

Neurocognitive function in patients with recurrent glioblastoma treated with bevacizumab

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Neurocognitive decline is a frequent adverse effect of glioblastoma. Antitumor therapies that are efficacious, as measured by traditional endpoints such as objective response (OR) and progression-free survival (PFS), and have beneficial effects on neurocognitive function (NCF) are of clinical benefit to these patients. We evaluated neurocognitive changes across time in 167 patients with recurrent glioblastoma treated with bevacizumab-based therapy in BRAIN, a phase II, randomized, multicenter trial. All patients underwent MRI and neurocognitive testing at baseline and every 6 weeks thereafter. Memory, visuomotor scanning speed, and executive function were evaluated using the Hopkins Verbal Learning Test–Revised, the Trail Making Test, and the Controlled Oral Word Association test, respectively. NCF relative to baseline for patients with an OR, PFS >6 months, or disease progression was evaluated at time of OR, 24 weeks, and time of progression, respectively. For

patients with an OR or PFS >6 months, median standardized test scores were examined from baseline to week 24. Most patients with an OR or PFS >6 months had poorer NCF performance compared to the general population at baseline and had improved or stable NCF at the time of response or at the 24-week assessment, respectively; most patients with progressive disease had neurocognitive decline at the time of progression. For patients with an OR or PFS >6 months, median standardized test scores were largely stable across the first 24 weeks on study. Neurocognitive testing was an objective, valid, and feasible method of monitoring NCF in patients with recurrent glioblastoma.

Keywords: bevacizumab, cognitive function, glioblastoma, quality of life.

Glioblastoma is a highly malignant and rapidly progressing disease. At the time of diagnosis, patients with glioblastoma frequently suffer from neurocognitive deficits.

Neurocognitive function (NCF) has been shown to be a predictor of survival in patients with recurrent malignant glioma¹ and has a direct bearing on health-related quality of life (QoL). Diminished NCF in patients with

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brain tumors has been associated with reduced independence, difficulty maintaining roles in the home and work environments, decreased ability to participate in daily living activities,²⁻⁴ and increased caregiver burden and distress.^{4,5} Neurocognitive decline often precedes reductions in daily functioning and QoL in these patients^{1,6-8} and has been shown to occur in advance of radiographic evidence of tumor progression.^{9,10}

Outcome assessment in neuro-oncology is oriented predominantly toward radiographic changes and survival time.¹¹ Radiographic response, in particular, is not always the best indicator of patient status. For instance, with anti-angiogenic therapy, apparent radiographic response may reflect a normalization of tumor vasculature rather than a true antitumor effect. Patient-centered outcomes assessed with neurocognitive testing can provide supportive information about the clinical benefit achieved with increased response rates and survival and may help patients and physicians to make decisions about the potential benefits of treatment. Furthermore, antitumor therapies that have beneficial effects on NCF, in addition to being efficacious in terms of radiological response and survival, would be of value to patients with high-grade gliomas in terms of improved QoL and functional independence.¹ To date, there has been no evaluation of NCF in multisite clinical trials of patients with recurrent glioblastoma.

In the phase II BRAIN trial of patients with recurrent glioblastoma,¹² the vascular endothelial growth factor

(VEGF) inhibitor bevacizumab (BEV; Genentech), either alone or in combination with irinotecan (CPT-11), demonstrated improved objective response (OR) rates and 6-month progression-free survival (PFS) compared with historical controls. As an exploratory outcome in BRAIN, NCF was assessed with a battery of neurocognitive tests widely used in neuropsychological clinical practice and research studies in patients with brain tumors.^{1,9} We took advantage of the available data to describe NCF in a population of patients with recurrent glioblastoma, evaluate how NCF changed with treatment, and assess the overall feasibility of using neurocognitive testing to monitor NCF in this rapidly progressing disease.

