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Clinical Trial Results

Temozolomide Plus Bevacizumab in Elderly Patients with Newly Diagnosed Glioblastoma and Poor Performance Status: An ANOCEF Phase II Trial (ATAG)

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Trial Information

- **ClinicalTrials.gov Identifier**: NCT02898012
- **Sponsor(s)**: Institut National du Cancer (PHRC program); Roche; Assistance Publique – Hôpitaux de Paris
- **Principal Investigator**: Jean-Yves Delattre
- **IRB Approved**: Yes

Lessons Learned

- Results suggest that the combination of bevacizumab plus temozolomide is active in terms of response rate, survival, performance, quality of life, and cognition in elderly patients with glioblastoma multiforme with poor performance status.
- Whether this combination is superior to temozolomide alone remains to be demonstrated by a randomized study.

Abstract

Background. The optimal treatment of glioblastoma multiforme (GBM) in patients aged ≥70 years with a Karnofsky performance status (KPS) <70 is not established. This clinical trial evaluated the efficacy and safety of upfront temozolomide (TMZ) and bevacizumab (Bev) in patients aged ≥70 years and a KPS <70.

Materials and Methods. Patients aged ≥70 years with a KPS <70 and biopsy-proven GBM were eligible for this multicenter, prospective, nonrandomized, phase II trial of older patients with impaired performance status. Treatment consisted of TMZ administered at 130–150 mg/m^2 per day for 5 days every 4 weeks plus Bev administered at 10 mg/kg every 2 weeks.

Results. The trial included 66 patients (median age of 76 years; median KPS of 60). The median overall survival (OS) was 23.9 weeks (95% confidence interval [CI], 19–27.6), and the median progression-free survival (PFS) was 15.3 weeks (95% CI, 12.9–19.3). Twenty-two (33%) patients became transiently capable of self-care (i.e., KPS >70). Cognition and quality of life significantly improved over time during treatment. Grade ≥3 hematological adverse events occurred in 13 (20%) patients, high blood pressure in 16 (24%), venous thromboembolism in 3 (4.5%), cerebral hemorrhage in 2 (3%), and intestinal perforation in 2 (3%).

Conclusion. This study suggests that TMZ + Bev treatment is active in elderly patients with GBM with low KPS and has an acceptable tolerance level. ***The Oncologist*** 2018;23:524–e44

Discussion

Our study indicates that tolerance to the Bev-TMZ combination was acceptable in this population. Hematological toxicity greater than grade 3 was reported in 20% of patients. As expected, the most frequent adverse event observed with Bev was high blood pressure, which responded to antihypertensive treatment. Although the rate of thromboembolic events does not appear to be exceedingly high in this bedridden GBM population, the two cases of intestinal perforation can be ascribed

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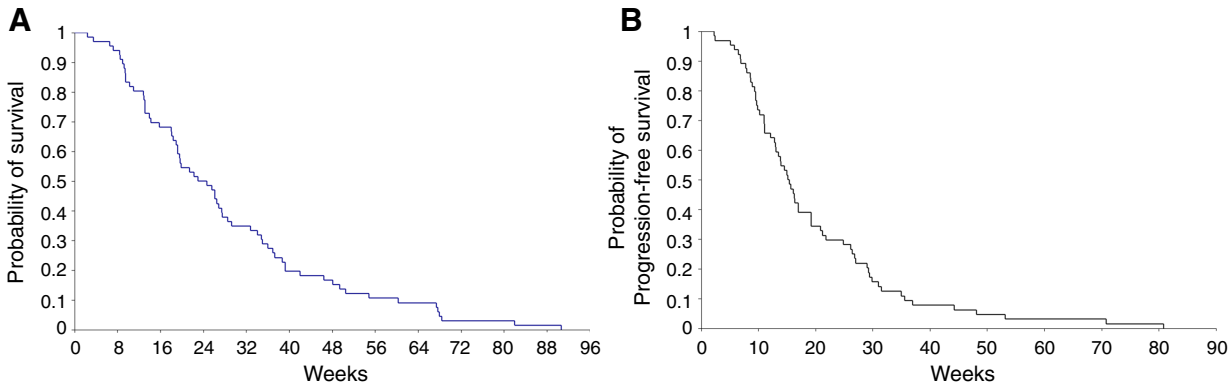

Figure 1. Kaplan-Meier plot: experimental arm, primary assessment, total patient population. **(A)**: Kaplan-Meier estimates of overall survival. **(B)**: Kaplan-Meier estimates of progression-free survival.

to Bev; furthermore, Bev may have played a role in the two cases of cerebral hemorrhage.

