



European Medicines Agency

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**REFUSAL
ASSESSMENT REPORT
FOR
AVASTIN**

**International non-proprietary name/Common name:
bevacizumab**

Procedure No. EMEA/H/C/582/II/0028

**Variation Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted**

I. SCIENTIFIC DISCUSSION

1.1. Introduction

Bevacizumab (Bv) is a recombinant humanized anti-vascular endothelial growth factor (anti-VEGF) monoclonal antibody (IgG1) that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). Increased levels of VEGF expression have been found in many human malignancies examined to date, including tumours of the lung, breast, thyroid, gastrointestinal tract, kidney, bladder, ovary, cervix and pancreas, as well as angiosarcomas and glioblastomas. Increased VEGF serum levels have been correlated with poor survival.

Bevacizumab has been developed for the treatment of a number of malignancies and has completed Phase III clinical trials in metastatic colorectal cancer (mCRC), non squamous non-small cell lung cancer (NSCLC), metastatic breast cancer (mBC), metastatic renal cell carcinoma (mRCC) and metastatic pancreatic cancer. On the basis of having been shown to significantly prolong survival when added to 5-FU-based and irinotecan containing first-line chemotherapy for the treatment of mCRC, bevacizumab received Marketing Authorization approval in this indication globally (including the USA and EU). Since initial approval, bevacizumab has received Marketing Authorization approval for the first-line treatment of patients with mBC, non squamous NSCLC and mRCC.

The data submitted in this dossier support an extension of the current bevacizumab indication to include the use of bevacizumab alone or in combination with irinotecan in patients with glioblastoma (WHO Grade IV malignant glioma) after relapse.

1.2 Clinical aspects

Brain tumours account for 85% to 90% of all primary central nervous system (CNS) tumours. Every year it is estimated that approximately 37,400 people in the European Union are diagnosed with brain tumours and there are approximately 28,900 deaths. Worldwide, approximately 176,000 new cases of brain and other CNS tumours were diagnosed in the year 2000, with an estimated mortality of 128,000. Malignant primary brain tumours represent about 1–2% of all newly diagnosed tumours, and account for about 2% of all cancer-related deaths. They are the third leading cause of death from cancer in young adults.

Overall, gliomas account for 78% of malignant brain tumours. Malignant glioma comprises of glioblastoma [World Health Organization (WHO) Grade IV], anaplastic astrocytoma (WHO Grade III), mixed anaplastic oligoastrocytoma (WHO Grade III) and anaplastic oligodendroglioma (WHO Grade III). Diagnosis after biopsy or tumour resection is made according to the revised WHO classification. It occurs mostly in adults (median age at diagnosis: 64 years) and its incidence is estimated to be 3.05/100,000 in the United States and less than 2/100,000 in Europe. With 1- and 5-year overall survival of 29% and 3%, respectively, the prognosis of glioblastoma remains particularly poor. Although some progress has been made in the treatment of relapsed glioblastoma, this uncommon disease constitutes a high unmet medical need with very limited treatment options.

Low tumour grade, good performance status, an intact neurological function, younger age, and completeness of tumour resection have been identified as more favourable prognostic factors.

The recommendation for malignant glioma is surgical debulking provided that unacceptable neurologic deficit can be avoided, followed by radiation therapy. Concomitant radiotherapy and temozolomide, followed by adjuvant temozolomide for 6 cycles has been shown to significantly prolong overall survival compared to radiotherapy alone.

At relapse, chemotherapy is often proposed as an option. Regimens include either monotherapy (e.g. CCNU, platinum compounds, temozolomide), or polychemotherapy (PCV and other agents). If possible, a second resection, with or without carmustine-impregnated wafers, can be performed in patients with good neurologic status and performance score.

Wong et al. determined aggregate outcomes and prognostic covariates from eight consecutive Phase II trials conducted between 1986 and 1995. Response assessment was performed by CT/MRI criteria and extent of corticosteroid use.

The protocol for the pivotal bevacizumab study (AVF3708g) used the analysis of Phase II studies by Wong et al. as an indication for the determination of sample size. Objective response rate and 6-month PFS in patients who received salvage chemotherapy, was assumed to be approximately 5% and 15%, respectively. With regard to the efficacy of irinotecan, objective response rates of 0-17%, and 6-month PFS of 0-26% have been reported in various clinical trials of irinotecan alone.

Endothelial proliferation has been recognized as a marker of high grade or aggressive glioma in several Grading classifications, and it has been demonstrated that the degree of microvasculature as assessed by the endothelial cell/capillary density correlates well with the biologic aggressiveness of these tumours. The level of VEGF expression in gliomas has been shown to correlate with blood vessel density, degree of malignancy, and prognosis. Glioblastoma is a highly vascularised tumour, expressing elevated levels of numerous pro-angiogenic factors, such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor, and interleukin-8. Genetic alterations in glioblastoma in favour of an angiogenic phenotype consist of upregulation of pro-angiogenic factors, down-regulation of angiogenesis inhibitors, and hypoxia induced expression of pro-angiogenic cytokines. These features suggest that high grade gliomas are a suitable target for angiogenesis inhibiting therapies

This submission is based on one pivotal trial, a Genentech-sponsored Phase II study (AVF3708g), supported by data from one NCI-sponsored Phase II study (NCI 06-C-0064E) and published clinical study results.

The pivotal study was carried out in accordance with GCP principles. It was conducted in accordance with the US Food and Drug Administration, applicable local and national health authority, and institutional review board requirements.

1. 2. 1. Clinical Pharmacology

Pharmacokinetics

No new studies of clinical pharmacology are presented. In particular, no pharmacokinetic studies in the target population are presented. The Marketing Authorisation Holder (MAH) has argued that no specific evaluation of the concentration or distribution of Bv in CNS is required due to the well-known mechanism of action of Bv (neutralization of VEGF within the lumen of tumour vasculature) and the inability of large mAb to cross the blood-brain barrier.

Pharmacodynamics

No new studies are presented.

1. 2. 2. Clinical efficacy

Dose-response studies and main clinical studies

The present application is supported by one pivotal study, an open-label, multicenter Phase II study (AVF3708g). In this study, 167 patients were randomized to receive treatment with Bv 10 mg/kg every two weeks (q2w) as single agent or in combination with irinotecan 125 mg/m² q2w (or 340 mg/m² q2w for patients receiving enzyme-inducing anti-epileptic drugs [EIAEDs] concomitantly). The results for this study represent the protocol-specified final efficacy analyses for which all randomized patients have been followed up for a minimum of 6 months. The clinical cut off date is 15 September 2007.

As support for the application, data from an open-label, single arm Phase II study (NCI 06-C-0064E) are included. In this study, patients were enrolled to receive Bv 10 mg/kg q2w.

The details of these two studies are presented in Table 1. The assessment will focus on the pivotal trial AVF3708g.

It is noted that the pivotal study was a Phase II study, and bevacizumab was given in both arms. The randomization was for +/- irinotecan, and it was not designed to compare the efficacy of the two arms but merely to evaluate response rate, progression free survival, and tolerance of the two regimens. Bevacizumab for patients with relapsed glioblastoma multiforme has not been evaluated in a randomized active-controlled trial.

