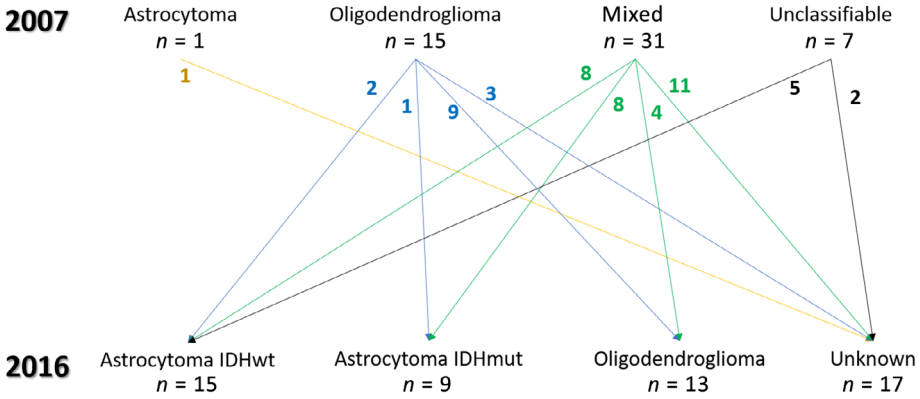

Figure 2. Histological diagnoses according to the World Health Organization (WHO) 2007 and WHO 2016 classifications. Abbreviations: IDHmut, IDH mutation; IDHwt, IDH wild type.

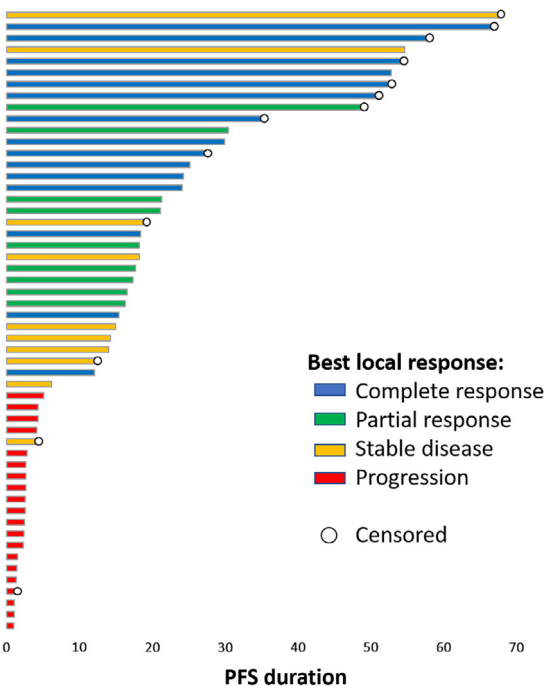

Figure 3. Response quality and progression-free survival. Abbreviation: PFS, progression-free survival.

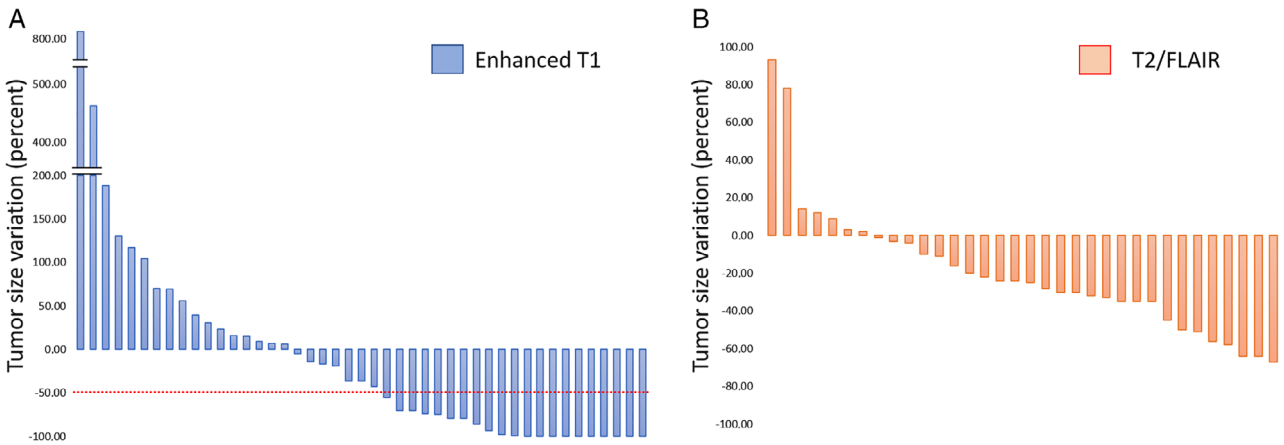

Figure 4. Best tumor response on T1 sequence after gadolinium injection **(A)** or on T2/FLAIR sequence **(B)**. Abbreviation: FLAIR, fluid-attenuated inversion recovery.