An objective radiological response in one third of patients and the fact that one third of patients also became autonomous and capable of self-care (i.e., KPS >70) is encouraging and in agreement with the observations of significant improvements in cognition and most quality-of-life scales during the treatment period. Additionally, the estimated OS median of 24 weeks (Figure 1) that we found appears higher that the 12 weeks OS that we found in a similar patient population treated with supportive care alone (personal data, unpublished).

There was a trend for increased PFS and OS in patients with methylated promoter O-6-methylguanine-DNA methyltransferase (MGMT) status; however, in contrast to our previous study that used TMZ alone, this difference did not reach statistical significance. This may reflect a lack of power. On the other hand, it is possible that some patients without methylated MGMT promoter also could benefit from Bev because its action is not believed to be influenced by MGMT methylation status.

Trial Information	
Disease	Brain cancer – primary
Stage of Disease/Treatment	Primary
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Tolerability
Secondary Endpoint	Health-related quality of life
Secondary Endpoint	Cognitive functioning

Additional Details of Endpoints or Study Design

The primary endpoint was median OS, and the secondary endpoints were PFS, tolerance of treatment, health-related quality of life (European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaires: core questionnaire [QLQ-C30], version 3.0, and brain cancer module [QLQ-BN20]) and cognitive functioning (mini-mental state examination [MMSE]). The sample size was based on the accuracy of the median survival estimation. Assuming a median survival of 22 weeks and a minimum follow-up of 12 months, it was estimated that 70 patients were needed to evaluate survival with a half width of its 95% confidence interval of 14 weeks. 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 MGMT status. Prognostic factors for survival were examined by a stepwise Cox regression model. The factors included in the model were age and KPS at inclusion (60 vs. <60). A second Cox regression model was performed on the patients for whom MGMT promoter methylation assessment was available, with MGMT status, age, and KPS as covariates. Changes from baseline of health-related quality of life scores, MMSE scores, and KPS were analyzed using a mixed-model analysis, with time as a fixed effect and the patient as a random effect. Logistic regression was used to identify predictive factors of clinical improvement defined by a KPS ≥ 70 at two consecutive visits. All analyses were performed using SAS software version 8.2 (SAS Institute, Cary, NC). The α level was set at 0.05.

Baseline assessments included physical and neurological examinations, assessments of KPS, health-related quality of life questionnaires (EORTC QLQ-C30, version 3.0, and QLQBN20), cognitive evaluations with MMSE, complete blood counts and blood chemistry tests, and contrast-enhanced brain computed tomography or magnetic resonance imaging. Patients were assessed every 2 weeks by physical and neurological examinations, complete blood counts, and urine strip tests. The blood chemistry tests, quality of life assessments, KPS evaluations, and MMSEs were repeated every month. Neuroimaging studies were repeated every 2 months, and tumor response was assessed using the response assessment in neuro-oncology criteria, 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 EORTC QLQ-C30

and QLQ-BN20 were used to assess health-related quality of life. The QLQ-C30 questionnaire includes 30 questions comprising five functioning scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, vomiting, and pain), and six single-item scales (dyspnea, insomnia, constipation, anorexia, diarrhea, and financial difficulties). The QLQ-BN20 questionnaire includes 20 items covering functional deficits, symptoms, toxic effects of treatment, and uncertainty about the future. Questionnaires were filled out by patients when possible or by a companion (always the same) when the patient was unable to complete the form. The MMSE was used as a measure of general cognitive status. Higher scores on this exam, which uses a 30-point scale, indicated better cognitive function.

