Key words: bevacizumab – glioblastoma – Asian continental ancestry group – Phase II – glioma

INTRODUCTION

Glioblastoma (GBM) is the most aggressive form of primary malignant brain tumor and the prognosis for patients with GBM is poor (1,2); the majority will relapse following initial treatment and <10% are alive at 5 years (3). The standard treatment for patients with newly diagnosed GBM is surgical resection followed by temozolomide (TMZ) and radiotherapy (RT), and then adjuvant TMZ alone (Stupp regimen) (4). Treatment options for patients with recurrent GBM, however, are limited and include repeat resection, RT and systemic chemotherapy, such as TMZ, nitrosoureas, platinum-based regimens (carboplatin, cisplatin), cyclophosphamide, irinotecan and etoposide, and appropriate treatment will depend on the patient and tumor characteristics (5). Currently there is no standard therapy for recurrent GBM and the estimated 6-month progression-free survival (PFS) rate for patients with recurrent disease is 9–28% (6–11) with a 1-year survival rate of 14–32% (6–8,10,11). Therefore, new treatment strategies for recurrent GBM are needed.

An alternative therapeutic approach is the inhibition of angiogenesis through the vascular endothelial growth factor (VEGF), a key regulator of angiogenesis. High levels of VEGF are expressed in GBM cells (12,13), and hypoxia and acidosis, conditions commonly seen in solid tumors, upregulate VEGF expression in glioma cells *in vivo* (14). In a mouse model, monoclonal antibodies to VEGF have been shown to inhibit the growth of the C6 glioma (15). Bevacizumab (Avastin®) is a monoclonal antibody that inhibits VEGF and is currently approved for a range of metastatic cancers (colorectal, non-small-cell lung, breast, ovarian cancer and renal cancers) (16–19) as well as for use in adults with recurrent GBM in many countries including the USA (20,21). Early Phase II studies in patients with recurrent GBM showed the efficacy of bevacizumab in combination with irinotecan (22,23). Subsequently, two Phase II studies (24–26) showed the efficacy of single-agent bevacizumab with regard to response rates and 6-month PFS in patients with recurrent GBM who had previously received RT and TMZ. These two studies formed the basis of bevacizumab's approval by the Food and Drug Administration (FDA) in 2009. Moreover, other studies have shown the efficacy of bevacizumab in recurrent GBM whether given as a single agent (27) or combined with irinotecan (28,29) and other chemotherapies, such as etoposide, carboplatin and fotemustine (30–33). Given the current evidence for bevacizumab in recurrent GBM in Western patient populations, we investigated the efficacy and safety of single-agent bevacizumab in a Phase II, single-arm, open-label study (JO22506) in Japanese patients with recurrent malignant glioma.

PATIENTS AND METHODS

The trial was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki; all patients provided written informed consent prior to any study-related procedure. The protocol was approved by the institutional review boards of all participating centers. The study was registered with the Japan Pharmaceutical Information Center-Clinical Trials Information (JapicCTI), trial number: JapicCTI-090841.

Eligibility

Eligible patients were aged ≥20 years with histologically confirmed GBM or World Health Organization (WHO) Grade III glioma, the latter being reconfirmed at the time of surgery for recurrent glioma. Patients had magnetic resonance imaging (MRI)-confirmed disease recurrence or progression with measurable lesions within 2 weeks prior to the first study treatment and no evidence of acute or subacute cerebral hemorrhage and had received prior TMZ and RT for malignant glioma. Other key inclusion criteria were a Karnofsky performance status (KPS) ≥70%, a life expectancy of ≥3 months and adequate hematologic, renal and hepatic function (i.e. absolute neutrophil count ≥1500/mm^3, platelet count ≥100 000/mm^3, hemoglobin ≥10 g/dl, bilirubin ≤ 1.5 × the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase ≤ 2.5 × ULN, serum creatinine ≤ 1.25 × ULN). The following minimum intervals of time must have elapsed between the termination of therapies and the start of bevacizumab treatment: RT 8 weeks; surgical therapy and incisional biopsy 4 weeks; endocrine therapy and immunotherapy 3 weeks; post-traumatic intervention (except for patients with non-healing wounds) 2 weeks; transfusion and the use of hematopoietic growth factors 2 weeks; aspiration cytology and needle biopsy 1 week; nitrosoureas 6 weeks, procarbazine 3 weeks, vincristine 2 weeks and other chemotherapies 4 weeks and other investigational new drugs and unapproved drugs 4 weeks. Patients were excluded if they had: prior treatment with bevacizumab; a history of treatment with carmustine wafers, stereotactic radiotherapy, proton therapy or neutron capture therapy; ≥3 prior regimens for malignant glioma and inadequately controlled hypertension, heart disease, symptomatic cerebrovascular disorder, gastrointestinal (GI) perforation, fistula or abdominal abscess within 6 months prior to enrollment.

