ORIGINAL ARTICLE

Lomustine and Bevacizumab in Progressive Glioblastoma

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ABSTRACT

BACKGROUND

Bevacizumab is approved for the treatment of patients with progressive glioblastoma on the basis of uncontrolled data. Data from a phase 2 trial suggested that the addition of bevacizumab to lomustine might improve overall survival as compared with monotherapies. We sought to determine whether the combination would result in longer overall survival than lomustine alone among patients at first progression of glioblastoma.

METHODS

We randomly assigned patients with progression after chemoradiation in a 2:1 ratio to receive lomustine plus bevacizumab (combination group, 288 patients) or lomustine alone (monotherapy group, 149 patients). The methylation status of the promoter of O^6-methylguanine–DNA methyltransferase (*MGMT*) was assessed. Health-related quality of life and neurocognitive function were evaluated at baseline and every 12 weeks. The primary end point of the trial was overall survival.

RESULTS

A total of 437 patients underwent randomization. The median number of 6-week treatment cycles was three in the combination group and one in the monotherapy group. With 329 overall survival events (75.3%), the combination therapy did not provide a survival advantage; the median overall survival was 9.1 months (95% confidence interval [CI], 8.1 to 10.1) in the combination group and 8.6 months (95% CI, 7.6 to 10.4) in the monotherapy group (hazard ratio for death, 0.95; 95% CI, 0.74 to 1.21; P=0.65). Locally assessed progression-free survival was 2.7 months longer in the combination group than in the monotherapy group: 4.2 months versus 1.5 months (hazard ratio for disease progression or death, 0.49; 95% CI, 0.39 to 0.61; P<0.001). Grade 3 to 5 adverse events occurred in 63.6% of the patients in the combination group and 38.1% of the patients in the monotherapy group. The addition of bevacizumab to lomustine affected neither health-related quality of life nor neurocognitive function. The *MGMT* status was prognostic.

CONCLUSIONS

Despite somewhat prolonged progression-free survival, treatment with lomustine plus bevacizumab did not confer a survival advantage over treatment with lomustine alone in patients with progressive glioblastoma. (Funded by an unrestricted educational grant from F. Hoffmann–La Roche and by the EORTC Cancer Research Fund; EORTC 26101 ClinicalTrials.gov number, NCT01290939; Eudra-CT number, 2010-023218-30.)

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No standard of care has been established for patients with progressive glioblastoma. Previous studies suggested that bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor, is safe and produces responses[1] that result in a decreased use of glucocorticoids and increased progression-free survival. The BRAIN trial,[1] supported by a single-group study,[2] led to accelerated approval in the United States, followed by a multitude of uncontrolled series and molecular[3] and imaging[4,5] biomarker research. Controlled data are lacking except for those of the BELOB trial,[6] which support the use of bevacizumab in combination with lomustine; data from an Italian phase 2 study showed the efficacy of bevacizumab to be inferior to that of fotemustine when used singly.[7] Randomized trials involving patients with newly diagnosed glioblastoma showed no overall survival benefit from bevacizumab alone.[8-10]

In the BELOB trial, the rate of overall survival at 9 and 12 months was higher with the combination of bevacizumab and lomustine than with either agent alone. Because bevacizumab was not accessible in the Netherlands, crossover to bevacizumab in the control group was restricted (one patient).[6] The EORTC (European Organization for Research and Treatment of Cancer) 26101 phase 2 trial was a four-group trial to evaluate the most effective sequence of bevacizumab and lomustine treatment. It was nearing completion when the first internal report of the BELOB trial was released. No end point of the phase 2 EORTC 26101 trial had been evaluated before the expansion to a phase 3 trial.[11]

After the ongoing phase 2 trial was modified into a phase 3 trial, patients were enrolled in a group receiving either bevacizumab and lomustine in combination or lomustine as a single agent. Here, we report the final data on safety and efficacy in the phase 3 trial.

