

## Phase II Study of Single-agent Bevacizumab in Japanese Patients with Recurrent Malignant Glioma<sup>†</sup>

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**Objective:** This single-arm, open-label, Phase II study evaluated the efficacy and safety of single-agent bevacizumab, a monoclonal antibody against vascular endothelial growth factor, in Japanese patients with recurrent malignant glioma.

**Methods:** Patients with histologically confirmed, measurable glioblastoma or World Health Organization Grade III glioma, previously treated with temozolomide plus radiotherapy, received 10 mg/kg bevacizumab intravenous infusion every 2 weeks. The primary endpoint was 6-month progression-free survival in the patients with recurrent glioblastoma.

**Results:** Of the 31 patients enrolled, 29 (93.5%) had glioblastoma and 2 (6.5%) had Grade III glioma. Eleven (35.5%) patients were receiving corticosteroids at baseline; 17 (54.8%) and 14 (45.2%) patients had experienced one or two relapses, respectively. The 6-month progression-free survival rate in the 29 patients with recurrent glioblastoma was 33.9% (90% confidence interval, 19.2–48.5) and the median progression-free survival was 3.3 months. The 1-year survival rate was 34.5% with a median overall survival of 10.5 months. There were eight responders (all partial responses) giving an objective response rate of 27.6%. The disease control rate was 79.3%. Eight of the 11 patients taking corticosteroids at baseline reduced their dose or discontinued corticosteroids during the study. Bevacizumab was well-tolerated and Grade  $\geq 3$  adverse events of special interest to bevacizumab were as follows: hypertension [3 (9.7%) patients], congestive heart failure [1 (3.2%) patient] and venous thromboembolism [1 (3.2%) patient]. One asymptomatic Grade 1 cerebral hemorrhage was observed, which resolved without treatment.

**Conclusion:** Single-agent bevacizumab provides clinical benefit for Japanese patients with recurrent glioblastoma.

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  $\geq 20$  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)  $\geq 70\%$ , a life expectancy of  $\geq 3$  months and adequate hematologic, renal and hepatic function (i.e. absolute neutrophil count  $\geq 1500/\text{mm}^3$ , platelet count  $\geq 100\,000/\text{mm}^3$ , hemoglobin  $\geq 10$  g/dl, bilirubin  $\leq 1.5 \times$  the upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase  $\leq 2.5 \times$  ULN, serum creatinine  $\leq 1.25 \times$  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;  $\geq 3$  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

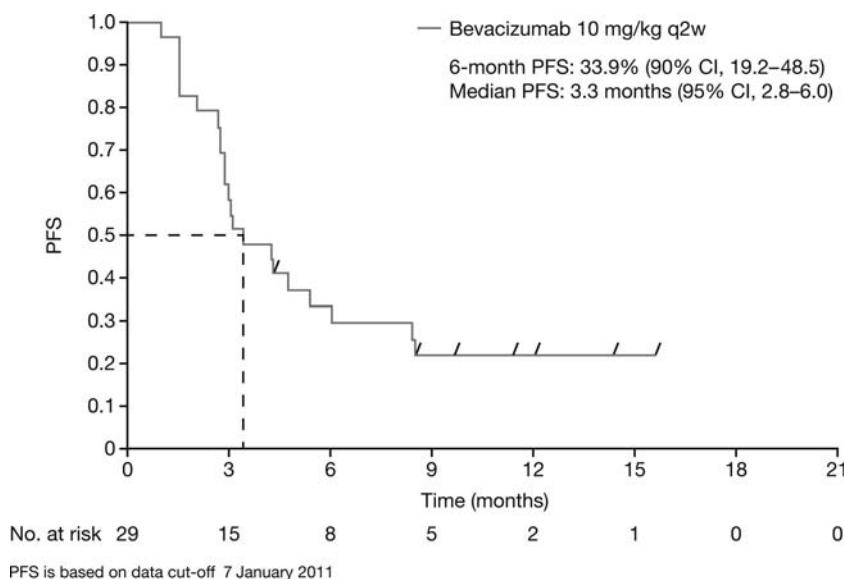
Parameter	All patients (n = 31)	GBM (n = 29)	WHO Grade III (n = 2) <sup>a</sup>
Median age, years (range)	54.0 (23–72)	57.0 (23–72)	32.5 (30–35)
Age groups in years, n (%)			
≤40	6 (19.4)	4 (13.8)	2 (100)
41–64	15 (48.4)	15 (51.7)	0 (0.0)
≥65	10 (32.3)	10 (34.5)	0 (0.0)
Gender, n (%)			
Male	16 (51.6)	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 <sup>b</sup>			
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 <sup>c</sup>			
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.