Table 1: Overview of Efficacy Studies with Bevacizumab in Glioblastoma Provided in this Dossier

Study/Source (Ref)	Study Design	N	Key Patient Characteristics
Pivotal Study			
AVF3708g CSR	Phase II, R, OL, MC, NC Arm 1: Bv 10 mg/kg q2w Arm 2: Bv 10 mg/kg q2w + irinotecan 125 mg/m ² q2w or 340 mg/m ² q2w for patients on EIAEDs	16 7	Histologically confirmed glioblastoma in first- or second-relapse Age ≥ 18 years Karnofsky performance status ≥ 70% Life expectancy > 12 weeks Prior standard radiotherapy and temozolomide
Supportive Study			
NCI 06-C- 0064E Summary Report	Phase II, OL, SC Arm 1: Bv 10 mg/kg q2w	56 ²	Histologically confirmed intracranial malignant glioma with evidence of tumor progression by MRI after RT Age ≥ 18 years Karnofsky performance status ≥ 60% No limit of prior systemic chemotherapies

Bv: bevacizumab; CSR: clinical study report; EIAEDs: enzyme-inducing anti-epileptic drugs; MC: multicenter; MRI: magnetic resonance imaging; NC: non-comparative; OL: open-label; q2w: every two weeks; R: randomized; RT: radiation therapy; SC: single center.

² only includes patients enrolled in the glioblastoma cohort and for which data are available in the summary report

No dose-response studies for glioblastoma are presented. The proposed dose of Bv for patients with relapsed glioblastoma is 10 mg/kg q2w or 15 mg/kg q3w (i.e., 5 mg/kg weekly equivalent). The recommendation of dosing Bv q2w or q3w is in line with its prescribing information for other indications. No direct comparison of the efficacy of Bv administered q2w or q3w has been performed in patients with relapsed glioblastoma. In study AVF3708g, the choice of bevacizumab (Bv) dose (10 mg/kg q2w) was based on the reported safety and efficacy of what was at the time an ongoing Phase II trial of bevacizumab plus irinotecan (AVF3311s – later reported by Vredenburgh et al at ASCO 2006).

Study AVF3708g

This was a Phase II, open-label, multicenter, randomized, non-comparative study consisting of two concurrent single arms. Patients were randomized in a 1:1 ratio to Arm 1 (Bv alone) or Arm 2 (Bv + irinotecan). The randomization scheme was designed to ensure an approximate 1:1 ratio to the two treatment arms stratifying for each category of relapse status (first or second) and Karnofsky performance status (70%-80% or 90%-100%).

Patients with histologically confirmed glioblastoma in first or second relapse, with a Karnofsky performance status of ≥ 70% and life expectancy of > 12 weeks were eligible for participation in this study.

Patients in the Bv arm received Bv alone at 10 mg/kg administered by intravenous (IV) infusion q2w for up to 104 weeks in the absence of disease progression or discontinuation due to unmanageable toxicity. Patients who experienced disease progression could have transitioned to an optional post-progression phase to receive Bv + irinotecan.

Patients in the Bv + irinotecan arm received Bv 10 mg/kg q2w and irinotecan 125 mg/m² q2w (or 340 mg/m² for patients taking EIAEDs) administered by IV infusion for a period of 104 weeks in the absence of disease progression or discontinuation due to unmanageable toxicity. Patients who experienced unmanageable toxicity could have discontinued the toxicity-causing agent (Bv or irinotecan) and continued with the remaining single agent for the rest of the 104-week treatment period in the absence of disease progression. Patients who experienced documented radiographic or clinical disease progression at any time were discontinued from the treatment phase and followed for survival.

The primary objectives of the study were to evaluate 6-month progression-free survival (PFS) and objective response rates in both treatment arms based on IRF assessments. Secondary objectives included characterization of the safety of Bv alone or in combination with irinotecan in this patient population, IRF assessments of PFS and duration of objective response, and overall survival (OS). An exploratory analysis of 6-month PFS, PFS, objective response rates and duration of objective response, as determined by investigators, was also performed.

Primary Endpoints

Six-month PFS

Six-month PFS, as determined by the IRF, was defined as the percentage of patients enrolled in each treatment arm who remained alive and progression free at 24 weeks. The definition of progression free is given below.

Data for patients who started to receive alternative anti-tumor therapy prior to disease progression were censored at the last tumor assessment date prior to receiving the alternative therapy. For patients who experienced the first disease progression or died more than 42 days after the last dose of study treatment, data were censored at the date of the last tumor assessment prior to the last dose of study treatment plus 42 days.

Objective Response Rate

Objective response was defined as a complete response (CR) or a partial response (PR) determined on two consecutive assessments ≥ 4 weeks apart, as determined by the IRF using the modified Macdonald criteria. The IRF determination of response, exclusive of corticosteroids given for chemoprophylaxis, was used in this analysis.

A CR was determined only if, in addition to meeting MRI criteria for a CR, corticosteroid levels were not above dose levels equivalent to 20 mg/day of hydrocortisone. A PR was determined only if, in addition to meeting MRI criteria for a PR, the corticosteroid dose at the time of the MRI was no greater than the maximum dose used in the first 6 weeks following initiation of therapy.

The objective response rate was the percentage of patients enrolled in each treatment arm who were judged to have an objective response.

Secondary Endpoints

PFS

PFS was defined as time from randomization to documented disease progression, as determined by the IRF using the modified Macdonald criteria, clear clinical progression in the absence of an MRI determination of progression, or death from any cause, whichever occurred first. Patients who had a clinical determination of progression should have undergone an MRI scan, if possible, to correlate radiographic findings with clinical findings. If a clinical determination of progression for a patient was confirmed by MRI, the date of the MRI scan was considered as the progression date for that patient.

The censoring method used was the same as that used for 6-month PFS.

Duration of Objective Response

Duration of objective response was defined as the time from the first tumor assessment that supported the patient's objective response to the time of disease progression, as determined by the IRF, clear clinical progression in the absence of an MRI determination of progression, or death due to any cause, whichever occurred first.

The censoring method used was the same as that used for 6-month PFS.

Overall Survival

OS was defined as the time from randomization to death from any cause.

Data were censored at the last date a patient was known to be alive prior to clinical cut off.

Exploratory Endpoints

Efficacy based on the investigator assessments was considered exploratory based on the following endpoints:

Six-month PFS

PFS

Objective response rate

Duration of objective response rate

In addition, neurocognitive function was assessed as a measure of the impact of treatment on the natural history of malignant glioma and its potential clinical benefit. Standard psychometric instruments known to be affected by brain tumors and treatments were used. These tests measured three domains within neurocognitive function:

1. Memory: Hopkins Verbal Learning Test (HVLN) – three separate tests (immediate recall [HVLTA], delayed recall [HVLTB], delayed recognition [HVLTC])
2. Visual-motor scanning speed: Trail Making Test A and Trail Making Test B
3. Executive function: Controlled Oral Word Association (COWA)

The tests were conducted by trained site personnel at baseline and every 6 weeks thereafter. Tests scored in terms of time to completion (Trail Making Tests) were discontinued at 5 minutes to reduce the time and burden for the patient. Each test took between 2-5 minutes to complete with a total time of approximately 20 minutes for completion of all tests.

• Sample size

The sample size calculations were based on the following:

In the Bv arm, a 6-month PFS of $\geq 28\%$ would indicate that Bv monotherapy has clinically meaningful activity in this population. Eighty patients treated with Bv alone would provide approximately 80% power (one-group χ^2 test: 79%; exponential maximum likelihood estimation test: 89%) to detect an increase in 6-month PFS from 15% (in historical controls) to 28% at the 2.5% two-sided significance level. An objective response rate of $\geq 18\%$ would indicate that Bv monotherapy had clinically meaningful activity in this population. Eighty patients would provide 92% power (exact binomial test) to detect an increase in objective response rate from 5% to 18% at the 2.5% two-sided significance level.