Methods

Trial Design

This randomized phase 3 trial compared patients with glioblastoma who received lomustine alone (monotherapy group) with those who received a combination of lomustine and bevacizumab (combination group) at first progression of glioblastoma after standard chemoradiotherapy.[12] The EORTC used four stratification criteria to centrally randomly assign patients who had entered the trial[13,14] (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). The primary end point was overall survival, defined as the time from randomization to death. Secondary end points included progression-free survival, landmark analyses for progression-free and overall survival, toxic effects according to version 4.0 of the Common Terminology Criteria for Adverse Events, response rates according to the Response Assessment in Neuro-Oncology (RANO) criteria[15] (see the Methods section in the Supplementary Appendix), neurologic deterioration–free survival (defined as the time from randomization to documentation of neurologic deterioration or death), clinical or neurologic deterioration–free survival, glucocorticoid use, health-related quality of life of both patients and health care proxies, the development of symptoms of neurocognitive deterioration, and assessments of predictive factors.

Eligibility

Patients were accepted into the trial after histologic confirmation of glioblastoma with unequivocal first progression after chemoradiotherapy at least 3 months after the end of radiotherapy. Tumor tissue was required for central review and translational research. Patients were excluded if they had undergone antiangiogenic treatment. Radiotherapy at a dose of no more than 65 Gy with stereotactic radiosurgery or brachytherapy was allowed if recurrence was histologically proven. Only non–enzyme-inducing antiepileptic drugs were allowed (for further eligibility criteria, see the Methods section in the Supplementary Appendix).

Treatment

Patients in the monotherapy group received lomustine at a dose of 110 mg per square meter of body-surface area every 6 weeks (maximum dose, 200 mg). Patients in the combination group received lomustine at a dose of 90 mg per square meter every 6 weeks (maximum dose, 160 mg) plus bevacizumab at a dose of 10 mg per kilogram of body weight every 2 weeks. In both groups, the trial regimen was followed by the investigator's choice of treatment at further progression. In the combination group, if there were no hematologic toxic effects of a grade of more than 1 during the first cycle, the dose of lomustine was increased to 110 mg per square meter (maximum dose, 200 mg) for the second

cycle. In each cycle, which was defined as 6 weeks for each group, day 1 was the first day of medication.

BASELINE EXAMINATIONS AND FOLLOW-UP

The baseline evaluation included magnetic resonance imaging (MRI), questionnaires on health-related quality of life, neurocognitive testing, full clinical and neurologic evaluations, electrocardiography, complete blood count, blood chemical analyses, and urinalysis. All patients were evaluated for vital signs, adverse events, blood counts, and urine dipstick results every 2 weeks. Between weeks 6 and 24, weekly full clinical and neurologic workup, blood examinations, and MRI were performed; questionnaires on health-related quality of life and neurocognitive testing were performed every 3 months. After week 24, examinations were carried out at 3-month intervals.

Images were assessed according to RANO criteria,[15] with additional quantification of changes on fluid-attenuated inversion recovery (FLAIR) images or T_2-weighted images.[16] All the assessments and interpretations of disease status were performed locally but with continuous central quality control and independent central assessment (see the Methods section in the Supplementary Appendix).

PATHOLOGICAL REVIEW AND MOLECULAR TESTING

Pathological reviews and molecular testing were performed centrally with the use of archival tissue from the primary surgery. Isocitrate dehydrogenase (*IDH*) mutations were assessed on the basis of the glioma CpG island methylator phenotype,[17] and O^6-methylguanine–DNA methyltransferase (*MGMT*) promoter methylation was assessed with the use of Illumina 450k methylation arrays based on the MGMT-STP27 model[18] (see the Methods section in the Supplementary Appendix).