Investigator's Analysis	Active and should be pursued further

Drug Information

Drug 1	
Generic/Working Name	Temozolomide
Drug Type	Small molecule
Drug Class	Alkylating agent
Dose	130–150 milligrams (mg) per square meter (m^2)
Route	Oral (p.o.)
Drug 2	
Generic/Working Name	Bevacizumab
Drug Type	Antibody
Drug Class	Angiogenesis – VEGF
Dose	10 mg milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	Every 2 weeks

Patient Characteristics

Number of Patients, Male	24
Number of Patients, Female	42
Age	Median (range): 76 years (70–87 years)
Number of Prior Systemic Therapies	Median: 0
Other	The median postoperative Karnofsky performance status was 60 (range, 30–60)

Primary Assessment Method

Title	Total Patient Population
Number of Patients Screened	71
Number of Patients Enrolled	66
Number of Patients Evaluable for Toxicity	66
Number of Patients Evaluated for Efficacy	66
Response Assessment CR	$n = 1$
Response Assessment PR	$n = 20$
Response Assessment SD	$n = 24$
Response Assessment PD	$n = 15$
(Median) Duration Assessments PFS	15.3 weeks; CI, 12.9–19.3
(Median) Duration Assessments OS	23.9 weeks; CI, 19–27.6
Kaplan-Meier Time Units	Weeks

Time of scheduled assessment and/or time of event, weeks	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0	0	0	100.00	100.00	66
2.42	1	0	100.00	98.48	65
3.57	1	0	98.48	96.97	64
6.57	1	0	96.97	95.45	63
7.28	1	0	95.45	93.94	62

8.42	1	0	93.94	92.42	61
8.57	1	0	92.42	90.91	60
9	1	0	90.91	89.39	59
9.28	1	0	89.39	87.88	58
9.42	1	0	87.88	86.36	57
9.57	2	0	86.36	83.33	55
10.2	1	0	83.33	81.82	54
11	1	0	81.82	80.30	53
12.85	1	0	80.30	78.79	52
13	1	0	78.79	77.27	51
13.14	3	0	77.27	72.73	48
14	1	0	72.73	71.21	47
14.28	1	0	71.21	69.70	46
15.85	1	0	69.70	68.18	45
18	1	0	68.18	66.67	44
18.14	1	0	66.67	65.15	43
18.42	1	0	65.15	63.64	42
19	1	0	63.64	62.12	41
19.28	2	0	62.12	59.09	39
19.57	1	0	59.09	57.58	38
19.71	1	0	57.58	56.06	37
19.85	1	0	56.06	54.55	36
21.42	1	0	54.55	53.03	35
22.28	1	0	53.03	51.52	34
23	1	0	51.52	50.00	33
24.71	1	0	50.00	48.48	32
25.57	1	0	48.48	46.97	31
26.14	2	0	46.97	43.94	29
26.57	1	0	43.94	42.42	28
26.85	1	0	42.42	40.91	27
27.42	1	0	40.91	39.39	26
27.57	1	0	39.39	37.88	25
28.57	1	0	37.88	36.36	24
29.28	1	0	36.36	34.85	23
32.85	1	0	34.85	33.33	22
34.14	1	0	33.33	31.82	21
34.85	1	0	31.82	30.30	20
35	1	0	30.30	28.79	19
36	1	0	28.79	27.27	18
37	1	0	27.27	25.76	17
37.28	1	0	25.76	24.24	16
38.71	1	0	24.24	22.73	15
39.28	2	0	22.73	19.70	13
42	1	0	19.70	18.18	12
46.42	1	0	18.18	16.67	11
48.14	1	0	16.67	15.15	10
49.42	1	0	15.15	13.64	9
50.57	1	0	13.64	12.12	8
54.85	1	0	12.12	10.61	7
60.28	1	0	10.61	9.09	6

67.42	1	0	9.09	7.58	5
67.71	1	0	7.58	6.06	4
68	1	0	6.06	4.55	3
68.42	1	0	4.55	3.03	2
82	1	0	3.03	1.52	1
90.71	1	0	1.52	0.00	0

Kaplan-Meier Plot Legend

Kaplan-Meier estimates of overall survival (OS)

Phase II Experimental Adverse Events

Tolerance to treatment was acceptable, and most adverse events (AEs) were mild to moderate. AEs of grade $\geq$3 were observed in 37 (56%) patients and are detailed in Table 2. High blood pressure was the most frequent AE and was detected in 16 (24%) patients. It was manageable with antihypertensive medication, and Bev discontinuation was not necessary in any of those cases. Hematological AEs of grade $\geq$3 were reported in 13 (20%) patients, including neutropenia ($n = 2$), anemia ($n = 1$), thrombocytopenia ($n = 5$), and lymphopenia ($n = 8$). Fatal myelosuppression was not observed.