In the Bv + irinotecan arm, a 6-month PFS of $\geq 30\%$ would indicate that Bv + irinotecan had clinically meaningful activity in this population. Eighty patients treated with Bv + irinotecan would provide approximately 90% power (one-group χ^2 test: 88%; exponential maximum likelihood estimation test: 95%) to detect a 15% increase in 6-month PFS from 15% (in historical controls) to 30% at the 2.5% two-sided significance level. An objective response rate of $\geq 25\%$ would indicate that Bv + irinotecan had clinically meaningful activity in this population. Eighty patients would provide 92% power (exact binomial test) to detect a 15% increase in objective response rate from 10% to 25% at the 2.5% two-sided significance level.

• Randomisation

A total of 167 patients were randomized.

Patients were randomized in a 1:1 ratio to Arm 1 (Bv alone) or Arm 2 (Bv + irinotecan). The randomization scheme was designed to ensure an approximate 1:1 ratio to the two treatment arms stratifying for each category of relapse status (first or second) and Karnofsky performance status (70%-80% or 90%-100%).

- **Statistical methods**

Analysis Populations

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all patients who were randomized, regardless of whether they received any study treatment or completed the full course of treatment. Patients were analyzed according to the treatment assignment at randomization.

Efficacy-evaluable patients were defined as randomized patients who received at least one dose of study treatment (either Bv or irinotecan) and either had at least one post-baseline tumor assessment with a response evaluation or failed to return for any tumor assessments because of death or clinical determination of progression. Additional analyses for objective response were performed on efficacy-evaluable patients, as well as, on patients with measurable disease at baseline, as identified by the IRF, and on patients with central pathology-confirmed glioblastoma at baseline.

Statistical Analyses of Efficacy Endpoints

Each treatment arm was analyzed separately for the primary and secondary efficacy endpoints. Because of the existence of two primary endpoints for each treatment arm, the primary efficacy analyses of 6-month PFS and objective response rate were performed at the two-sided 0.025 level of significance.

Six-month PFS

The 6-month PFS with salvage chemotherapy was assumed to be approximately 15% based on historical data. Therefore, for the Bv arm, the following hypothesis was tested at the $\alpha = 0.025$ (two-sided) significance level:

$$H_0: 6\text{-month PFS} = 15\% \text{ versus } H_1: 6\text{-month PFS} \neq 15\%$$

The 6-month PFS with irinotecan alone was also assumed to be 15% based on historical data. Therefore, for the Bv + irinotecan arm, the following hypothesis was tested at the $\alpha = 0.025$ (two-sided) significance level:

$$H_0: 6\text{-month PFS} = 15\% \text{ versus } H_1: 6\text{-month PFS} \neq 15\%$$

Kaplan–Meier methods were used to estimate 6-month PFS, along with the standard error and the corresponding 97.5% confidence intervals (CIs) using Greenwood’s formula. The normal approximation method was used to evaluate whether each treatment had a statistically significant effect, as measured by 6-month PFS.

If the primary efficacy analysis of 6-month PFS in the Bv arm produced a two-sided p-value that was statistically significant at the $\alpha = 0.025$ significance level with a 6-month PFS $> 15\%$, then it would be concluded that Bv monotherapy resulted in a statistically significant increase in 6-month PFS compared with salvage chemotherapy in this population.

If the primary efficacy analysis of 6-month PFS in the Bv + irinotecan arm produced a two-sided p-value that was statistically significant at the $\alpha = 0.025$ significance level with a 6-month PFS $> 15\%$, it would be concluded that combination therapy resulted in a statistically significant increase in 6-month PFS compared with irinotecan alone in this population.

Objective Response Rate

The objective response rate to salvage chemotherapy was assumed to be 5% based on historical data. Therefore, for the Bv arm, the following hypothesis was tested at the $\alpha = 0.025$ (two-sided) significance level:

$$H_0: \text{objective response rate} = 5\% \text{ versus } H_1: \text{objective response rate} \neq 5\%$$

The objective response rate to irinotecan alone was assumed to be 10% based on historical data. Therefore for the Bv + irinotecan arm, the following hypothesis was tested at the $\alpha = 0.025$ (two-sided) significance level:

$$H_0: \text{objective response rate} = 10\% \text{ versus } H_1: \text{objective response rate} \neq 10\%$$

The exact binomial test was used to evaluate whether the treatment resulted in a statistically significant increase in objective response rate. Exact 97.5% CIs were estimated using the Blyth–Still–Casella method.

If the primary efficacy analysis of objective response rate in the Bv arm produced a two-sided p-value that was statistically significant at the $\alpha = 0.025$ significance level with an objective response rate $> 5\%$, it would be concluded that Bv monotherapy resulted in a statistically significant increase in objective response rate compared with salvage chemotherapy in this population.

If the primary efficacy analysis of objective response rate in the Bv + irinotecan arm produced a two-sided p-value that was statistically significant at the $\alpha = 0.025$ significance level with an objective response rate $> 10\%$, it would be concluded that combination therapy resulted in a statistically significant increase in objective response rate compared with irinotecan alone in this population.

Secondary Endpoints

Estimates for the secondary endpoints of PFS, duration of objective response and OS for each treatment arm were based on the Kaplan–Meier method. The 95% CIs for median PFS were computed using the Brookmeyer and Crowley method. The 95% CIs for median duration of objective response and median OS were computed using Greenwood’s formula.

Sensitivity Analyses

The following sensitivity analyses were performed:

Six-month PFS and PFS (IRF and investigator assessments)

Only data for patients who did not have an event at the time of the clinical cut off were censored (ie, all events were included in the analysis); data for patients without an event were censored at the date of their last tumor assessment prior to data cut off.

Objective response rate (IRF assessment)

Data for all administered corticosteroids were included.

Only data for corticosteroids not given for chemoprophylaxis were included. For this analysis, baseline corticosteroid use was defined as the average corticosteroid dose within 4 days of the first study treatment administration.

Exploratory Analyses

As an exploratory analysis, the relative efficacy between the Bv and Bv + irinotecan arms was assessed for the endpoints objective response rate, PFS, duration of objective response and OS.

Objective response rates between the two arms were compared using a Cochran-Mantel-Haenszel test, stratified for relapse status (first or second) and Karnofsky performance status (70%-80% vs 90%-100%). Confidence intervals for the difference in response rates were determined using the normal approximation of the binomial distribution.

For the time-to-event endpoints PFS, duration of objective response and OS, a two-sided stratified log-rank test was used to compare the arms, using the following stratification factors: relapse status (first or second) and Karnofsky performance status (70%-80% vs 90%-100%). Hazard ratios were estimated using a stratified Cox-regression model. Results from an unstratified analysis are also provided.

For the analysis of neurocognitive function, data from each test were analyzed separately. All test scores were normalized using the patient’s age. The COWA tests scores were adjusted by the patient’s educational level in addition to age. For each test, neurocognitive progression was defined as a worsening in normative test score from baseline by 3 standard deviations (SDs) in the test’s normative distribution. Data were censored at the earliest occurrence of discontinuation from the study, initiation of additional brain-related treatment or death. The distribution of time to neurocognitive progression for each test was estimated using the Kaplan-Meier method. Both univariate and multiple-covariate proportional hazards models were used to assess the effect of prognostic factors on time to neurocognitive progression. The

models included, but were not limited to, the variables relapse status (first or second) and baseline Karnofsky performance status (70%-80% or 90%-100%).