QUESTIONNAIRES ON HEALTH-RELATED QUALITY OF LIFE

The EORTC Quality of Life Questionnaire–Core 30 (QLQ-C30) and EORTC brain-cancer module (BN20) are well-established tools that have been validated and translated into all eight languages of patients involved in this trial.[19] Items from both measurements were scaled, scored[20] (whereby responses were aggregated and transformed to a linear scale that ranged from 0 to 100, in which a higher score represented a higher level of functioning [function scales] or a higher level of symptoms [symptom scales]), and evaluated.[21] If at least half the items in the scale were completed, the scale score was calculated with only those items for which values existed. Preselected scales for analysis were global health status, physical functioning, social functioning, motor dysfunction, and communication deficit. Scores for health-related quality of life during the last assessment after baseline until week 36 were calculated and compared between treatment groups, as well as mean changes from baseline until weeks 12, 24, and 36. A difference of at least 10 points between treatment groups was considered to be clinically relevant. More details are provided in the Methods section in the Supplementary Appendix.

ASSESSMENT OF NEUROCOGNITIVE FUNCTIONING

Neurocognitive functioning was assessed with standardized psychometric instruments: the Hopkins Verbal Learning Test–Revised,[22] Trail Making Test (A and B),[23] and Controlled Oral Word Association.[24] Neurocognitive assessments were performed in a fixed order with the use of alternative forms to control for test–retest effects at baseline and every 12 weeks (see the Methods section in the Supplementary Appendix).

TRIAL OVERSIGHT

Staff at the EORTC and the first author reviewed all the data. The EORTC was the trial sponsor and vouches for the integrity, accuracy, and completeness of the data. All the analyses were done by the investigators and EORTC staff, who vouch for the adherence of the trial to the protocol (available at NEJM.org). The first draft of the manuscript was written by the first author. No one who is not an author contributed to the writing of the manuscript. F. Hoffmann–La Roche supported EORTC 26101 through an educational grant and provided bevacizumab free of charge but had no role in analyzing the data or writing the manuscript.

STATISTICAL ANALYSIS

We calculated that at least 327 overall survival events (deaths) would be required for the trial to have 80% power to detect a hazard ratio of 0.72

(rate of overall survival at 9 months of 51.7% in the combination group and 40% in the monotherapy group), on the basis of a one-sided log-rank test at a significance level of 2.5%. The accrual assumptions for the two groups in the phase 3 trial are summarized in the Methods section in the Supplementary Appendix. Overall and progression-free survival curves were estimated with the use of the Kaplan–Meier technique. Analyses were conducted on an intention-to-treat basis. Differences in overall and progression-free survival between the two groups were formally compared with the use of a stratified one-sided log-rank test at a 2.5% significance level. The stratification factors are those used at randomization (except institution) and a variable indicating whether the patient was recruited in the phase 2 or 3 portion. Analyses used the stratification according to the EORTC online randomization system. The treatment effect was estimated as a hazard ratio (with a two-sided 95% confidence interval) with the use of a stratified Cox proportional-hazards model (same stratification factors). Assessments of predictive factors are detailed in the Methods section in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 437 patients underwent randomization; 149 (38 in the phase 2 part and 111 in the phase 3 part of the trial) received lomustine alone and 288 (77 and 211, respectively) received lomustine plus bevacizumab over a period of 37 months from November 2011 through December 2014 at 38 institutions in eight countries. Patient characteristics were well balanced between the two groups (Table 1, and Table S1 in the Supplementary Appendix). Molecular information was available for 367 of 437 patients (84.0%), and a central neuroradiologic review was performed in 418 of 437 patients (95.7%) (Fig. 1).

TREATMENT DELIVERY AND ADVERSE EVENTS

Randomized treatment was started for 98.7% of the patients in the monotherapy group and 98.3% in the combination group (Fig. 1). Patients in the monotherapy group received a median of 1 cycle of lomustine (range, 1 to 8), and patients in the combination group received a median of 3 cycles of lomustine (range, 1 to 8) and 3 cycles of bevacizumab (range, 1 to 16). The main reason for discontinuing treatment was disease progression, in 120 of 144 patients (83.3%) in the lomustine group, 186 of 264 patients (70.5%) for lomustine in the combination group, and 208 of 264 patients (78.8%) for bevacizumab in the combination group. The discrepancy between stopping bevacizumab and stopping lomustine in the combination group was a result of treatment scheduling or toxic effects (15 of 144 patients [10.4%] in the monotherapy group, 53 of 264 [20.1%] for lomustine in the combination group, and 38 of 264 [14.4%] for bevacizumab in the combination group).