Serious Adverse Events

Name	Grade	Attribution
Cerebral hemorrhage (1 patient)	3	Probable
Cerebral hemorrhage (1 patient)	5	Probable
Intestinal perforation (1 patient)	4	Probable
Intestinal perforation (1 patient)	5	Probable
Lymphopenia (7 patients)	3	Probable
Lymphopenia (1 patient)	4	Probable
Neutropenia (1 patient)	3	Probable
Neutropenia (1 patient)	4	Probable
Thrombocytopenia (2 patients)	3	Probable
Thrombocytopenia (3 patients)	4	Probable
High blood pressure (16 patients)	3	Probable
Infection (1 patient)	3	Probable
Infection (3 patients)	4	Probable
Liver enzyme elevation (4 patients)	3	Probable
Venous thrombosis (3 patients)	3	Probable
Pulmonary embolism (1 patient)	4	Probable
Pulmonary embolism (1 patient)	5	Probable
Rectal hemorrhage (2 patients)	3	Probable
Asthenia (2 patients)	3	Probable
Encephalopathy (1 patient)	3	Probable
Extracerebral hematoma (1 patient)	3	Probable
Anemia (1 patient)	4	Probable
Digestive tract dysfunction (3 patients)	3	Probable

Serious Adverse Events Legend

Serious adverse events included deep venous thrombosis (three cases), pulmonary embolism (two cases, including one fatal), intestinal perforation (two cases, including one fatal), and cerebral hemorrhage (two cases, including one fatal grade 5 toxicity).

Assessment, Analysis, and Discussion

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

Elderly patients aged 65 years and older account for approximately 45% of patients with glioblastoma multiforme (GBM) [1], and this figure is expected to rise concurrently with the aging population of most countries [2]. Unfortunately, few trials have been performed in this setting [3–7]. In elderly patients with good functional status (Karnofsky performance status [KPS] >70 or Eastern Cooperative Oncology Group score 0–2), the standard treatment is now the combination of radiotherapy (RT) and temozolomide (TMZ; concomitant and adjuvant). In elderly patients with poor functional status at the time of diagnosis (KPS <70), there is no standard treatment. One trial suggested that accelerated 1-week RT could be of help, but this trial mixed various populations, including younger patients and elderly patients in good clinical condition [8]. In elderly, bedridden patients with unresectable GBM, the benefit of radiotherapy is unproven and questionable; indeed, it requires daily trips to the hospital, resulting in increased fatigue and an increased risk of acute complications, including intracranial hypertension and herniation, particularly when high doses per fraction are used. In this very difficult patient population, we previously showed that TMZ alone was associated with improvement in functional status in one third of cases and appeared to increase survival compared with supportive care alone [9].

Bevacizumab (Bev) is an antiangiogenic monoclonal antibody targeting vascular endothelial growth factor that is commonly used in GBM. Although recent phase III studies did not show a significant effect of adding Bev to alkylating agents (TMZ or nitrosoureas) on overall survival (OS), a favorable impact of this combination on progression-free survival was demonstrated both as a first-line treatment and in the recurrent setting [10–16].

Treatment of GBM in elderly patients with impaired functional status is challenging. In a recursive partitioning analysis, the estimated median OS in elderly patients with GBM with a KPS <70 without surgical resection was only 10 weeks (95% CI, 9–13.5) [17]. In a recent phase II trial focusing on this frail elderly population, we found that TMZ alone was helpful with a median OS of 25 weeks (95% CI, 19–28); 25% of patients became able to provide self-care and had significant improvements in quality of life and cognition before disease progression [9].

In this study, we evaluated the efficacy and safety of the upfront combination of TMZ + Bev as an initial treatment for elderly patients with GBM and impaired functional status (KPS <70). Bev has a well-known steroid-sparing effect, presumably because of the blood-brain and blood-tumor barrier restoration [10]. Indeed, corticosteroids could be reduced (in 56% of cases) or even discontinued (10%) in our patients with inoperable tumors. This steroid-sparing effect is clearly favorable given the poor tolerance of elderly patients for steroids [18].