Results

• Participant flow

Table 2
Patient Disposition (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Randomized patients	85 (100.0%)	82 (100.0%)
Treated patients	84 (98.8%)	79 (96.3%)
Enrolled in optional post-progression phase ^a	44 (51.8%)	—
On treatment ^b		
Planned treatment period	22 (25.9%)	20 (24.4%)
Optional post-progression treatment	2 (2.4%)	—
Discontinued all treatment ^c	22 (25.9%)	18 (22.0%)
Discontinued study ^d	39 (45.9%)	44 (53.7%)

BV= bevacizumab; CPT-11=irinotecan.

^a Includes patients who experienced disease progression and received post-progression treatment of irinotecan in combination with bevacizumab.

^b Includes patients still on study treatment as of the data cutoff date, 15 September 2007.

^c Includes patients who discontinued all treatment and remain in survival follow-up.

^d All patients discontinued the study as the result of death.

In both studies bevacizumab (10 mg/kg/q2w administration) was to be continued until progression or unacceptable toxicity, but was limited to a maximum of 104 weeks in study AVF3708g. No dose reductions for bevacizumab were allowed in either study, only interruption or withdrawal. Agent-specific criteria for the discontinuation of bevacizumab were specified in each protocol (as well as for irinotecan in study AVF3708g). In study AVF3708g, patients who discontinued trial treatment prior to progression were followed for survival, but not for progression. Subsequent anti-cancer therapy after trial treatment discontinuation was not specified in any protocol, but was not to be initiated until after progression. For patients randomised to the bevacizumab single-agent arm of study AVF3708g, post-progression treatment of irinotecan in combination with bevacizumab was a protocol specified option after disease progression. Information regarding any subsequent anticancer treatment used before or after progression was not collected.

Six-month PFS is defined as the number of patients who are alive and progression-free at the scheduled 24 week assessment. The censoring used for the main analyses of PFS in the AVF3708g CSR is described below:

- Data for patients without a PFS event at the time of the clinical cut-off for the analysis were censored on the date of their last tumour assessment prior to the cut-off.
- Data for patients who started to receive alternative anti-tumour therapy prior to disease progression were censored at the last tumour assessment date prior to receiving the alternative therapy.
- Data for patients who experienced the first disease progression or died more than 42 days after the last dose of study treatment, data were censored at the date of the last tumour assessment prior to the last dose of study treatment plus 42 days.

Study AVF3708g also included measures of performance status and neurological function based in part on validated neurocognitive tests as well as evidence of corticosteroid-sparing.

In study AVF3708g, clinical progression (patient considered to have clearly worsened neurologically) and corticosteroid use were added into the MRI response evaluation criteria for the investigator assessment of response (MacDonald criteria). Subjectivity was reduced by the use of a blinded independent radiographic

review (IRF) of MRI for the determination of response and progression in study AVF3708g, and of response in study NCI 06-C-0064E.

Initially presented results of the pivotal study (AVF3708g), represent the protocol-specified final analysis of the study (minimum of 6 months follow-up of each patient), with a clinical cut-off of September 15, 2007. The PFS analyses are mature with 68-75% of patients having had an event according to the investigator at the time of the clinical cut-off. Approximately 50% of patients had died at the time of the clinical cut-off. The study was initiated in June 30, 2006 meaning that follow-up ranged between a minimum 6 months to a maximum of 14.5 months.

Study Populations

The population of patients with glioblastoma after relapse enrolled into study AVF3708g and NCI 06-C-0064E was representative of the adult population expected to receive bevacizumab should marketing in this indication be approved. However, primary and secondary glioblastoma are two distinct disease entities which develop through different genetic pathways. As only seven patients with secondary glioblastoma have been included in the study it is not possible to conclude on the efficacy in these patients. At present, it is considered acceptable that limited data is available in this patient group. However, in future studies patients should be stratified according to genetic factors.

The inclusion of an independent central pathology review of baseline histology confirmed the diagnosis of glioblastoma for 165/167 patients in study AVF3708g. The majority of patients were in first relapse (81%), and all but 14 patients had at least a partial resection upon initial diagnosis. All patients had received prior radiotherapy and at least one systemic therapy including temozolomide. The MAH has clarified that 89% of the enrolled patients received temozolomide concomitant with RT, and all but 3% of patients completed at least 6 cycles of temozolomide or stopped prior to the 6th cycle due to disease progression.

At baseline, 55% of patients in the Bv arm and 62% in the Bv + irinotecan arm had the lowest Karnofsky Performance Status allowed of 70-80. The median age was 54-57 years in each study treatment arm, with an overall age range of 23-79 years. The majority of patients were male (69%), and 90% were white.

The demographic characteristics of the patients in the pivotal trial are shown below.

Study AVF3708g: Demographic Characteristics (ITT Population)

	BV (n = 85)	BV/CPT-11 (n = 82)
Age (yr)		
Mean (SD)	53.8 (11.0)	55.0 (12.4)
Median	54.0	57.0
Range	23.0–78.0	23.0–79.0
Age group (yr)		
18–40	11 (12.9%)	12 (14.6%)
41–64	63 (74.1%)	52 (63.4%)
≥ 65	11 (12.9%)	18 (22.0%)
Sex		
Male	58 (68.2%)	57 (69.5%)
Female	27 (31.8%)	25 (30.5%)
Race/ethnicity		
White	77 (90.6%)	73 (89.0%)
Black	3 (3.5%)	2 (2.4%)
Asian or Pacific Islander	2 (2.4%)	0 (0.0%)
Hispanic	3 (3.5%)	5 (6.1%)
Other	0 (0.0%)	2 (2.4%)
Karnofsky performance status		
90–100	38 (44.7%)	31 (37.8%)
70–80	47 (55.3%)	51 (62.2%)
EIAED use		
Yes	18 (21.2%)	30 (36.6%)
No	67 (78.8%)	52 (63.4%)

BV = bevacizumab; CPT-11 = irinotecan; EIAED = enzyme-inducing anti-epileptic drug; SD = standard deviation.

Their baseline disease characteristics were:

Study AVF3708g: Baseline Disease Characteristics (ITT Population)

	BV (n = 85)	BV/CPT-11 (n = 82)
Prior diagnosis of glioma at initial diagnosis		
Anaplastic astrocytoma	2 (2.4%)	5 (6.1%)
Other ^a	5 (5.9%)	1 (1.2%)
GBM	78 (91.8%)	76 (92.7%)
Extent of initial surgery		
Partial resection	42 (49.4%)	44 (53.7%)
Complete resection	36 (42.4%)	31 (37.8%)
Biopsy only	7 (8.2%)	7 (8.5%)
Relapse status		
First	69 (81.2%)	66 (80.5%)
Second	16 (18.8%)	16 (19.5%)

BV = bevacizumab; CPT-11 = irinotecan.

^a Other diagnoses included oligoastrocytoma, Grade 2 astrocytoma, low-grade glioma-oligodendroglioma, and anaplastic mixed oligoastrocytoma.

Their baseline corticosteroid medications were:

Study AVF3708g: Corticosteroid Use at Baseline (ITT Population)

	BV (n = 85)	BV/CPT-11 (n = 82)
Corticosteroid dose at baseline (mg/day)	43 (50.6%)	43 (52.4%)
≤ 2	14 (16.5%)	9 (11.0%)
2–4	13 (15.3%)	9 (11.0%)
4–6	4 (4.7%)	2 (2.4%)
6–8	5 (5.9%)	9 (11.0%)
10–20	3 (3.5%)	13 (15.9%)
> 20	4 (4.7%)	1 (1.2%)

BV = bevacizumab; CPT-11 = irinotecan.