Patients and Methods

Patients

One hundred sixty-seven patients with glioblastoma at first or second relapse were randomized to receive BEV ($n = 85$) or BEV + CPT-11 ($n = 82$) in the BRAIN study. BRAIN methodology, including study design, eligibility, treatment, assessments, and analyses, has been published in detail.¹² BRAIN is registered at www.clinicaltrials.gov (NCT00345163). The protocol was approved by the institutional review board at each study site, and all patients provided informed consent

Table 1. Overview of neurocognitive tests

Test	Description	Possible range of score	Reliable change index threshold (from baseline)
Hopkins Verbal Learning Test-Revised (HVLT-R)	The Hopkins Verbal Learning Test-Revised (HVLT-R) ¹⁵ is a learning and memory test, in which the patient is asked to learn and recall a list of 12 words over three trials.	0-36	± 5 words ¹⁵
Total Recall (HVLT-R TR)			
Delayed Recall (HVLT-R DR)			
Delayed Recognition (HVLT-R RECOG)	Spontaneous recall is assessed before and after a delay. Recognition discriminability is also assessed after a delay. Four alternate versions of the test were used to minimize practice effects over time.	-12-+12	± 2 words
Trail Making Test (TMT)	The Trail Making Test (TMT) ²⁸ Part A (TMTA) assesses visual scanning and motor tracking requiring focused attention. Patients are required to sequentially connect numbered dots in ascending order that are randomly scattered across the test page. Part B (TMTB) includes a divided attention component requiring mental flexibility (i.e., executive function). On this subtest, dots with numbers and letters are randomly scattered on the test page. Patients are required to alternate between connecting numbers and letters in an ascending sequential order. Both tests require the patient to complete the sequence as fast as possible. TMTA was discontinued after 3 min and TMTB was discontinued after 5 min for patients that had difficulty in order to reduce patient burden.	1-2750 1-3750	± 12 s ²⁹ ± 26 s
Part A (TMTA)			
Part B (TMTB)			
Controlled Oral Word Association (COWA)	The Controlled Oral Word Association [COWA] ³⁰ test assesses lexical fluency. Given a specific letter of the alphabet, patients are required to produce as many words as possible that begin with that letter. There are two alternate forms of the COWA, each with three unique letter exemplars.	0 - unlimited	± 12 words ¹⁷

prior to participation in the study. All patients underwent clinical, laboratory, MRI, and neurocognitive testing at baseline and prior to the beginning of each treatment cycle (i.e., every 6 weeks) up to 52 weeks or until disease progression or discontinuation.

Neuroimaging

Co-primary endpoints of BRAIN, OR rate and 6-month PFS, were assessed by a blinded, independent radiology facility (IRF; RadPharm, Inc., Princeton, NJ) according to World Health Organization Response Evaluation Criteria,¹³ taking corticosteroid dose into account.¹⁴ Non-contrast-enhancing lesions were considered non-target lesions in tumor assessment. Progression was determined by contrast-enhancing and non-contrast-

enhancing lesions. As mandated by the protocol, in the absence of radiographic documentation, clinical progression, assessed by the investigator according to his/her judgment of neurological progression, was used to determine disease progression. (Notably, each determination of disease progression in BRAIN was based on radiographic documentation.) All patients were followed until discontinuation from the study, loss to follow-up, study termination, or death.

Neurocognitive Testing

Memory, visuospatial scanning speed, and executive function were evaluated using 3 objective, standard, valid tests (Table 1). The maximum time to complete

Table 2. Patient demographics and baseline characteristics

	BEV (n = 85)	BEV + CPT-11 (n = 82)
Age in years		
Mean (SD)	53.8 (11.0)	55.0 (12.4)
Median	54	57
Range	23–78	23–79
% Male	68.2	69.5
% White	90.6	89.0
Education, ^a years		
Mean (SD)	15.1 (2.6)	15.2 (3.0)
Median	16	16
Range	9–22	6–22
Relapse, %		
First	81.2	80.5
Second	18.8	19.5
KPS, %		
90–100	44.7	37.8
70–80	55.3	62.2
Initial surgery, %		
Complete resection	42.4	37.8
Partial resection	49.4	53.7
Biopsy only	8.2	8.5
Medication use at baseline, %		
Anticonvulsants	21.2	36.6
Corticosteroids	50.6	52.4
Opioids	15.3	11.0
Psychostimulants	12.9	4.9
Median months from radiotherapy to study treatment	6.2	6.6
Median months from surgery for recurrent disease to study treatment	7.4	7.9
Standardized neurocognitive test scores at baseline, mean (SD), median		
HVL-T-R TR	n = 83, -2.47 (1.85), -2.22	n = 75, -2.30 (1.89), -2.21
HVL-T-R DR	n = 81, -2.72 (2.16), -2.67	n = 74, -2.43 (2.19), -2.11
HVL-T-R RECOG	n = 79, -1.92 (2.61), -1.29	n = 75, -1.61 (2.44), -0.57
TMTA	n = 82, -4.81 (5.65), -2.65	n = 73, -12.34 (59.67), -2.54
TMTB	n = 73, -7.52 (11.96), -2.91	n = 70, -7.70 (12.81), -3.65
COWA	n = 81, -1.67 (1.07), -1.89	n = 74, -1.55 (1.38), -1.58