Although the analysis included only 66 patients (5 patients were excluded because they did not take any dose of treatment), the precision obtained at the end of the trial of the estimation of the median survival was higher than expected (standard error of 5 weeks instead of 14 weeks). Additionally, the estimated OS median of 24 weeks that we found appears higher that the 12 weeks of OS that we found in a similar patient population treated with supportive care alone (personal data, unpublished). However, it is comparable to the 25 weeks that we reported in similar patients receiving TMZ alone [9]. Whether this combination is superior to TMZ alone remains to be demonstrated by a randomized study.

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Disclosures

Olivier Chinot: Roche, IPSEN Celldex (C/A), Servier, Astra-Zeneca (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

Table 1. Baseline patient characteristics

Characteristics	*n* (%)
Age, years, median (range)	76 (70–87)
Sex	
Female	42 (64)
Male	24 (36)
Onset symptoms	
Epilepsy	2 (3)
Headache	11 (17)
Motor/sensory deficit	40 (60)
Visual deficit	10 (15)
Aphasia	15 (22)
Confusion	17 (25.7)
Frontal syndrome	12 (18)
Other	23 (34)
Tumor topography	
Frontal	23 (34)
Parietal	24 (36)
Temporal	24 (36)
Occipital	9 (14)
Corpus callosum	19 (29)
Other	17 (26)
Type of biopsy	
Stereotactic	54 (82)
Surgical	12 (18)
Time from symptoms onset to biopsy, days, median (range)	35 (3–216)
Time from biopsy to TMZ+Bev treatment, days, median (range)	25.5 (14–52)
Karnofsky performance score, median (range)	60 (30–60)
Corticosteroid use at baseline	63 (95)
Initial MMSE, median (range)	22 (5–30)

Abbreviations: Bev, bevacizumab; MMSE, mini-mental state examination; TMZ, temozolomide.

Table 2. Number of patients with grade $\geq$ 3 adverse events

Adverse event	Grade 3, *n*	Grade 4, *n*	Grade 5, *n*	Total, *n*
Hematologic				
Anemia		1		1
Lymphopenia	7	1		8
Neutropenia	1	1		2
Thrombocytopenia	2	3		5
Other AEsadverse events				
High blood pressure	16			16
Infection	1	3		4
Liver enzyme elevation	4			4
Venous thrombosis	3			3
Pulmonary embolism		1	1	2
Cerebral hemorrhage	1		1	2
Digestive tract dysfunction	3			3
Rectal hemorrhage	2			2
Intestinal perforation		1	1	2
Asthenia	2			2
Encephalopathy	1			1
Extracerebral hematoma	1			1

Table 3. Variations in MMSE and HRQoL scores over time before progression

Measure	Estimate of variation, (points per month)	Standard error	*p* value
MMSE	0.28	0.13	0.04
QLQ QLQ-C30			
Global	1.9	0.561	0.002
Functioning			
Physical	3.5	0.7	<0.0001
Role	4.3	0.86	<0.0001
Emotional	2.8	0.76	0.0003
Cognitive	3.2	0.67	<0.0001
Social	3.06	0.87	0.0006
Symptoms			
Fatigue	−1.75	0.73	0.02
Nausea	No significant variation over time		
Pain	No significant variation over time		
Single Single-item scale			
Dyspnea	No significant variation over time		
Insomnia	−2.5	0.84	0.004
Anorexia	No significant variation over time		
Constipation	−2.25	0.85	0.009
Diarrhea	No significant variation over time		
Financial difficulties	No significant variation over time		
QLQ QLQ-BN20			
Future uncertainty	2.6	0.7	0.0004
Visual disorder	−0.99	0.4	0.02
Motor dysfunction	−3.6	0.7	0.0001
Communication deficit	No significant variation over time		
Drowsiness	−2	0.9	0.02
Bladder control	−2.7	0.8	0.0009
Headaches	No significant variation over time		
Seizures	No significant variation over time		

Abbreviations: HRQoL, health-related quality of life; MMSE, mini-mental state examination; QLQ-BN20, quality of life questionnaire, brain cancer module; QLQ-C30, quality of life core questionnaire.