Note: Baseline corticosteroid dose is defined as the average corticosteroid dose within 4 days before the first study treatment. Corticosteroids used for chemoprophylaxis/inhaled/topical corticosteroids are not included in this table. All corticosteroids were converted to a dexamethasone-equivalent dose.

Patient disposition was reasonably consistent between treatment arms and studies. The proportion of patients that withdrew from trial treatment prior to PD or death was lower in the Bv arm (7%) of study AVF3708g, compared to either the Bv+irinotecan arm (20%) of study AVF3708g, or study NCI 06-C-0064E (23%).

• **Numbers analysed**

167 patients (the ITT population) were compared to historical control data.

Comparison of Efficacy across Studies

In the pivotal study (AVF3708g), the protocol-defined main analysis of efficacy (using the IRF assessment) established that bevacizumab used as single-agent or in combination with irinotecan for treatment of patients with glioblastoma after relapse resulted in:

- Kaplan-Meier estimated 6-month PFS of 42.6% (95% CI 29.6-55.5%) in the Bv arm and 50.3% (95% CI 36.8-63.9%) in the Bv + irinotecan arm, representing a statistically significant increase ($p < 0.0001$) compared with protocol-defined historical controls for both treatment arms (6-month PFS assumed to be 15%).
- Objective response rates of 28.2% (95% CI 18.5-40.3%) in the Bv arm and 37.8% (95% CI 26.5-50.8%) in the Bv + irinotecan arm, representing a statistically significant increase ($p < 0.0001$) in objective response rates compared with protocol-defined historical controls for both treatment arms (assumed to be 5% for salvage chemotherapy, and 10 % for irinotecan alone).
- Durable responses in both treatment arms, Kaplan-Meier estimated median duration of response of 5.6 months (95% CI 3.0- 5.8) in the Bv arm and 4.3 months (95% CI 4.2- no estimate) in the Bv + irinotecan arm.
- Kaplan-Meier estimated median PFS of 4.2 months (95% CI 2.9-5.8) in the Bv arm and 5.6 months (95% CI 4.4-6.2) in the Bv + irinotecan arm, with approximately 73% and 61% of patients in each arm having had a PFS event by the time of the analysis.
- Kaplan-Meier estimated median overall survival of 9.3 months (95% CI 8.2- no estimate) in the Bv arm and 8.8 months (95% CI 7.8- no estimate) in the Bv + irinotecan arm, with approximately 46% and 54% of patients in each arm having died at the time of the analysis.

At the time of the protocol-specified final analysis, the duration of follow-up did not allow an accurate estimation of the upper confidence interval for duration of response and overall survival.

Compared to the IRF assessment, the objective response rate and duration of response was considerably higher according to the investigator assessment; 41% (7.2 months) in the Bv arm and 51% (8.3 months) in the Bv+irinotecan arm. According to the investigators' assessment, using the sensitivity analysis of PFS

(with censoring only for patients who did not have an event), approximately 75% and 68% of patients in each arm had a PFS event at the time of the analysis, and the Kaplan-Meier estimated median PFS was 4.2 months and 5.8 months. The MAH has clarified that the sensitivity analysis can be considered to represent an ITT analysis.

In the IRF assessment, using the less censored sensitivity analysis of PFS, approximately 77% of patients in each arm had a PFS event at the time of the analysis, and the Kaplan-Meier estimated median PFS was 4.2 months and 5.5 months.

In addition to these tumour responses and progression results, overall survival was also longer than evident in historical controls. In the MAH's answer to the CHMP RSI, an updated OS analysis of study AVF3708g did not show notable differences to the initial analysis.

The statistical tests and calculations are standard. The major problem is the lack of an internal control and comparisons based on historical data.

The historical data on which the comparisons are based stem mainly from the data from Wong et al (JCO 1999). These data were collected from 8 Phase II trials conducted at the MD Anderson Cancer Center during the period 1986 to 1995. As can be gathered from the publication, these historical patients could have a lower Karnofsky score than the patients in the AVF3708g trial; they had on the whole received more treatment before protocol entry, and had had less complete tumour removal initially. In the absence of a controlled, randomized trial, the MAH has been asked to perform a far more elaborate inter-trial comparison of the efficacy and safety of Bv to other available therapies in recurrent GBM and to include a critical discussion of potential biases and emphasis on the results of more recent trials of alternative therapies.

Consequently, the MAH has performed a very thorough and critical inter-trial comparison of the *efficacy* and *safety* of bevacizumab compared to:

- the predefined historic controls (various agents (Wong et al., Ballman et al., Lamborn et al.))
- in addition Prados – the results from the NABTC clinical trials database were included for comparison
- contemporary phase III studies (hydroxyurea, hydroxyurea + imatinib, enzastaurin, lomustine)
- data from other, more recent phase II trials (dose-intense temozolomide regimens, temozolomide re-challenge, continuous low-dose temozolomide, fotemustine)

•

• **Outcomes and estimation**

Bevacizumab used as single agent or in combination with irinotecan for treatment of patients with relapsed glioblastoma resulted in:

- A statistically significant increase ($p < 0.0001$) in the IRF-assessed 6-month PFS in both treatment arms compared with historical controls: 42.6% in the Bevacizumab arm and 50.3% in the Bevacizumab + irinotecan arm versus 15% in historical controls.
- A statistically significant increase ($p < 0.0001$) in the IRF-assessed objective response rates in both treatment arms compared with historical controls: 28.2% in the Bevacozumab arm and 37.8% in the Bevacizuamb + irinotecan arm versus 5% and 10% in historical controls, respectively.
- Durable responses in both treatment arms, with a median of 5.6 months (95% CI 3.0, 5.8) in the Bevacizumab arm and 4.3 months (95% CI 4.2, -) in the Bevacozumab + irinotecan arm.
- A median overall survival of 9.3 months (95% CI 8.2, -) in the Bevacizumab arm and 8.8 months (95% CI 7.8, -) in the Bevacizuamb + irinotecan arm.

The results are summarized below:

Study AVF3708g: Summary of Efficacy Results (ITT Population)

	Bv¹ N=85	Bv + irinotecan² N=82
Primary Endpoints		
6-months PFS (IRF assessed)		
Event-free rate (97.5% CI) p-value ³	42.6% (29.6, 55.5) < 0.0001	50.3% (36.8, 63.9) < 0.0001
Objective response rate (IRF assessed)		
Overall	24 (28.2%)	31 (37.8%)
Complete response	1 (1.2%)	2 (2.4%)
Partial response	23 (27.1%)	29 (35.4%)
(97.5% CI for objective response rate)	(18.5, 40.3)	(26.5, 50.8)
p-value ⁴	< 0.0001	< 0.0001
Secondary Endpoints		
PFS (IRF assessed) (months)		
Median (95% CI)	4.2 (2.9, 5.8)	5.6 (4.4, 6.2)
Duration of objective response ³ (months)		
Median (95% CI)	5.6 (3.0, 5.8)	4.3 (4.2, -)
Overall survival (months)		
Median (95% CI)	9.3 (8.2, -)	8.8 (7.8, -)

Bv: bevacizumab; CI: confidence interval; IRF: independent radiology facility; PFS: progression-free survival.