^aBEV n = 64; BEV + CPT-11 n = 62. HVL-T-R, Hopkins Verbal Learning Test-Revised; TR, Total Recall; DR, Delayed Recall; RECOG, Delayed Recognition; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; COWA, Controlled Oral Word Association; BEV, bevacizumab; CPT-11, irinotecan.

each test ranged from 3 to 5 min, for a total evaluation time of ~25 min.

Statistical Analysis

For each NCF test, raw scores and standardized scores (mean = 0, SD = 1) using published normative data from a healthy population¹⁵⁻¹⁷ were calculated for analyses. For Trail Making Test Parts A and B, raw scores were prorated (percent prorated: Part A = 4.73%, Part B = 19.38%) if the test was discontinued or the maximal time was reached secondary to a neurological difficulty, according to the method described by Heaton et al.¹⁶ If a test was not administered, or the patient was unable to attempt a test, it was excluded from the analysis. The percentage of patients with analyzable data (completed and/or prorated tests) for each NCF test at each assessment was calculated.

At each assessment, change in raw test score relative to baseline was calculated, and neurocognitive status was categorized as improved, stable, or declined, using the Reliable Change Index (RCI).¹⁸ The RCI is derived from the standard error of measurement of each test and represents the 90% confidence interval for the

difference in raw score from baseline to the next assessment that would be expected if no real change occurred:

$$\text{RCI} = 1.64(\text{SEdiff}), \text{ where SEdiff} \\ = [2(\text{SEM}^2)]^{1/2} \text{ and SEM} = \text{SD}_1[(1 - r_{xy})^{1/2}]$$

where SEdiff is the standard error of difference, SEM is the standard error of measurement, SD is the standard deviation, and r_{xy} is the test-retest reliability statistic. All RCI thresholds were rounded to the nearest whole number. Changes that did not meet the RCI threshold for improvement or decline were categorized as stable performance. Changes (i.e., improvement, decline) from baseline neurocognitive status were confirmed at the next neurocognitive assessment, when available.

To assess the relationship among 3 clinical and radiographic tumor response outcomes and change in NCF, neurocognitive status relative to baseline was evaluated for 3 subgroups of patients at specific timepoints: patients with an IRF-determined OR at the time of first response, patients with IRF-determined PFS >6 months at the Week 24 assessment, and patients with investigator-determined progressive disease at the time of progression. Changes in standardized scores over

Table 3. Frequency of analyzable neurocognitive data^a

Test, % Completed	BEV			BEV + CPT-11		
	Baseline (n = 85)	Week 6 (n = 76)	Week 24 (n = 29)	Baseline (n = 82)	Week 6 (n = 75)	Week 24 (n = 34)
HVLT-R TR	98	96	93	92	89	91
HVLT-R DR	95	92	90	90	89	88
HVLT-R RECOG	93	92	90	92	87	88
TMTA	97	95	90	89	87	94
TMTB	86	91	79	85	79	88
COWA	95	93	93	90	87	94

^aIncludes patients for whom test scores were prorated. *n* = number of patients eligible (i.e., progression free and still on study) for assessment at time indicated. BEV, bevacizumab; CPT-11, irinotecan; HVLT-R, Hopkins Verbal Learning Test-Revised; TR, Total Recall; DR, Delayed Recall; RECOG, Delayed Recognition; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; COWA, Controlled Oral Word Association.