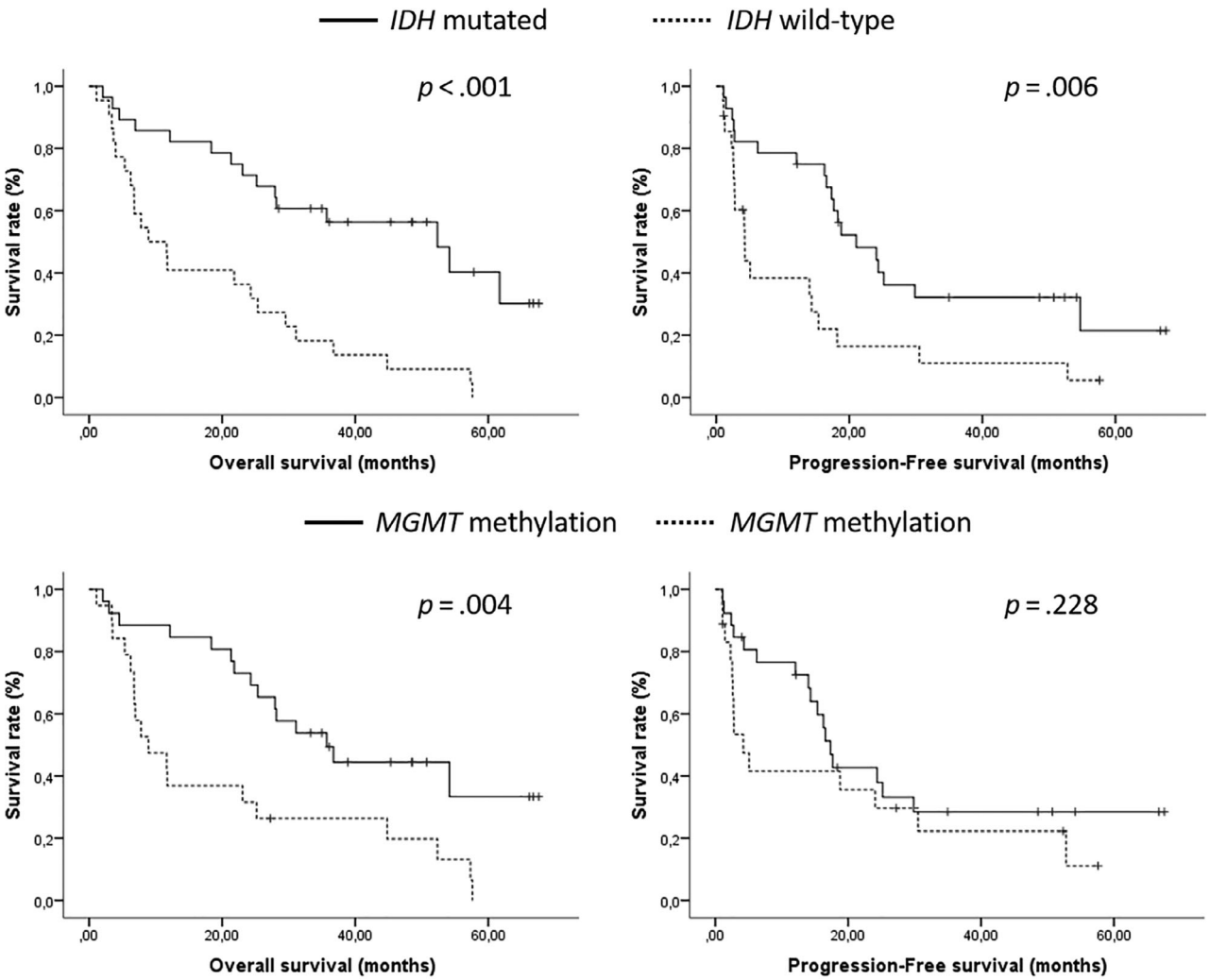

Figure 5. Overall survival (left) and progression-free survival (right) according to IDH mutation status (top) or MGMT promoter methylation (bottom) status.