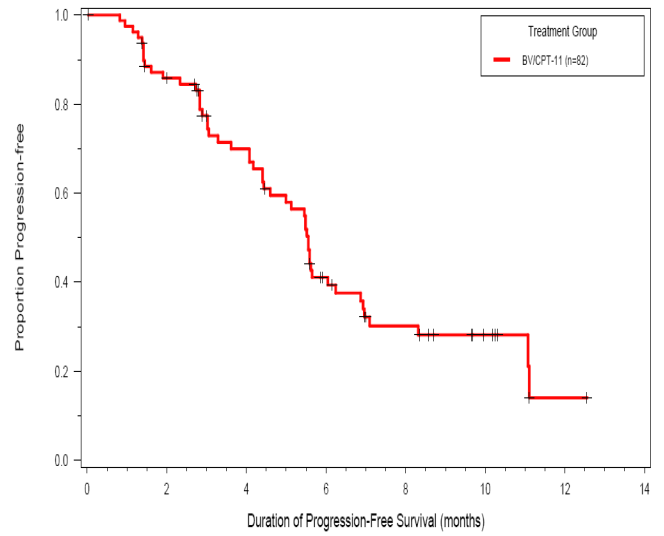
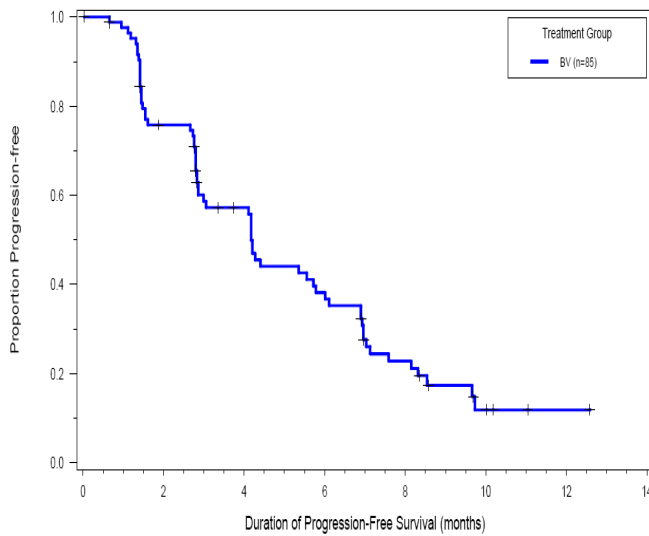
¹ bevacizumab 10 mg/kg q2w IV

² bevacizumab 10 mg/kg q2w IV + irinotecan 125/340 mg/m² q2w IV

³ difference in rates relative to 15% 6-month PFS with salvage chemotherapy (Bv arm) or with irinotecan alone (Bv + irinotecan arm)

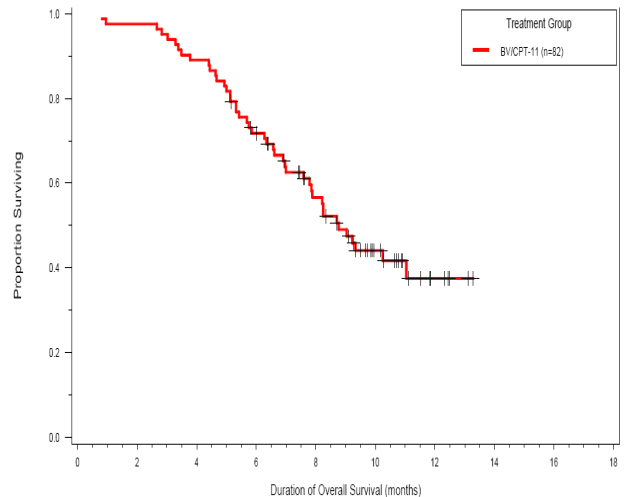
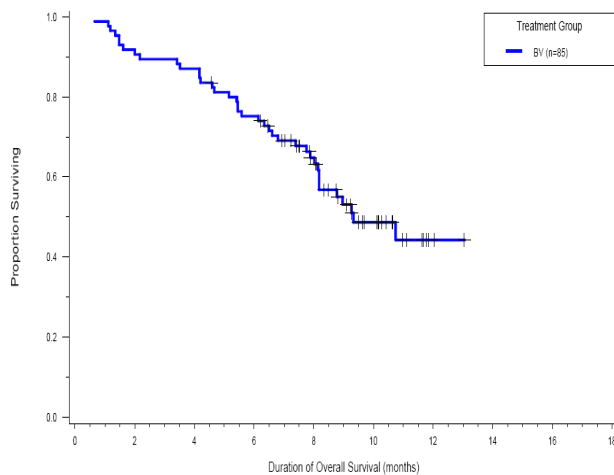
⁴ difference in objective response rates relative to 5% response rates with salvage chemotherapy (Bv arm) and 10% response rates with irinotecan alone (Bv + irinotecan arm)

Study AVF3708g: Kaplan-Meier Estimates of Progression-Free Survival, as Determined by the Independent Radiology Facility (ITT Population)



BV = bevacizumab; CPT-11 = irinotecan.

Study AVF3708g: Kaplan-Meier Estimates of Overall Survival (ITT Population)



BV = bevacizumab; CPT-11 = irinotecan.

Subgroup analyses did not show any significant qualitative differences in the outcome between different groups. However, the data material is relatively small.

- **Ancillary analyses, Other endpoints**

No formal Quality of Life evaluation was implemented in study AVF3708g. However, information on the following parameters was collected in the study: Neurocognitive function, steroid dose and dependence, KPS.

In order to address the problem of lack of a control group, the MAH has performed several post-hoc analyses that evaluate the effect of Bv by comparing the on-treatment data for each of the parameters above with baseline data, assessing each patient as his/her internal control.

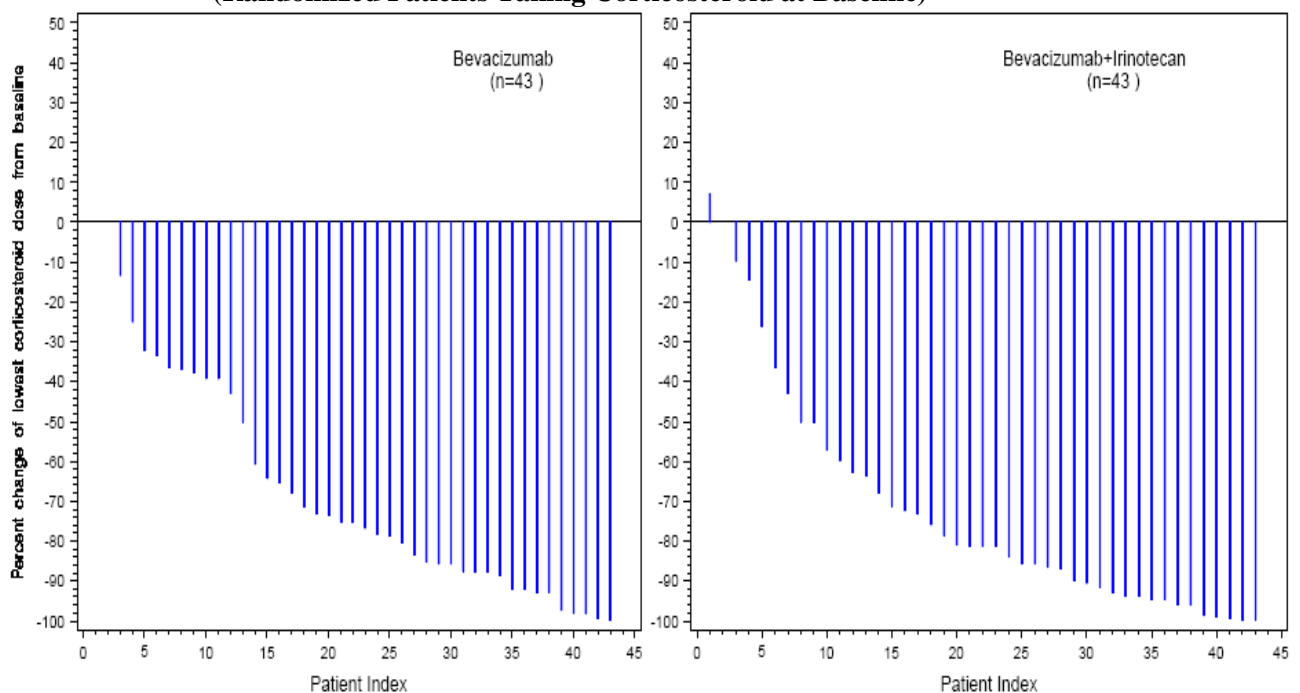
When applying the Reliable Change Index (RCI) criteria to assess the change from baseline, the majority of responding patients experienced a stable/improved neurocognitive function while on Bv treatment. For the purpose of assessing changes over time, the neurocognitive test scores were converted to standardized scores by use of published normative data. Overall, median neurocognitive test scores of patients with an IRF-determined OR remained stable or improved from baseline to Week 24 both in the Bv and Bv+irinotecan arms.