Table 4. Neurocognitive status relative to baseline for key patient subgroups

Patient subgroup	RCI-determined neurocognitive status			
	BEV		BEV + CPT-11	
	Stable or improved on all tests	Declined on at least one test	Stable or improved on all tests	Declined on at least one test
Patients with an IRF-determined OR (at time of response) ^a	18/24 (75.0%)	6/24 (25.0%)	17/28 (60.7%)	11/28 (39.3%)
Patients with IRF-determined PFS >6 months (at Week 24 assessment) ^b	19/27 (70.4%)	8/27 (29.6%)	20/30 (69.0%)	9/30 (30.0%)
Patients with investigator-determined disease progression (at time of progression) ^c	15/49 (30.6%)	34/49 (69.4%)	11/25 (44.0%)	14/25 (56.0%)

^a3 BEV + CPT-11,

^b2 BEV and 3 BEV + CPT-11 and

^c8 BEV and 21 BEV + CPT-11 patients with missing data were excluded. BEV, bevacizumab; CPT-11, irinotecan; IRF, independent review facility; RCI, Reliable Change Index; OR, objective response; PFS, progression-free survival.

time were also plotted for the first 2 subgroups of patients. Finally, concomitant medications that could affect NCF were summarized for patients who had an IRF-determined OR.

Results

Patient Demographics and Baseline Characteristics

Between June 2006 and February 2007, 167 patients with glioblastoma in first or second relapse were randomized to receive BEV ($n = 85$) or BEV + CPT-11 ($n = 82$) in the BRAIN study (Table 2). Negative mean standardized

test scores in all tests indicated that patients were performing below the mean of the general population.

Neurocognitive Outcomes

Eighty-five to 98% of all patients completed the neurocognitive tests at baseline; and the majority of patients who remained on study completed tests at each assessment. Table 3 shows the percentage of patients who completed individual tests at baseline, Week 6, and Week 24).

The majority of patients who had an IRF-determined OR or IRF-determined PFS >6 months had stable or