Study Design

This single-arm, open-label, Phase II study was conducted at 10 sites in Japan. One cycle of treatment was defined as one

bevacizumab infusion administered on Day 1 every 2 weeks. Eligible patients received 10 mg/kg bevacizumab as an intravenous infusion administered over 90 ($\pm$ 15) min on Day 1 of each cycle, which could be reduced to 30 min by Cycle 3 if no infusion reactions occurred. Treatment continued until disease progression (PD) or unacceptable toxicity. Bevacizumab doses were adjusted only for changes of $\geq$10% in body weight during the study. In the event of unacceptable toxicity, bevacizumab treatment was delayed or discontinued according to pre-specified criteria. Bevacizumab was discontinued if multiple adverse events (AEs) fulfilling the pre-specified delay or discontinuation criteria occurred in the same cycle, if cerebral hemorrhage occurred and if delayed treatment could not be restarted within 6 weeks of the last bevacizumab infusion. Patients who discontinued bevacizumab were followed for survival. Bevacizumab was provided by Chugai Pharmaceutical Co. Ltd (Tokyo, Japan).

Assessment of Efficacy

The primary endpoint was 6-month PFS in patients with recurrent GBM only. Six-month PFS was defined as the percentage of patients who remained alive and progression free at 24 weeks and was chosen based on published evidence demonstrating its extrapolation to the overall survival (OS) (6,7). Secondary efficacy endpoints included the 1-year survival, PFS, objective response rate (ORR), duration of response (DOR), OS and disease control rate (DCR).

Efficacy was assessed every third cycle (i.e. Cycles 3, 6, 9 etc.). Progression and objective response were determined by comprehensive evaluation of the results from MRI scans, corticosteroid dose assessment and neurocognitive function assessment. They were assessed by an independent radiology facility (IRF) by reference to Macdonald's Criteria (34). Response was classified according to the following categories: complete response (CR), partial response (PR), no change (NC) and PD. Confirmation of the response was determined on two consecutive assessments $\geq$4 weeks apart: patients who were determined as having CR or PR were defined as responders; patients who were determined as having NC or PD were defined as non-responders.

Percentage tumor shrinkage was also assessed and was calculated from the sum of the products of the diameters (SPD) at baseline and the smallest SPD after baseline.

Assessment of Safety

AEs were assessed throughout the study and were graded according to the Common Terminology Criteria for AEs version 3.0 (35). Body weight, vital signs and laboratory tests were assessed prior to the start of each cycle.

Statistical Methods

The efficacy analysis population comprised all patients with recurrent GBM. Patients with Grade III glioma were also evaluated for efficacy, but were not included in the primary analysis. All patients were evaluated for safety.

Statistical analysis to detect a 6-month PFS of 35% was established based on data from previous studies [BRAIN study [24] (42.6% with bevacizumab monotherapy) and the NCI-06-C-0064E study [26] (29% with bevacizumab monotherapy)], in which a 15% threshold for 6-month PFS was defined. Under these conditions, 28 patients with recurrent GBM would provide at least 80% power to detect a 20% increase in 6-month PFS from 15 to 35% at the 5% one-sided significance level. Assuming that other WHO Grade III glioma patients would be enrolled, the overall target sample size was 32 patients.

The 6-month PFS, median PFS, OS and DOR were calculated by the Kaplan–Meier method and confidence intervals (CIs) calculated by Greenwood's formula (36). Exact binomial CIs were used for estimated intervals for response rates.

RESULTS

Patients

Between August 2009 and July 2010, 31 patients were enrolled, 29 of whom were included in the efficacy analysis population. All enrolled patients received a median of 6 bevacizumab doses. Treatment was discontinued in a total of 25 patients: 23 (74.2%) due to PD; 2 (6.5%) due to AEs. Efficacy and safety analyses, except for OS, were performed after an observation period of $\geq$6 months (data cut-off 7 January 2011); the OS analyses, which included data collected through to 22 August 2011, were performed after all enrolled patients had been observed for $\geq$1 year.