Likewise, a considerable number of patients on steroids were able to reduce their steroid dose whilst on Bv treatment: Approximately 50% of patients received steroids at baseline and around half of these patients had a steroid reduction of at least 50% for a minimum of 4 weeks. Particularly in patients who were progression-free at 6 months, the magnitude and duration of steroid reductions were noteworthy.

Finally, 85% of Bv-treated patients and 87% of Bv+irinotecan treated patients maintained a stable or improved KPS for approximately 70% of their progression-free period on average. In study AVF3708g, within 24 weeks of starting trial treatment, the majority of patients that were progression-free had Karnofsky Performance Scores that generally remained stable, in the range of 70-100.

During the study, most patients in both treatment arms had a decrease of corticosteroid dose relative to their dose at baseline:

Study AVF3708g: Percent Change of the Lowest Corticosteroid Dose from Baseline (Randomized Patients Taking Corticosteroid at Baseline)



BV = bevacizumab; CPT-11 = irinotecan.

Note: The lowest corticosteroid dose is defined as the minimum of the average corticosteroid dose of every 4 weeks after the first treatment until planned treatment discontinuation. The baseline corticosteroid dose is defined as the average corticosteroid dose within 4 days before the first study treatment.

For patients in the BV arm who received optional post-progression treatment of irinotecan, corticosteroid use during the optional post-progression phase is not included in the graph. All corticosteroids were converted to a dexamethasone-equivalent dose.

Each needle represents 1 patient.

A total of 6 neurocognitive function tests were administered to patients: HVLTA (immediate recall), HVLTB (delayed recall), HVLTC (delayed recognition), Trail Making Test A, Trail Making Test B and the COWA.

For each test, median scores at baseline, week 12 and week 24, as well as, median change from baseline scores are shown in the two tables below.

In the Bevacizumab arm, median scores improved with time for the visual motor scanning speed tests (Trail Making Tests A and B), the COWA test and the immediate recall memory test (HVLTA). Median scores did not worsen with time for the delayed recall and delayed recognition memory tests (HVLTB and HVLTC).

In the Bevacizumab + irinotecan arm, median scores improved with time for the visual motor scanning speed tests (Trail Making Tests A and B) and the COWA test. Median scores did not worsen with time for the three memory tests (HVLTA, HVLTB and HVLTC). However, as the number of patients in both treatment arms completing the tests declines considerably with time, these results should be interpreted with caution.

Study AVF3708g: Neurocognitive Function Hopkins Verbal Learning Tests: Scores and Change from Baseline Scores during the Planned Treatment Period (ITT Population)

Neurocognitive Function Test		Bv (N=85)		Bv + irinotecan (N=82)	
		Value	Change from BL	Value	Change from BL
Memory – HVLTA (Immediate Recall)					
Baseline	N	83	83	75	75
	Median	-2.2	0.0	-2.2	0.0
	Range	-7.3-0.8	0.0-0.0	-7.1-1.4	0.0-0.0
Week 12	N	54	53	57	55
	Median	-1.9	0.2	-2.2	-0.2
	Range	-6.8-1.1	-5.8-3.2	-7.1-0.8	-2.6-3.5
Week 24	N	32	32	38	37
	Median	-1.4	0.3	-1.6	0.3
	Range	-6.8-1.7	-3.2-3.2	-6.0-1.5	-2.6-4.2
Memory – HVLTB (Delayed Recall)					
Baseline	N	81	81	74	74
	Median	-2.7	0.0	-2.1	0.0
	Range	-6.6-1.2	0.0-0.0	-6.1-1.0	0.0-0.0
Week 12	N	53	50	57	54
	Median	-2.1	0.0	-3.1	0.0
	Range	-6.1-1.2	-6.5-5.9	-6.1-1.0	-4.1-3.5
Week 24	N	30	30	37	35
	Median	-1.6	0.0	-2.1	0.0
	Range	-6.1-1.2	-2.4-4.4	-6.1-1.2	-2.2-3.9
Memory – HVLTC (Delayed Recognition)					
Baseline	N	79	79	75	75
	Median	-1.3	0.0	-0.6	0.0
	Range	-12.9-0.9	0.0-0.0	-10.2-0.9	0.0-0.0
Week 12	N	54	51	56	54
	Median	-0.2	0.7	-0.8	0.0
	Range	-7.5-0.9	-5.5-7.3	-10.2-0.9	-7.3-5.5
Week 24	N	30	30	37	36
	Median	-0.8	0.0	-1.3	0.0
	Range	-8.4-0.9	-3.6-2.1	-7.5-0.9	-3.6-5.0

BL: baseline; Bv: bevacizumab; HVLTA: Hopkins Verbal Learning Test.

Raw test scores were standardized based on normative distribution adjusted by age.

Study AVF3708g: Neurocognitive Function Tests: Scores and Change from Baseline Scores during the Planned Treatment Period (ITT Population)

Neurocognitive Function Test		Bv (N=85)		Bv + irinotecan (N=82)	
		Value	Change from BL	Value	Change from BL
Visual Motor Scanning Speed - Trail Making Test A					
Baseline	N	82	82	73	73
	Median	-2.7	0.0	-2.5	0.0
	Range	-39.0-1.0	0.0-0.0	-746.5-1.3	0.0-0.0
Week 12	N	54	53	58	55
	Median	-1.8	0.4	-2.5	0.6
	Range	-579.8-1.2	-568.1-22.0	-124.0-1.6	-30.3-67.0
Week 24	N	31	31	39	37
	Median	-0.6	0.7	-1.1	0.6
	Range	-24.9-1.3	-22.9-10.2	-77.6-1.5	-22.7-66.9
Visual Motor Scanning Speed - Trail Making Test B					
Baseline	N	73	73	70	70
	Median	-6.7	0.0	-7.4	0.0
	Range	-125.1-1.4	0.0-0.0	-105.7-1.6	0.0-0.0
Week 12	N	51	47	53	49
	Median	-3.8	0.7	-4.1	1.0
	Range	-42.6-1.3	-14.5-50.7	-60.6-1.5	-40.8-58.5
Week 24	N	28	26	36	32
	Median	-2.3	0.5	-3.6	2.1
	Range	-49.9-1.6	-27.4-28.0	-157.3-1.9	-8.8-59.3
Executive Function – COWA¹					
Baseline	N	62	62	58	58
	Median	26.0	0.0	27.0	0.0
	Range	8.0-55.0	0.0-0.0	6.0-56.0	0.0-0.0
Week 12	N	41	39	45	43
	Median	30.0	3.0	27.0	2.0
	Range	2.0-55.0	-11.0-15.0	0.0-72.0	-12.0-32.0
Week 24	N	23	23	30	29
	Median	35.0	6.0	31.0	5.0
	Range	6.0-53.0	-15.0-13.0	5.0-67.0	-10.0-22.0

BL: baseline; Bv: bevacizumab; COWA: Controlled Oral Word Association.