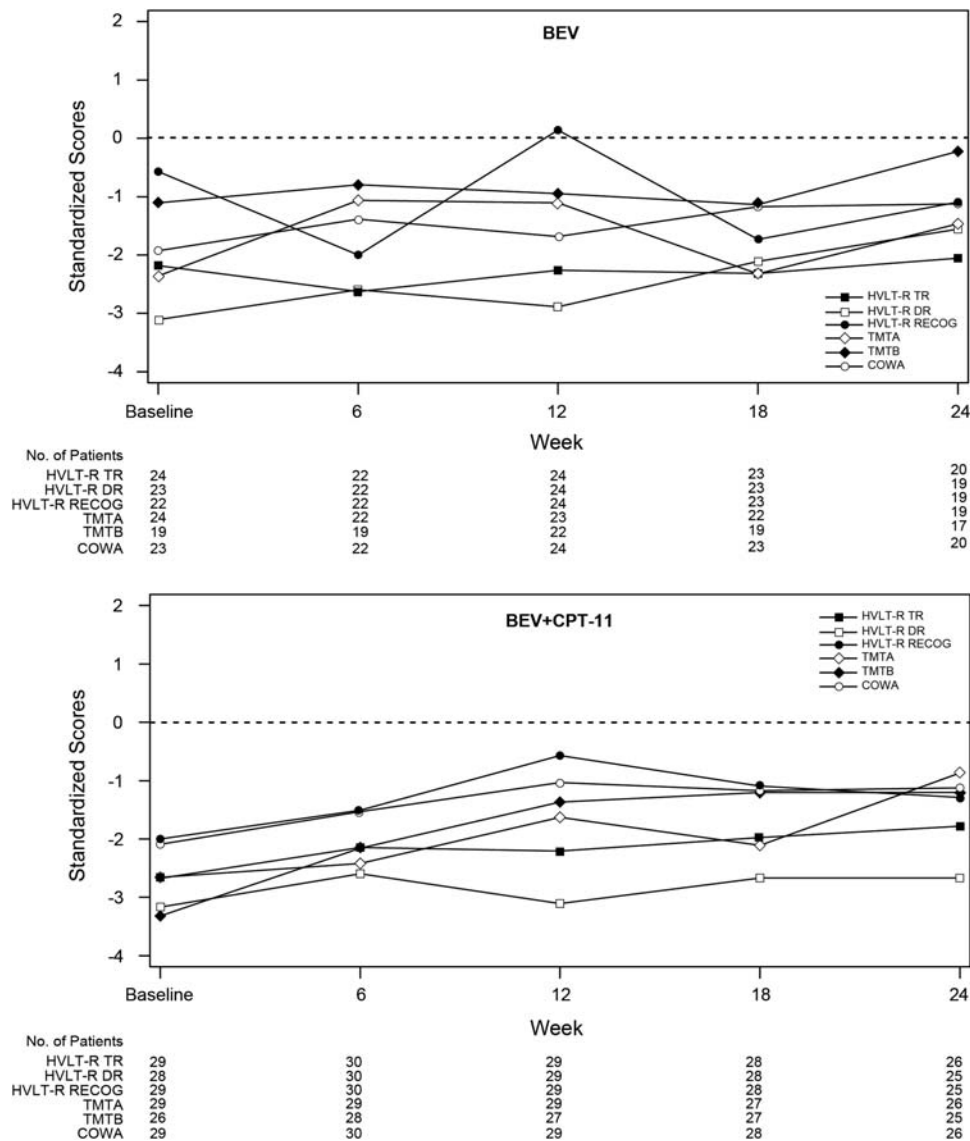


Fig. 1. Neurocognitive test scores across time for patients with an objective response. Values represent median test scores of patients in the BEV (upper panel) and BEV + CPT-11 (lower panel) study groups who had an IRF-determined objective response and completed neurocognitive tests at the indicated time of assessment, standardized using normative data from the general population (i.e., mean = 0, SD = 1). Values under the x-axis represent the number of patients assessed at each corresponding timepoint. BEV, bevacizumab; CPT-11, irinotecan; HVLT-R, Hopkins Verbal Learning Test-Revised; TR, Total Recall; DR, Delayed Recall; RECOG, Delayed Recognition; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; COWA, Controlled Oral Word Association; IRF, independent review facility.

improved performance on all tests relative to baseline at the time of OR (BEV = 75.0%; BEV + CPT-11 = 60.7%) or at the Week 24 assessment (BEV = 70.4%; BEV + CPT-11 = 69.0%), respectively (Table 4). In contrast, the majority of the patients who had investigator-determined disease progression had declined on at least one test at the time of progression (BEV = 69.4%; BEV + CPT-11 = 56.0%; Table 4), and >40% declined on multiple tests.

Compared with the general population, patients with an IRF-determined OR or PFS >6 months had poorer

performance on all neurocognitive tests at baseline (Figs 1 and 2); and the median standardized scores of these patients remained stable from baseline to Week 24, with trends suggesting improvement in some patients.

Concomitant Medication

Given the low rate of use, it is unlikely that psychostimulants or opioids affected neurocognitive status at the time of IRF-determined OR. The prevalent use of anti-onvulsants and corticosteroids makes it difficult to