Demographic Data

The majority of patients (29; 93.5%) had GBM; 2 (6.5%) had Grade III glioma (Table 1). The median age was 54.0 years (range: 23–72); 10 (32.3%) patients were aged $\geq$65 years. The percentage of males to females was well balanced. Patients were in relatively good health with 61.3% having a KPS of 90–100, and 64.5% of patients not receiving corticosteroids at the start of the study. Similar numbers of patients had experienced 1 [17 (54.8%)] or 2 [14 (45.2%)] relapses.

Efficacy Outcomes

At the time the PFS and OS analyses were performed, 22 PD events and 21 death events had been reported in the 29 patients with recurrent GBM. The 6-month PFS rate in the 29 patients with recurrent GBM (primary endpoint) was 33.9% (90% CI, 19.2–48.5), and this exceeded the 15% threshold ($P = 0.0170$). Kaplan–Meier estimates of PFS showed a steady decline over the initial 6 months with a median PFS of 3.3 months (95% CI 2.8–6.0) (Fig. 1). The 1-year survival rate for these patients was 34.5% (90%

Table 1. Demographic and baseline disease characteristics

Parameter	All patients ($n = 31$)	GBM ($n = 29$)	WHO Grade III ($n = 2$)[a]
Median age, years (range)	54.0 (23–72)	57.0 (23–72)	32.5 (30–35)
Age groups in years, *n* (%)			
≤40	6 (19.4)	4 (13.8)	2 (100)
41–64	15 (48.4)	15 (51.7)	0 (0.0)
≥65	10 (32.3)	10 (34.5)	0 (0.0)
Gender, *n* (%)			
Male	16 (51.6)	14 (48.3)	2 (100)
Female	15 (48.4)	15 (51.7)	0 (0.0)
KPS, *n* (%)			
70–80	12 (38.7)	12 (41.4)	0 (0.0)
90–100	19 (61.3)	17 (58.6)	2 (100)
Relapse/progression status, *n* (%)			
First	17 (54.8)	17 (58.6)	0 (0.0)
Second	14 (45.2)	12 (41.4)	2 (100)
Duration of malignant glioma[b]			
Median, months (range)	15.2 (5.6–213.3)	15.0 (5.6–213.3)	46.8 (27.8–65.8)
Time from RT to bevacizumab[c]			
Median, months (range)	13.2 (3.8–209.6)	13.1 (3.8–209.6)	44.8 (25.5–64.1)
Corticosteroid use at baseline, *n* (%)			
Yes	11 (35.5)	10 (34.5)	1 (50.0)
No	20 (64.5)	19 (65.5)	1 (50.0)

GBM, glioblastoma; WHO, World Health Organization; KPS, Karnofsky performance status; RT, radiotherapy; q2w, every 2 weeks.
[a]One patient had anaplastic astrocytoma and one patient had anaplastic oligoastrocytoma.
[b]Time since the initial diagnosis of malignant glioma.
[c]Time from the last RT to the first dose of bevacizumab.

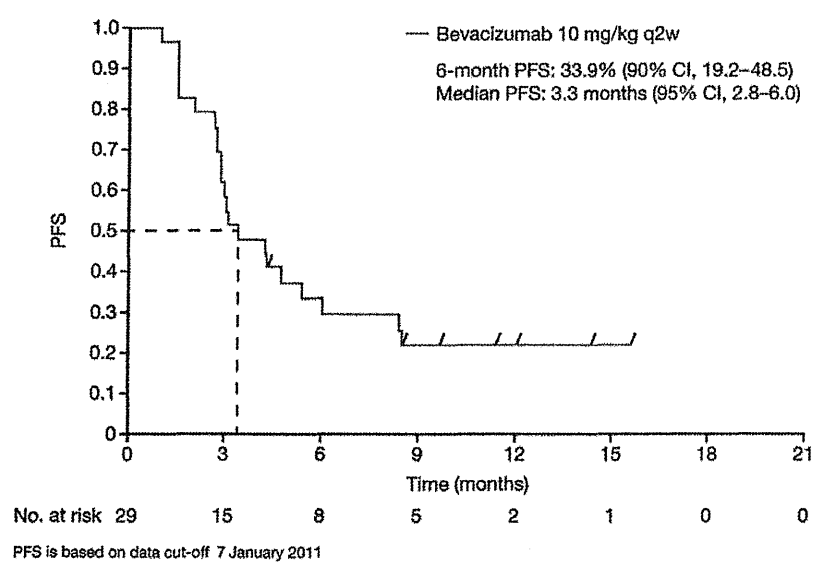

Figure 1. Progression-free survival determined by independent radiology facility in patients with recurrent glioblastoma (GBM).