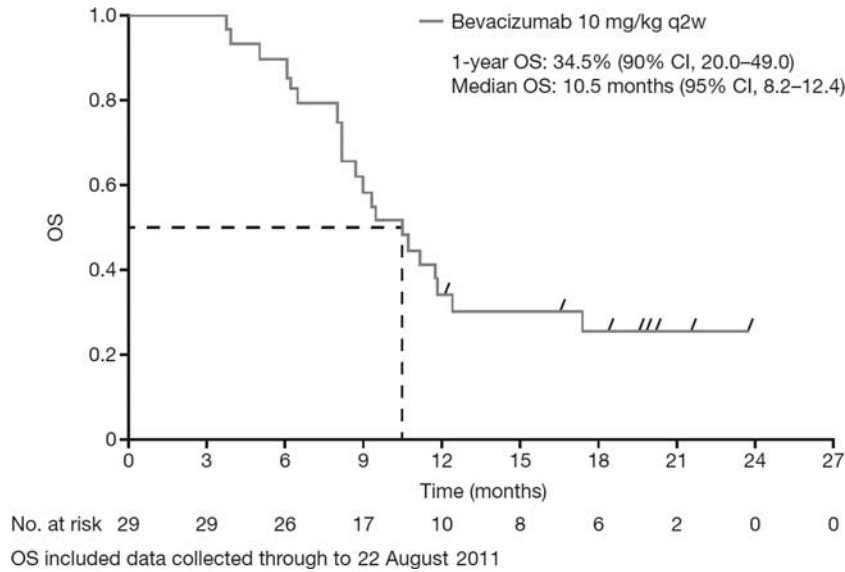
<sup>a</sup>One patient had anaplastic astrocytoma and one patient had anaplastic oligoastrocytoma.

<sup>b</sup>Time since the initial diagnosis of malignant glioma.

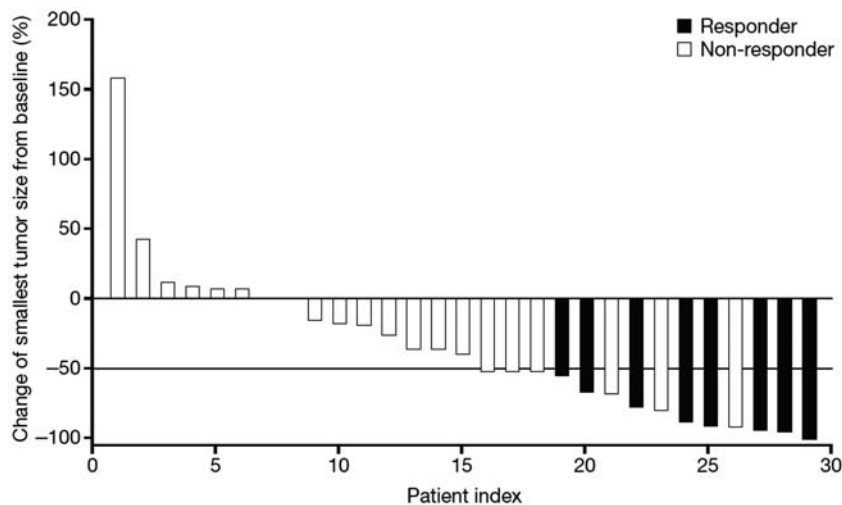
<sup>c</sup>Time from the last RT to the first dose of bevacizumab.



**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.

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

**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 <sup>a,b</sup>	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.

<sup>a</sup>All events were Grade 1.

<sup>b</sup>Includes: epistaxis, gingival bleeding, conjunctival hemorrhage, infusion site hemorrhage, blood urine present, cerebral hemorrhage, hemorrhage subcutaneous, metrorrhagia.

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.

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**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.

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