Grade 3 to 5 adverse events occurred in 38.1% of the patients in the monotherapy group and in 63.6% of the patients in the combination group. Adverse events of grade 3 to 5 of special interest were pulmonary embolism, arterial hypertension, and hematologic toxic effects. One patient in the monotherapy group died from a lung infection that was unrelated to the tumor. In the combination group, five deaths were noted (two from myocardial infarction and one each from large-intestine perforation, sepsis, and intracranial hemorrhage) (Table 2).

EFFICACY END POINTS

With 329 overall survival events (75.3%), the combination treatment did not provide a survival advantage. The median overall survival was 8.6 months (95% confidence interval [CI], 7.6 to 10.4) in the monotherapy group and 9.1 months (95% CI, 8.1 to 10.1) in the combination group according to local assessments (hazard ratio for death in the combination group, 0.95; 95% CI, 0.74 to 1.21; $P=0.65$) (Fig. 2A). The median progression-free survival was 1.5 months (95% CI, 1.5 to 2.5) in the monotherapy group and 4.2 months (95% CI, 3.7 to 4.3) in the combination group according to local assessments (hazard ratio for disease progression or death in the combination group, 0.49; 95% CI, 0.39 to 0.61; $P<0.001$) (Fig. 2B). Landmark survival at 9 and 12 months is shown in Figure 2A.

No subgroup showed particular benefits from bevacizumab; male patients derived the least benefit. No factor predicted benefit (Table S2A in the Supplementary Appendix). A total of 397 of 430 patients (92.3%) had measurable disease,

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Lomustine Alone (N=149)	Lomustine plus Bevacizumab (N=288)	Total (N=437)
Sex — no. (%)			
Male	91 (61.1)	174 (60.4)	265 (60.6)
Female	58 (38.9)	114 (39.6)	172 (39.4)
Age — yr			
Median	59.8	57.1	57.7
Range	21.2–79.2	23.1–82.3	21.2–82.3
WHO performance status — no. (%)†‡			
0	49 (32.9)	100 (34.7)	149 (34.1)
1	81 (54.4)	160 (55.6)	241 (55.1)
2	19 (12.8)	28 (9.7)	47 (10.8)
Use of glucocorticoids — no. (%)‡			
No	78 (52.3)	144 (50.0)	222 (50.8)
Yes§	71 (47.7)	144 (50.0)	215 (49.2)
MGMT status — no. (%)			
Methylated	37 (24.8)	67 (23.3)	104 (23.8)
Unmethylated	38 (25.5)	87 (30.2)	125 (28.6)
Undetermined	13 (8.7)	23 (8.0)	36 (8.2)
Missing data	61 (40.9)	111 (38.5)	172 (39.4)
GCIMP status — no. (%)			
Positive	4 (2.7)	12 (4.2)	16 (3.7)
Negative	145 (97.3)	276 (95.8)	421 (96.3)
Time between first progressive disease and treatment			
No. of patients analyzed	147	283	430
Median — days	23.1	27.1	26.1
Range — days	1.1–231.1	1.1–219.1	1.1–231.1
Histologic confirmation of glioblastoma with unequivocal first progression after chemoradiotherapy at least 3 mo after the end of radiotherapy — no. (%)			
No	0	2 (0.7)	2 (0.5)
Yes	149 (100)	286 (99.3)	435 (99.5)