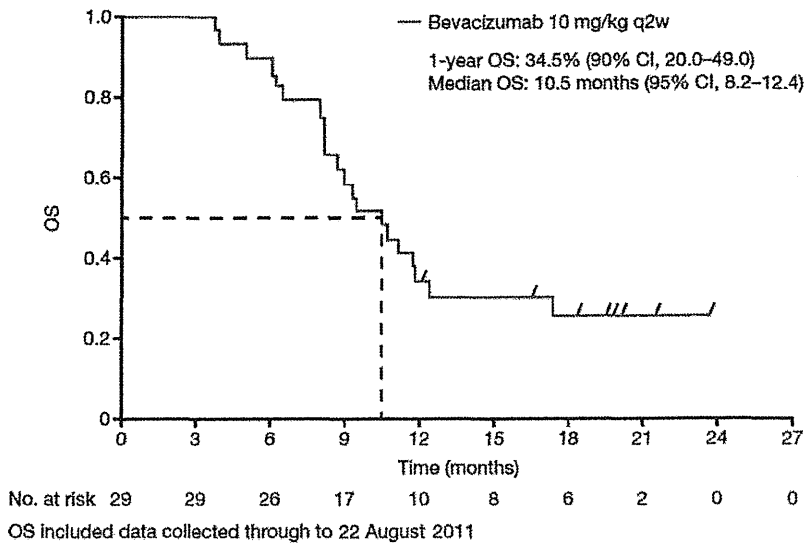

Figure 2. Overall survival in patients with recurrent GBM.

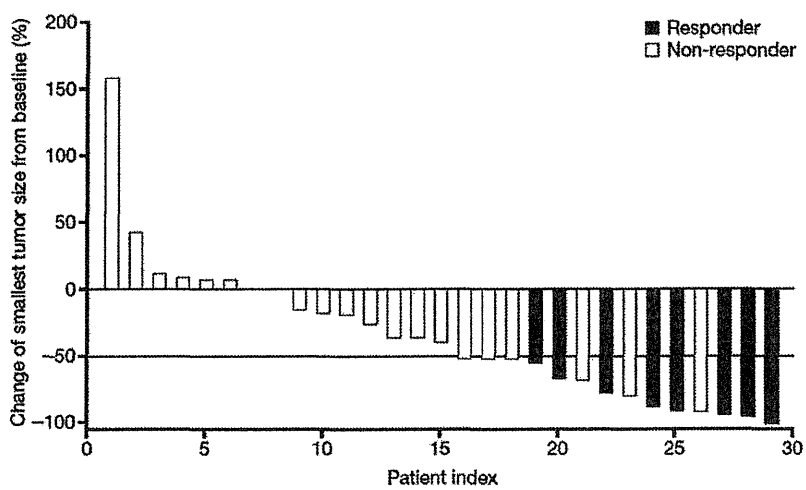

Figure 3. Waterfall plot showing the change in tumor size from baseline.

CI 20.0–49.0) with a median OS of 10.5 months (95% CI 8.2–12.4) (Fig. 2).

There were eight responders (all PR) with an ORR of 27.6% (95% CI 12.7–47.2). The DCR (0 CR + 8 PR + 15 NC) was 79.3% (95% CI 60.3–92.0). The two patients with WHO Grade III glioma completed one and two cycles of treatment, respectively; both experienced PD. Twenty-one patients (72.4%) with recurrent GBM experienced tumor shrinkage during the treatment period (Fig. 3), including 13 patients who were classified as non-responders. Of the 11 patients who were taking corticosteroids at baseline, dose reductions or discontinuation of corticosteroids occurred in 8 patients.

Efficacy endpoints were investigated in different patient subgroups (Table 2). Patients who were aged <50 years or <65 years, male, with a high KPS (90–100), on their first treatment relapse, not receiving corticosteroid therapy at baseline, or having been diagnosed with GBM at the initial diagnosis of malignant glioma, appeared to have a better response to bevacizumab treatment than other patients.