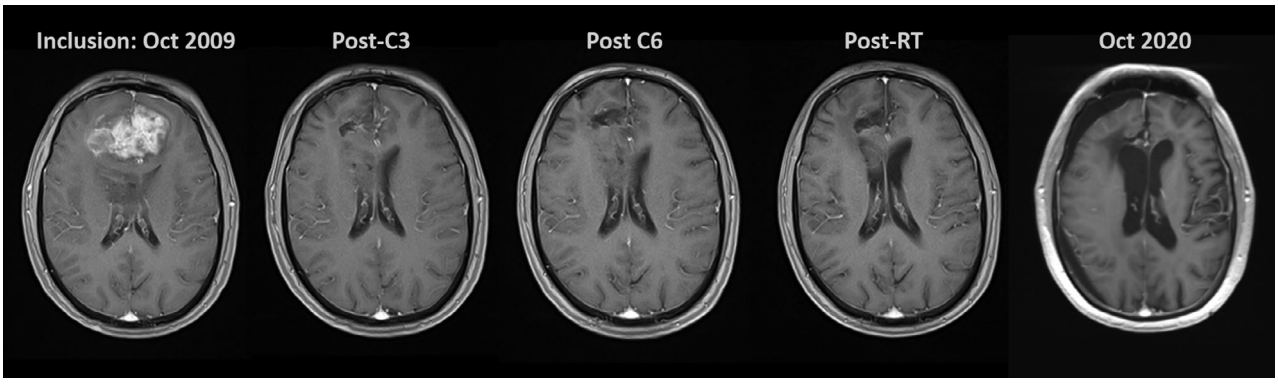

Figure 6. Illustrative MRI of complete and durable response after temozolomide-BCNU neoadjuvant chemotherapy.
Abbreviation: RT, radiotherapy.

Table 2. Severe adverse effects during trial

	Grade III		Grade IV		Grade V	
AEs	**All, *n* (%)**	**Related, *n* (%)**	**All, *n* (%)**	**Related, *n* (%)**	**All, *n* (%)**	**Related, *n* (%)**
Hematology						
Thrombopenia	26 (47)	26 (47)	17 (31)	17 (31)	0	0
Leukopenia	5 (9)	5 (9)	1 (2)	1 (2)	0	0
Neutropenia	14 (25)	14 (25)	5 (9)	5 (9)	0	0
Lymphopenia	8 (15)	8 (15)	0	0	0	0
Anemia	3 (5)	3 (5)	0	0	0	0
Aplasia	0	0	1 (2)	1 (2)	0	0
Septic shock	0	0	0	0	1 (2)	1 (2)
Other						
Asthenia	3 (5)	3 (5)	0	0	0	0
Nausea	1 (2)	1 (2)	0	0	0	0
Vomiting	1 (2)	1 (2)	0	0	0	0
Hepatic cytolysis	1 (2)	1 (2)	0	0	0	0
Hepatic cholestatic	0	0	1 (2)	1 (2)	0	0
Febrile pneumonia	1 (2)	1 (2)	0	0	0	0
Seizure	2 (4)	1 (2)	0	0	0	0
Deep vein thrombosis	1 (2)	0	1 (2)	0	0	0
Leukemia	0	0	0	0	1 (2)	1 (2)
Pulmonary fibrosis	0	0	0	0	1 (2)	1 (2)

Abbreviation: AE, adverse event.

Table 3. Patient characteristics

Characteristics	*n* (%)
Median age (range), years	53.1 (20.5–70.2)
Gender (male/female)	36/19 (65/35)
Karnofsky performance status	
60	6 (11.1)
70	13 (24.1)
80	19 (35.2)
90	13 (24.1)
100	3 (5.6)
T1gado product of diameters, median (range), mm^2	676 (32–3,168)
T2/FLAIR product of diameters, median (range), mm^2	2,688 (481–8,200)
Type of surgery	
Stereotaxic biopsy	28 (50.9)
Surgical biopsy	9 (16.4)
Partial resection	18 (32.7)
Gross total resection	0 (0.0)
Centralized reviewed histology	
Oligodendroglioma	15 (27.0)
Oligo-astrocytoma	31 (56.0)
Astrocytoma	1 (2.0)
Unclassifiable	7 (15.0)
Local oligodendroglioma	4
Local oligo-astrocytoma	2
Local astrocytoma	1
Centralized reviewed grade	
II	1 (2.1)
III	44 (91.7)
IV	3 (6.3)
IDH status	
Wild-type	22 (40)
Mutated	28 (51)
Unknown	5 (9)
MGMT status	
Methylated	19 (35)
Unmethylated	26 (47)
Unknown	10 (18)
p53 expression (median percent, range)	5 (0–90)

Abbreviations: FLAIR, fluid-attenuated inversion recovery; KPS, Karnofsky performance status.

Table 4. Prognostic factors

	Progression-free survival			Overall survival		
Factor	**Univariate**	**Multivariate[a]**	**HR (95% CI)**	**Univariate**	**Multivariate[a]**	**HR (95% CI)**
Age	.121			.122		
KPS	<.0001			<.0001		
$T1_{gado}$ size	.557			.199		
T2 size	.118			.158		
Surgery type	.208			.646		
IDH	.006	.001	3.199 (1.563–6.546)	<.0001	<.0001	5.631 (2.640–12.014)
MGMT	.228	.330		.004	.004	2.999 (1.427–6.306)

[a]adjusted by age and KPS
Abbreviations: CI, confidence interval; HR, hazard ratio; KPS, Karnofsky performance status.

Table 5. Objective response rates according to molecular subtypes

	IDH 1			***MGMT* promoter**		
Response	***IDHmut*, %**	***IDHwt*, %**	***p* value**	**Methylated, %**	**Unmethylated, %**	***p* value**
Complete or partial response	64	20	.002	58	35	.151
Stable disease or progression	36	80		42	65	

Abbreviations: *IDHmut*, IDH mutation; *IDHwt*, IDH wild type.