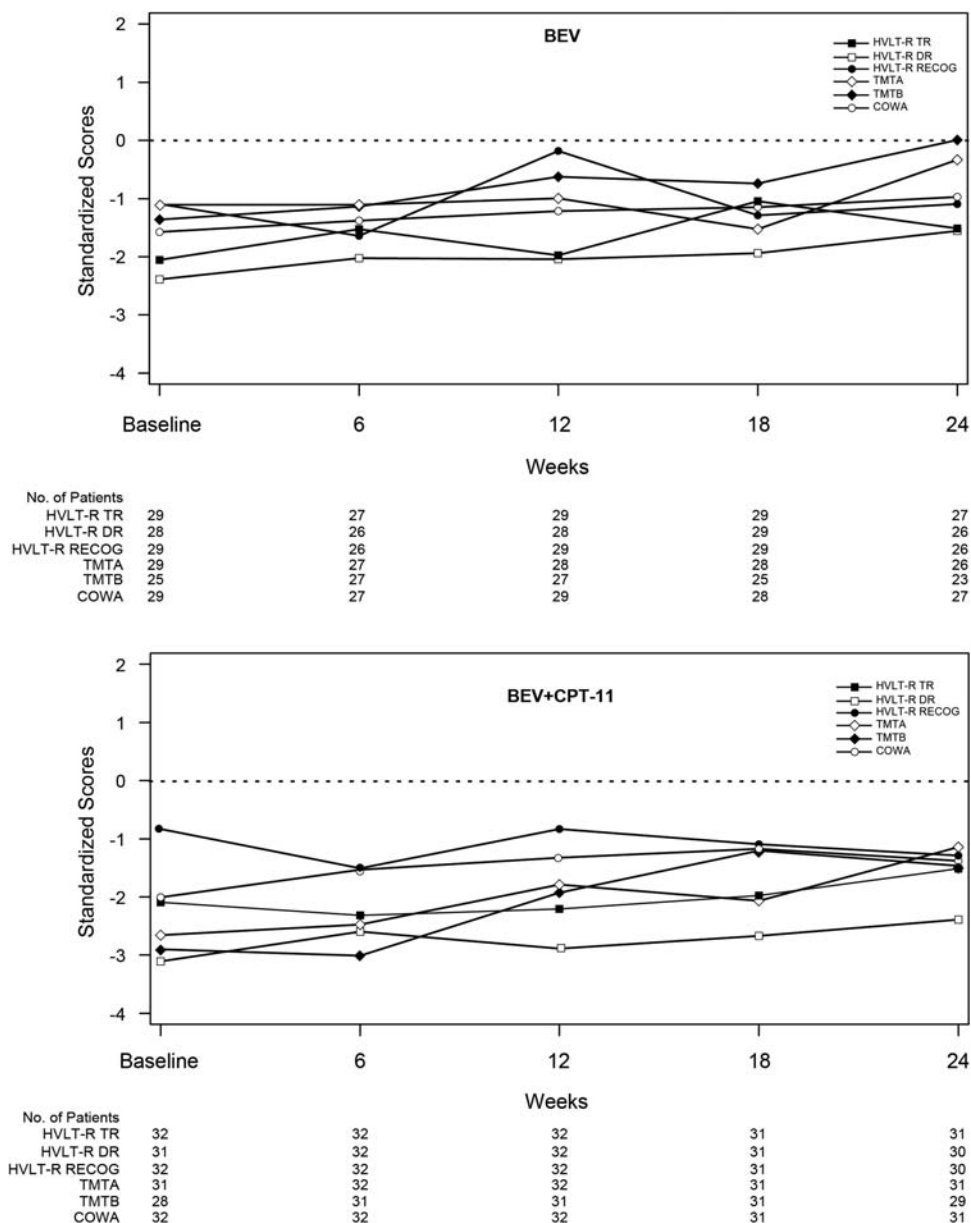


Fig. 2. Neurocognitive test scores across time for patients with progression-free survival >6 months. Values represent median test scores of patients in the BEV (upper panel) and BEV + CPT-11 (lower panel) study arms with progression-free survival >6 months, according to IRF review, and completed tests at the indicated time of neurocognitive assessment, standardized using normative data from the general population (i.e., mean = 0, SD = 1). Values under the x-axis represent the number of patients assessed at each corresponding timepoint. BEV, bevacizumab; CPT-11, irinotecan; HVLTR, Hopkins Verbal Learning Test–Revised; TR, Total Recall; DR, Delayed Recall; RECOG, Delayed Recognition; TMTA, Trail Making Test Part A; TMTB, Trail Making Test Part B; COWA, Controlled Oral Word Association; IRF, independent review facility.

Table 5. Frequency of concomitant medication use at the time of independent review facility-determined objective response

Concomitant medication	% Patients at time of IRF-determined objective response	
	BEV (n = 24)	BEV + CPT-11 (n = 31)
Anticonvulsants	71	65
Corticosteroids	54	45
Opioids	17	7
Psychostimulants	8	10

IRF, independent review facility; BEV, bevacizumab; CPT-11, irinotecan.

determine their effects, if any, on NCF in this patient population (Table 5).

Discussion

The BRAIN study evaluated NCF in the largest sample of patients with progressive glioblastoma to date. Test completion rates were high and consistent with other large multicenter trials,¹⁹ indicating that the approximately 25-min assessment was feasible and not overly burdensome for patients with glioblastoma in first or second relapse or study sites.

Neurocognitive tests were sensitive to changes in NCF over time and demonstrated that, relative to baseline, the majority of patients who had an IRF-determined OR or PFS >6 months had improved or stable NCF at the time of response or at the 24-week assessment, respectively; while those who had investigator-determined progressive disease demonstrated evidence of neurocognitive decline at the time of progression.