Safety Outcomes

All 31 patients experienced AEs with a total of 220 AEs reported during the study (Table 3). Serious AEs occurred in 11 (35.5%) patients, the most common being convulsion [2 (6.5%) patients]. Two (6.5%) patients discontinued the study due to AEs: one patient experienced a Grade 1 cerebral hemorrhage, and one patient had Grade 2 neutropenia that meant re-treatment within 6 weeks was not possible. A total of 13 (41.9%) patients experienced an AE of Grade ≥3, the most common being hypertension [3 (9.7%) patients]. No

Table 2. Six-month PFS and ORR by subgroup in patients with recurrent GBM

Variable	Bevacizumab 10 mg/kg, q2w ($n = 29$)	
	Six-month PFS, % (95% CI)	ORR, %
Age, years		
<65 ($n = 19$)	42.1 (19.9–64.3)	36.8
≥65 ($n = 10$)	15.0 (0.0–40.2)	10.0
Age, years		
<50 ($n = 11$)	45.5 (16.0–74.9)	45.5
≥50 ($n = 18$)	26.7 (5.7–47.6)	16.7
Gender		
Female ($n = 15$)	24.0 (1.3–46.7)	20.0
Male ($n = 14$)	42.9 (16.9–68.8)	35.7
KPS		
70–80 ($n = 12$)	16.7 (0.0–37.8)	8.3
90–100 ($n = 17$)	47.1 (23.3–70.8)	41.2
Relapse/progression status		
First ($n = 17$)	46.3 (22.3–70.4)	35.3
Second ($n = 12$)	16.7 (0.0–37.8)	16.7
Corticosteroid use at baseline		
Yes ($n = 10$)	20.0 (0.0–44.8)	10.0
No ($n = 19$)	42.1 (19.9–64.3)	36.8
Initial diagnosis of malignant glioma by site		
GBM ($n = 23$)	43.0 (22.6–63.5)	34.8
Other ($n = 6$)	0.0 (0.0–0.0)	0.0

PFS, progression-free survival; ORR, objective response rate; CI, confidence interval.

Table 3. Adverse events ≥Grade 3 and adverse events of special interest to bevacizumab

Patients, *n* (%)	Bevacizumab 10 mg/kg, q2w ($n = 31$)	
	All grade	Grade ≥3
Total patients with at least one AE	31 (100.0)	13 (41.9)
Irregular menstruation	3 (9.7)	2 (6.5)
Pyrexia	7 (22.6)	1 (3.2)
Convulsion	3 (9.7)	1 (3.2)
Depressed level of consciousness	1 (3.2)	1 (3.2)
Hydrocephalus	1 (3.2)	1 (3.2)
Increased intracranial pressure	1 (3.2)	1 (3.2)
Brain edema	1 (3.2)	1 (3.2)
Hemiplegia	1 (3.2)	1 (3.2)
Appendicitis	1 (3.2)	1 (3.2)
Urinary tract infection	1 (3.2)	1 (3.2)
Delirium	1 (3.2)	1 (3.2)
Neutropenia	5 (16.1)	1 (3.2)
Leukopenia	5 (16.1)	1 (3.2)
AEs of special interest to bevacizumab	22 (71.0)	5 (16.1)
Proteinuria	13 (41.9)	—
Hemorrhage[a,b]	10 (32.3)	—
Hypertension	10 (32.3)	3 (9.7)
Congestive heart failure	1 (3.2)	1 (3.2)
Venous thromboembolism	1 (3.2)	1 (3.2)

AE, adverse event.
[a]All events were Grade 1.
[b]Includes: epistaxis, gingival bleeding, conjunctival hemorrhage, infusion site hemorrhage, blood urine present, cerebral hemorrhage, hemorrhage subcutaneous, metrorrhagia.

incidence of Grade 4 or 5 hypertension was observed. One patient died of brain edema (Grade 5 AE), which was considered by the investigator to be related to PD with no causal relationship with bevacizumab treatment.

A total of 22 (71.0%) patients experienced AEs of special interest to bevacizumab, comprising proteinuria, hemorrhage, hypertension, congestive heart failure and venous thromboembolism (Table 3). One Grade 1 cerebral hemorrhage was observed on MRI; this was asymptomatic and resolved without treatment. Five (16.1%) patients had Grade 3 AEs of special interest to bevacizumab, comprising congestive heart failure [1 (3.2%) patient], venous thromboembolism [1 (3.2%) patient] and hypertension [3 (9.7%) patients]. No patients reported the other AEs of special interest to bevacizumab, i.e. reversible posterior leukoencephalopathy syndrome, wound-healing complications, GI perforation or fistulae.

Abnormal laboratory results were reported in 74.2% of patients. The most common abnormal laboratory result was proteinuria, which was reported in 41.9% of patients. Abnormal laboratory results classed as ≥Grade 3 were observed in two patients, reported as neutropenia and leukopenia.

DISCUSSION

This is the first clinical trial to investigate the safety and efficacy of single-agent bevacizumab in Japanese patients with recurrent GBM. Our data demonstrated that single-agent bevacizumab 10 mg/kg was effective in terms of the 6-month PFS, ORR, OS and 1-year survival, and was well tolerated in this Japanese population. In addition, the majority [21 (72.4%)] of patients with recurrent GBM experienced some tumor shrinkage during the treatment period.