* GCIMP denotes glioma CpG island methylator phenotype, and *MGMT* O^6-methylguanine–DNA methyltransferase. Percentages may not total 100 because of rounding.
† The World Health Organization (WHO) performance status is scored on a scale of 0 to 5, with 0 indicating full activity, 1 unable to carry out heavy physical work, and 2 up and about more than half the day but unable to work.
‡ Data were gathered with the use of the European Organization for Research and Treatment of Cancer online randomization system.
§ These patients received a stable or decreasing dose for 7 days before magnetic resonance imaging at baseline.

including 137 of 147 (93.2%) in the monotherapy group and 260 of 283 (91.9%) in the combination group. An objective response was noted in 19 of 137 patients (13.9%; 95% CI, 8.6 to 20.8) in the monotherapy group and 108 of 260 (41.5%; 95% CI, 35.5 to 47.8) in the combination group. One patient in the monotherapy group and 5 patients in the combination group had complete responses.

Central review determined that the median

progression-free survival was 1.5 months (95% CI, 1.5 to 1.6) in the monotherapy group and 3.8 months (95% CI, 3.0 to 4.2) in the combination group (hazard ratio for disease progression or death in the combination group, 0.59; 95% CI, 0.48 to 0.74; P<0.001). Central and local neuroradiologic review had a concordance of 48%; the central review called progression before the local assessment in 28.4% of the patients and after the local assessment in 17.8% of the patients (Table S3 in the Supplementary Appendix).

Glucocorticoid use was equally distributed between the two groups and almost evenly split between use and no use (Table 1). Of the 222 patients (78 in the monotherapy group and 144 in the combination group) who did not receive glucocorticoids at baseline, 86 patients (30 [38.5%] and 56 [38.9%] in the respective groups) began to receive them during treatment. No significant difference in the time before starting glucocorticoids was observed between the combination group (median, 8.3 months; 95% CI, 6.8 to not reached) and the monotherapy group (median, 8.6 months; 95% CI, 4.5 to 12.7) (P=0.33).

After disease progression occurred while they were receiving the trial treatment, 65.9% of the patients in the monotherapy group and 53.0% of the patients in the combination group received further therapy (401 patients had a progression event, of whom 368 had follow-up information), including crossovers to off-label use of bevacizumab in 35.5% of the monotherapy group and 18.7% of the combination group (Table 3).

HEALTH-RELATED QUALITY OF LIFE

Data on health-related quality of life at baseline were available for 92.0% of the patients (402 of 437), with a decrease to 66.3% at week 36, limiting further analysis. There were no significant differences between the treatment groups until week 36, when adherence favored the combination group (71.2%, vs. 50.0% in the monotherapy group). No significant between-group differences were observed for preselected scales, apart from a lower score for social functioning in the combination group than in the monotherapy group (mean, 66 vs. 81; P=0.001) (Table S4 in the Supplementary Appendix); the difference was considered to be clinically relevant. The baseline score for social functioning was 66 in the monotherapy group and 71 in the combina-