Median test scores during the first 24 weeks on study for patients with an IRF-determined OR or PFS >6 months were generally stable, with trends suggesting improvement in some patients. While this is consistent with many anecdotal reports of significant improvement in patient NCF while on therapy, the absence of a control arm in the BRAIN study does not permit us to rule out the possibility that the trend suggesting improvement may also reflect practice effects, despite efforts to diminish this possibility by using alternate forms of the tests across time.²⁰

In some patients with recurrent glioblastoma, the degree of neurocognitive impairment can be so great at baseline that it is unlikely that subsequent test scores will exceed the RCI threshold necessary to determine a decline in NCF (i.e., floor effect). Sensitivity analyses in the subset of BEV-group patients who had an OR showed that only one of the neurocognitive tests, the HVLT-R-DR (Hopkins Verbal Learning Test-Revised-Delayed Recognition), showed a potential for floor effects. Even when taking this into account, the majority of responders did not experience a decline in NCF at the time of OR relative to baseline. Thus, although patients

were quite cognitively debilitated at baseline relative to a healthy population, change from baseline NCF did not appear to have been influenced by potential floor effects.

Antiangiogenic therapies have complicated the interpretation of classic radiographic outcomes (e.g. van den Bent 2009; Wen et al. 2010),^{21,11} primarily due to the effects of tumor vasculature normalization confounding true antitumor effects. In the current trial there was evidence of a trend suggesting some degree of consistency between radiographically determined outcomes and NCF outcomes at key radiographic time points. However, in a substantial minority of patients there was discordance between radiographic outcomes and NCF outcomes. Further examination of these discrepancies in the future may enhance our understanding of the clinical impact of different radiographic features/patterns.

In addition to alternative imaging modalities for tumor assessment and determination of response and progression,¹¹ data increasingly demonstrate that patient-centered endpoints, such as NCF, may be used to measure clinical benefit;²² NCF is an attractive endpoint, as it provides a direct, objective, valid, and standardized measure of a cardinal, early, and frequent symptom of brain tumor.^{22,23} In high-grade glioma, pre-treatment NCF²⁴ and NCF 16 months after treatment²⁵ were predictive of survival, even after controlling for age, KPS, histology, and time since diagnosis.¹ Changes in NCF can occur in a predictable relationship with evidence of changing lesion burden, as seen in the current analysis; and they have also been demonstrated to occur in advance of radiographic evidence of tumor progression.^{7,9,10} Additionally, NCF is a direct measure of patient well-being that is associated with functional independence, and subjective QoL^{2,5,6} is more sensitive to disease progression than self-reported QoL,^{2,5,6} activities of daily living,^{1,5,6} and the results of mental status screening tests, such as the Mini-Mental State Examination.^{26,27} Furthermore, decline in NCF is associated with caregiver distress and burden.^{4,5} As demonstrated in this analysis of BRAIN participants, integrating NCF testing as an outcome in brain tumor trials is feasible and yields critical information about clinical benefit that may not be captured by radiographic imaging alone. Of note, potential confounding variables, such as treatment toxicities or unrecognized comorbidities (e.g., subclinical seizures) were not taken into account when assessing NCF.

To summarize, NCF testing with objective and valid tests to measure patient functioning was feasible in patients with recurrent glioblastoma. The majority of patients who had an IRF-determined OR or PFS >6 months had improved or stable NCF at the time of response or at the 24-week assessment, respectively; and most patients who had investigator-determined progressive disease demonstrated evidence of neurocognitive decline at the time of progression. Inclusion of a control or comparison arm in future studies will facilitate more detailed interpretations of these data.

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behalf of Genentech. Patrick Y. Wen has received research support from and has served on an advisory board for Genentech. Tom Mikkelsen has received honoraria and speaking fees from Genentech. David Schiff has served on Genentech advisory boards each of the last 3 years. Lauren E. Abrey has received honoraria and consulting fees from Genentech and Roche. W.K. Alfred Yung has had consulting relationships with Novartis and Merck/Schering Plough and advisory affiliations with Novartis, Eden, and Merck. Nina Paleologos has served as a speaker for Merck and Genentech and a consultant for Merck, Genentech, and Eisai. Martin K. Nicholas has served on an advisory board for Genentech. James Vredenburgh has received consulting fees, honoraria, and speaker fees from Genentech and Roche. Asha Das is an employee of Genentech and owns stock in Roche. Henry S. Friedman has served as a paid consultant and speaker for Genentech.

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