The observed 6-month PFS of 33.9% and ORR of 27.6% seen in our study were more favorable than previous published data. These data are numerically higher than those reported for other studies with other chemotherapy and/or RT regimens (6-month PFS 9–21% and ORR 4–9%)

(6,7,10,11,37), and comparable with those reported for single-agent bevacizumab (42.6 and 28.2% for 6-month PFS and ORR, respectively) (24).

The use of Macdonald's Criteria was standard when this study was initiated; however, subsequently the Response Assessment in Neuro-Oncology (RANO) Working Group has recommended assessing MRI T2-weighted or fluid-attenuated inversion recovery (FLAIR) of non-enhancing lesions in addition to enhancing lesions (38). As the Macdonald's Criteria only assess contrast-enhancing lesions, there are risks that pseudoprogression and pseudoresponses may be considered real treatment effects. In our study an IRF assessed the changes in the T2/FLAIR signal, which was not included in the primary response evaluation based on Macdonald's Criteria. No significant increase in the T2/FLAIR signal was confirmed in the eight responders for the DOR, and seven out of eight responders exhibited $\geq$6 months' DOR. Based on these results, we are convinced that the objective response seen in our study is not a pseudoresponse.

Of the 29 GBM patients treated, 21 exhibited tumor shrinkage, including 8 patients who had a PR and 13 'non-responders' who were determined as NC or PD but exhibited some benefit with bevacizumab that was not captured by the response criteria; the maximum percentage of tumor shrinkage in 6 patients was >50%. The apparent discrepancy between the number of responders and the number of patients with tumor shrinkage is likely to be due to the ways in which the endpoints are calculated. The percentage of tumor shrinkage is calculated from the SPD at baseline and the smallest SPD after baseline, whereas for a patient to be classed as a responder, there had to be a decrease in tumor volume by $\geq$50% in the product of two diameters according to confirmation MRI performed $\geq$4 weeks after an observed response, as well as no increase in corticosteroid dosage and no neurologic deterioration. This leads to the difference between the number of patients with tumor shrinkage and the number of responders.

The 6-month PFS and ORR results were better for patients who had experienced one relapse than for those who had experienced two relapses, which is the same as a previously published observation (24). In addition, in our study bevacizumab improved the 6-month PFS and the ORR in the subgroups of patients who were aged <50 or <60 years compared with older patients. Although neither our study nor the previously published study (24) was powered to detect a statistical difference in these subgroups, the results could suggest that earlier administration of bevacizumab, or treatment with bevacizumab in younger patients, may lead to better tumor response and is something that requires investigation in further clinical trials.

Regarding the survival endpoints, our study showed results that were better than previously published data. The median OS of 10.5 months in GBM patients and 9.4 months in all patients was longer than that reported in other GBM trials (5.0–7.3 months) (6–8,10,11) and comparable with data with single-agent bevacizumab (9.3 months) (24,25). In addition, the 1-year survival rate for GBM patients (34.5%) was as good as the published data (14–32%) (6–8,10,11).

In addition to the favorable efficacy measures, a trend was also observed where 8 of the 11 patients who were taking corticosteroids at baseline were able to reduce their dose or discontinue corticosteroids altogether during the course of the study. This is consistent with other findings that suggest that bevacizumab may have corticosteroid-sparing effects in patients with recurrent GBM (39). Corticosteroid reduction may reduce infection rates and other related toxicities and therefore is expected to improve the health-related quality of life for patients.

Bevacizumab was well tolerated in our study and the incidence of AEs of special interest to bevacizumab was similar to that seen in other published studies with single-agent bevacizumab (24–26,40). No new bevacizumab safety signals were seen in this Japanese population.

In our study, and in the other single-agent bevacizumab studies (24–26,40), bevacizumab was administered after prior treatment with TMZ and RT. We observed an apparently greater benefit with bevacizumab in those patients with one relapse compared with those who have had two relapses following treatment with TMZ and RT. It is expected that bevacizumab may also provide benefit when administered concurrently with TMZ and RT rather than after TMZ/RT therapy. Currently, two randomized, double blind, Phase III studies are ongoing (AVAglio (41) and RTOG 0825 (42)) in which the addition of bevacizumab to standard of care (concurrent RT plus TMZ followed by adjuvant TMZ) is being evaluated in patients with newly diagnosed GBM.