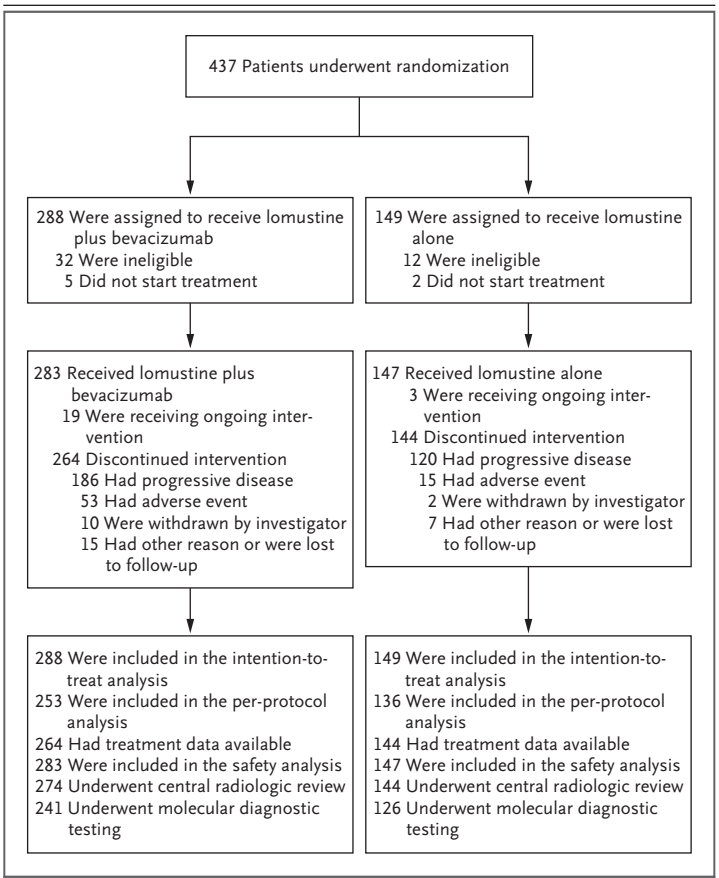

Figure 1. Randomization, Follow-up, and Analyses.

Table 2. Adverse Events.

Event	Lomustine Alone (N=147)	Lomustine plus Bevacizumab (N=283)
	number (percent)	
Any adverse event	139 (94.6)	278 (98.2)
Treatment-related adverse event	78 (53.1)	241 (85.2)
Grade 3–5 adverse event	56 (38.1)	180 (63.6)
Treatment-related serious adverse event	14 (9.5)	109 (38.5)
Pulmonary embolism	0	14 (4.9)
Arterial hypertension	1 (0.7)	67 (23.7)
Hematologic toxic effects	73 (49.7)	152 (53.7)
Death*	1 (0.7)	5 (1.8)

* In the monotherapy group, one patient died from a lung infection. In the combination group, two patients died from myocardial infarction and one each died from large-intestine perforation, sepsis, and intracranial hemorrhage.

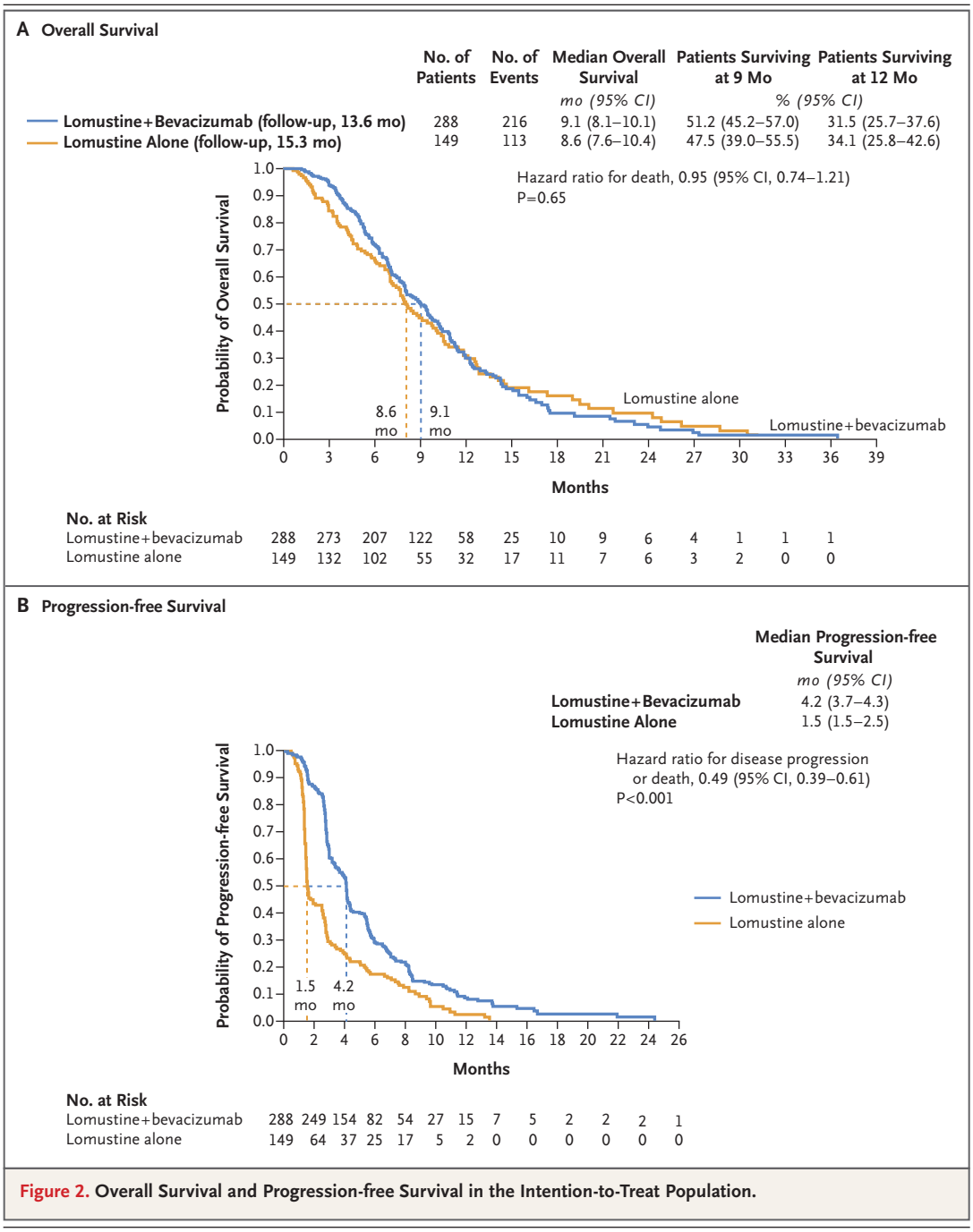

Figure 2. Overall Survival and Progression-free Survival in the Intention-to-Treat Population.

tion group, with patients in the combination group showing stable social functioning and patients in the monotherapy group showing improved social functioning. There were no significant differences between the groups in the mean change in health-related quality of life from baseline at weeks 12 and 24, but at week 36, scores for global health status and social functioning were lower in the combination group than in the monotherapy group (mean change, –5.6 vs. 4.6 for global health status and –1.1 vs. 9.3 for social functioning, with available data from 35 patients in the combination group and 9 patients in the monotherapy group).

If progression was not included as an event, there was no significant difference in time to deterioration in health-related quality of life between the monotherapy group and the combination group (median, 13.0 weeks and 13.1 weeks, respectively; P=0.65). This contrasts with deterioration-free survival, which was longer in the combination group than in the monotherapy group (12.4 weeks vs. 6.7 weeks; P<0.001), reflecting the difference in time to progression.

NEUROCOGNITIVE OUTCOME

Adherence to the assessment of neurocognitive function was 94.5% at baseline and 61.4% at the third follow-up visit at 36 weeks. Adherence never differed significantly between the treatment groups. The primary analysis compared the six neurocognitive function scores at the last disease assessment before or at the third follow-up visit. Time points of the assessment of neurocognitive function are shown in Table S5 in the Supplementary Appendix. No significant differences were observed at baseline and follow-up between the two trial groups (Fig. S1 in the Supplementary Appendix).