There are many novel targeted agents under investigation for the treatment of gliomas (43); however, results with these new agents have been disappointing to date. Single-target agents alone may not be able to prevent tumor growth given the multiple pathways involved in many intracellular processes of tumor development. A key to future improvements in the treatment of gliomas will be the combination of other chemotherapeutic agents or molecular targeted therapies with bevacizumab to block these multiple pathways. This potential approach needs to be explored in future clinical trials.

In conclusion, the results of this study show that single-agent bevacizumab could provide significant clinical benefit for Japanese patients with recurrent GBM.

Acknowledgements

We are indebted to Dr Kazuhiro Nomura, Dr Shigeki Aoki and Tomoki Todo for their help in the assessment of efficacy and the evaluation of safety. We are also grateful to Dr Yoichi Nakazato for careful pathologic diagnosis.

Funding

This work was supported by Chugai Pharmaceutical Co. Ltd.

Conflict of interest statement

Dr Masao Matsutani is a coordinating investigator of this study, a member of the advisory committee on MSD KK and a member of the independent safety review board for Nobelpharma Co. Ltd; consulting fees as a coordinating investigator of this study have been received by him from Chugai Pharmaceutical Co. Ltd. Dr Ryo Nishikawa is a member of the Avaglio study steering committee (funded by F. Hoffmann-La Roche, Ltd) and has received research funding and speaking fees from MSD KK, and honoraria from Nobelpharma Co. Ltd. No other conflicts of interest were declared.

References

1. Hou LC, Veeravagu A, Hsu AR, Tse VC. Recurrent glioblastoma multiforme: a review of natural history and management options. *Neurosurg Focus* 2006;20:E5.
2. Ohgaki H. Epidemiology of brain tumors. *Methods Mol Biol* 2009;472:323–42.
3. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 2009;10: 459–66.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96.
5. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology*. Central Nervous System Cancers V.2.2011. http://www.nccn.org/professionals/physician_gls/PDF/cns.pdf.
6. Lamborn KR, Yung WK, Chang SM, et al. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. *Neuro Oncol* 2008;10:162–70.
7. Ballman KV, Buckner JC, Brown PD, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for phase II trials in patients with glioblastoma multiforme. *Neuro Oncol* 2007;9:29–38.
8. van den Bent MJ, Brandes AA, Rampling R, et al. Randomized phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. *J Clin Oncol* 2009;27:1268–74.
9. Wong ET, Hess KR, Gleason MJ, et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials. *J Clin Oncol* 1999;17:2572–8.
10. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010;28:1168–74.
11. Yung WK, Albright RE, Olson J, et al. A phase II study of temozolomide vs. procarbazine in patients with glioblastoma multiforme at first relapse. *Br J Cancer* 2000;83:588–93.
12. Huang H, Held-Feindt J, Buhl R, Mehdorn HM, Mentlein R. Expression of VEGF and its receptors in different brain tumors. *Neurol Res* 2005;27:371–7.
13. Chaudhry IH, O'Donovan DG, Brenchley PE, Reid H, Roberts IS. Vascular endothelial growth factor expression correlates with tumor grade and vascularity in gliomas. *Histopathology* 2001;39: 409–15.
14. Fukumura D, Xu L, Chen Y, Gohongi T, Seed B, Jain RK. Hypoxia and acidosis independently up-regulate vascular endothelial growth factor transcription in brain tumors *in vivo*. *Cancer Res* 2001;61: 6020–4.
15. Stefanik DF, Fellows WK, Rizkalla LR, et al. Monoclonal antibodies to vascular endothelial growth factor (VEGF) and the VEGF receptor, FLT-1, inhibit the growth of C6 glioma in a mouse xenograft. *J Neurooncol* 2001;55:91–100.
16. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;350:2335–42.
17. Johnson DH, Fehrenbacher L, Novotny W, et al. Randomised Phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell-lung cancer. *J Clin Oncol* 2004;22:2184–91.
18. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; 357:2666–76.
19. Yang JC, Haworth L, Sherry RM, et al. A randomised trial of bevacizumab, and anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N Engl J Med* 2003;349:427–34.
20. *How Avastin is Designed to Work [Internet]*. USA: Genentech, 2012 (cited 23 March 2012). http://www.avastin.com/avastin/patient/gbm/index.html.
21. *FDA Approves Drug for Treatment of Aggressive Brain Cancer [Internet]*. MD, USA: Food and Drug Administration, 2009 (cited 12 January 2012). www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm152295.htm.
22. Stark-Vance V. Bevacizumab and CPT-11 in the treatment of relapsed malignant glioma. *Neuro-Oncol* 2005;7:369. Abstract 342.
23. Vredenburgh JJ, Desjardins A, Herndon JE, II, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. *J Clin Oncol* 2007;25:4722–9.
24. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009;27:4733–40.
25. Cloughesy T, Vredenburgh JJ, Day B, Das A, Friedman HS. Updated safety and survival of patients with relapsed glioblastoma treated with bevacizumab in the BRAIN study. *J Clin Oncol* 2010;28(Suppl):181s. Abstract 2008.
26. Kreisl TN, Kim L, Moore K, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. *J Clin Oncol* 2009; 27:740–5.
27. Raizer JJ, Grimm S, Chamberlain MC, et al. Phase 2 trial of single-agent bevacizumab given in an every-3-week schedule for patients with recurrent high-grade gliomas. *Cancer* 2010;116:5297–305.
28. Kairouz VF, Elias EF, Chahine GY, Comair YG, Dimassi H, Kamar FG. Final results of an extended phase II trial of bevacizumab and irinotecan in relapsed high grade gliomas. *Neuro-Oncol* 2010;12(Suppl 4):iv40–1. Abstract NO-20.
29. Gil MJ, de las Peñas R, Reynés G, et al. Bevacizumab plus irinotecan in recurrent malignant glioma showed high overall survival in a retrospective study. *Neuro-Oncol* 2010;12(Suppl. 4):iv53. Abstract NO-73.
30. Nghiemphu PL, Liu W, Lee Y, et al. Bevacizumab and chemotherapy for recurrent glioblastoma: a single-institution experience. *Neurology* 2009;72:1217–22.
31. Sathornsumetee S, Desjardins A, Vredenburgh JJ, et al. Phase II trial of bevacizumab and erlotinib in patients with recurrent malignant glioma. *Neuro-Oncol* 2010;12:1300–10.
32. Francesconi AB, Dupre S, Matos M, et al. Carboplatin and etoposide combined with bevacizumab for the treatment of recurrent glioblastoma multiforme. *J Clin Neurosci* 2010;17:970–4.
33. Soffietti R, Trevisan E, Ruda R, et al. Phase II trial of bevacizumab with fotemustine in recurrent glioblastoma: final results of a multicenter study of AINO (Italian Association of Neuro-oncology). *J Clin Oncol* 2011;29(Suppl):146. Abstract 2027.
34. Macdonald DR, Cascino TL, Schold SC, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990;8:1277–80.
35. Trotti A, Colevas AD, Setser A, et al. CTCAE v3.0: development of a comprehensive grading system for the adverse effects of cancer treatment. *Semin Radiat Oncol* 2003;13:176–81.
36. Greenwood M. Reports on public health and medical subjects. The Error of Sampling of the Survivorship Tables. No 33, Appendix 1, London, UK: H.M Stationary Office, 1926.
37. Happold C, Roth P, Wick W, et al. ACNU-based chemotherapy for recurrent glioma in the temozolomide era. *J Neurooncol* 2009; 92:45–8.

38. Wen PY, Macdonald DR, Reardon DA, et al. Update response assessment criteria for high-grade gliomas: Response Assessment in Neuro-Oncology Working Group. *J Clin Oncol* 2010;28:1963–72.
39. Vredenburgh JJ, Cloughesy T, Samante M, et al. Corticosteroid use in patients with glioblastoma at first or second relapse treated with bevacizumab in the BRAIN study. *Oncologist* 2010;15:1329–34.
40. Chamberlain MC, Johnston SK. Salvage therapy with single-agent bevacizumab for recurrent glioblastoma. *J Neurooncol* 2010;96:259–69.
41. *A Study of Avastin (bevacizumab) in Combination with Temozolomide and Radiotherapy in Patients with Newly Diagnosed Glioblastoma [Internet]*. USA: Clinicaltrials.gov, 2009 (cited 4 October 2011). http://clinicaltrials.gov/ct2/show/NCT00943826.
42. *Temozolomide and Radiation Therapy with or Without Bevacizumab in Treating Patients with Newly Diagnosed Glioblastoma [Internet]*. USA: Clinicaltrials.gov, 2009 (cited 4 October 2011). http://clinicaltrials.gov/ct2/show/NCT00884741.
43. Van Meir EG, Hadjipanayis CG, Norden AD, et al. Exciting new advances in neuro-oncology: the avenue to a cure for malignant glioma. *CA Cancer J Clin* 2010;60:166–93.