MGMT STATUS

Technically sound *MGMT* results could not be obtained for 97 patients; in 70, no tumor tissue of appropriate quality was available. Of the remaining 270 patients, 124 (45.9%) had *MGMT* promoter hypermethylation. In the population as a whole, *MGMT* promoter methylation was prognostic, with a median progression-free survival of 2.8 months (95% CI, 2.6 to 2.9) among patients with unmethylated promoters (146 patients with 143 events), 5.7 months (95% CI, 4.4 to 6.9) among patients with methylated promoters (124 patients with 103 events), 3.0 months (95% CI, 2.8 to 4.2) among patients with undetermined results (97 patients with 89 events), and 2.9 months (95% CI, 2.7 to 3.5) among patients for whom no material was available (70 patients with 68 events) (Table S6 in the Supplementary Appendix). The hazard ratio for disease progression or death with methylated *MGMT* status as compared with unmethylated *MGMT* status was 0.37 (95% CI, 0.29 to 0.49). *MGMT* status was not predictive of efficacy outcomes with the combination treatment (Table S2B and S2C in the Supplementary Appendix). When data were separated according to treatment and *MGMT* status, progression-free but not overall survival was longer in the combination group than in the monotherapy group, whether the *MGMT* promoter was unmethylated or methylated in tumors (Table S7 in the Supplementary Appendix). Patients with methylated *MGMT* status had a longer median overall survival from the time of randomization than those with unmethylated *MGMT* status: 13.5 months (95% CI, 10.6 to 15.4) versus 8.0 months (95% CI, 5.9 to 8.8) (hazard ratio for death, 0.48; 95% CI, 0.35 to 0.66; P<0.001).

Table 3. Therapy after Disease Progression.*

Treatment	Lomustine Alone (N=138)	Lomustine plus Bevacizumab (N=230)
	number (percent)	
Any further treatment	91 (65.9)	122 (53.0)
Chemotherapy	45 (32.6)	88 (38.3)
Bevacizumab	49 (35.5)	43 (18.7)
Temozolomide	13 (9.4)	40 (17.4)
Targeted therapies	58 (42.0)	54 (23.5)
Repeat radiotherapy	19 (13.8)	22 (9.6)
Surgery	13 (9.4)	17 (7.4)
Any other therapy	7 (5.1)	11 (4.8)

* Of 401 patients with documented progression, 368 had follow-up information.

DISCUSSION

EORTC 26101 provided phase 3 data on the efficacy of bevacizumab in patients with progressive glioblastoma. Adding bevacizumab to lomustine did not confer a survival advantage over lomustine alone but prolonged progression-free survival somewhat. This benefit was consistent across the assessments of the trial, although there were some local and central deviations. EORTC 26101 shows the feasibility of implementing a uniform MRI protocol in an international neuro-oncology trial. The central review deemed progression earlier than the local assessment in 96 patients in the combination group (Table S3 in the Supplementary Appendix).[25]

There were no unexpected findings from assessments of toxic effects, although absolute numbers were higher and deaths more frequent

in the combination group than in the monotherapy group. Although important given the lack of overall survival benefit, the higher numbers of adverse effects should be assessed relative to the longer treatment period in the combination group (Table 2). In addition to the difference in toxic effects, combination therapy had a negative effect on scores of social functioning and global health status at late time points (Table S4 in the Supplementary Appendix). These results are consistent with findings regarding health-related quality of life in the BELOB trial.[26] The addition of bevacizumab did not improve neurocognitive functioning, although the high performance level at baseline may prevent a systematic improvement. However, the combination of bevacizumab and lomustine also did not lead to poorer neurocognitive function than lomustine alone, although the 36 weeks during which patient adherence was satisfactory might have been too short to observe long-term differences between the groups (Fig. S1 in the Supplementary Appendix).

Although earlier reports from the BRAIN trial (involving patients with recurrent glioblastoma)[1] and from the Avastin in Glioblastoma trial (involving patients with newly diagnosed glioblastoma)[8] suggested that bevacizumab had glucocorticoid-sparing effects, the addition of bevacizumab in the current trial did not result in reduced use of glucocorticoids. *MGMT* status was not predictive of benefit from the combined therapy.[27] Earlier data suggested that lomustine had little effect on *MGMT* unmethylated glioblastomas, and adding bevacizumab did not alter this conclusion.[6]

EORTC was unable to confirm the conclusion of phase 2 trials that the addition of bevacizumab to lomustine improves survival in patients with progressive glioblastoma. The effect on progression-free survival was not associated with an increase in overall survival, and combination therapy was associated with increased toxicity.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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