Raw test scores were standardized based on normative distribution adjusted by age (and education level for the COWA test).

¹ the normative distribution for this test has a median of 38, Q1=32, Q4=44.

Due to the low number of neurocognitive progression events per test, median time to neurocognitive progression could not be estimated for any of the tests administered. Therefore, no conclusions can be made regarding the impact of study treatment on neurocognitive progression.

Efficacy in Patient Subgroups

In study AVF3708g, analyses of objective response and 6-month PFS were performed in the following subgroups of patients:

- Age (< 65, ≥ 65 years)
- Gender (male, female)
- Race (White, non-White)
- Karnofsky performance status (70%-80%, 90%-100%)
- Relapse status (first relapse, second relapse)
- Baseline EIAED use (yes, no)
- Baseline corticosteroid use (yes, no)

- Prior diagnosis of glioma (glioblastoma, other)
- Extent of initial surgery (complete resection, partial resection, biopsy only)

There were no significant differences in the outcome in any of the subgroups analysed. The number of patients is, however, relatively small, and some of the analyses are rather uncertain.

Correlative Assessment of Biomarkers

No formal collection and assessment of potential biomarkers are described in the protocol of study AVF3708g. During the Bevacizumab development program, the MAH has investigated a large number of potential biomarkers across indications. So far no correlation between levels of these biomarkers and clinical outcome in Bv-treated patients has been identified. Specifically, no association between Bv efficacy and tumour VEGF expression or plasma VEGF levels has been observed. In study AVF3311s tumour specimens from the time of diagnosis were available from 45 (27 glioblastoma) of the 60 recruited patients. Radiographic response and survival outcome were explored for correlation with VEGF, VEGF receptor-2, CD31, hypoxia-inducible carbonic anhydrase 9 (CA9), and hypoxia-inducible factor-2 α assessed semi-quantitatively by immunohistochemistry (data not shown).

Chen et al. showed that a reduction in metabolic activity, as measured by 18F-fluorothymidine PET scanning, correlated with response and survival in patients with Grade III and IV glioma treated with bevacizumab plus irinotecan. Not surprisingly, FDG-PET seems promising for evaluation of prognosis after treatment. Tumour hypoxia may well contribute to the poor prognosis of glioblastoma.

The MAH has included a comprehensive list of biomarkers that will be studied in the currently enrolling, large, randomized, placebo-controlled phase III trial (BO21990 trial) in patients with newly diagnosed glioblastoma.

Efficacy reported from independent phase II studies

At the time that study AVF3708g was conducted, the NCI sponsored an independent, single-site, phase II study to evaluate Bv monotherapy for the treatment of patients with relapsed glioblastoma who had failed previous treatment for glioblastoma (study [NCI 06-C-0064E](#)).

Inclusion criteria for Study NCI 06-C-0064E

Patients must have progressed after radiation therapy

Patients must have recovered from the toxic effects of prior therapy: 2 weeks from any investigational agent, 4 weeks from prior cytotoxic therapy, two weeks from vincristine, 6 weeks from nitrosoureas, 3 weeks from procarbazine administration, and 1 week for non-cytotoxic agents, e.g., interferon, tamoxifen, thalidomide, cis-retinoic acid, etc. (radiosensitizer does not count). All patients enrolled in the study had received prior surgery, radiotherapy, and systemic therapy, including temozolomide.

Efficacy Results

The results were an ORR of 35%, median response duration of 3.7 months, PFS6 of 29%, and median OS of 7.8 months (Kreisl 2009), providing further support for the clinically meaningful efficacy results of study AVF3708g).

The NCI 06-C-0064E study that was presented in the variation application (efficacy data summarised in [Table 3](#) of the Clinical Overview) has since been published by Kreisl et al. In the publication of the NCI 06-C-0064 study, the authors state that a significant number of patients derived clinical benefit from bevacizumab treatment, manifested as decreased cerebral edema (24 (50%) patients), improved neurologic symptoms (25 patients (52%) had improved neurologic symptoms, including a number who were not progression-free at 6 months), and decreased requirement for corticosteroids (15 (58%) of 26 patients receiving corticosteroids at the start of treatment were able to decrease their requirement for corticosteroids by an average dose reduction of 59%). However, further data from this study are not available in the public domain, or to Roche.

The situation for study NCI 06-C-0064E was less clear in the protocol. However, the IRF report of this study stated that all patients enrolled in the study had received prior surgery, radiotherapy, and systemic therapy, including temozolomide.

Study NCI 06-C-0064E was an NCI-sponsored trial for which the MAH does not have direct access to the data. The NCI made the tumor assessment scans from the study available to Genentech, for an independent review of tumor assessments. A report of the independent review facility's (IRF) assessment of these scans was prepared by Genentech, and this report formed part of the variation application.

Additional results from the NCI 06-C-0064E study have been published since the MAA submission. A summary of the efficacy results from this publication and the IRF report (presented in the variation application) are presented in Table 3. The results from the publication are based on 48 patients enrolled into the study, rather than 56 patients as in the IRF report. The reason for this difference is that the manuscript was prepared by the authors' based on the first 48 glioblastoma patients enrolled into the trial (enrollment from January 2006 to July 2007), representing all patients that had been fully evaluated by the authors' at the time of the data cut-off used for the investigator's analysis. According to the Investigator's assessment, 17 of the 48 patients (35%) achieved radiographic response based on Macdonald criteria. Median progression-free survival (PFS) was 3.7 months (95% CI, 2.8 to 6.0 months). The 6-month PFS was 29% (95% CI, 18% to 48%). The 6-month overall survival was 57% (95% CI, 44% to 75%). Median overall survival was 7.1 months (95% CI, 4.8 to 12.4 months).

Table 3 Summary of Efficacy Results from Study NCI 06-C-0064E

Study [ref]	Study Medication Dosing	N	Response (%)			%			KM-Median Duration (months)	
			Complete	Partial	Overall	6-month PFS	12-month OS	PFS	Overall Survival	
NCI 06-C-0064E [8145] [8889]	Phase 2, NC, OL Bv10 mg/kg/q2w single-agent	56	0	20	20	N	NA	NA	NA	
	IRF Assessment Investigator Assessment	48	2	33	35	A	NA	3.7	7.1	

In addition, the publication reported that evidence for the clinical benefit of bevacizumab was provided by:

- 24 patients (50%) having decreased cerebral edema,
- 15 (58%) of 26 patients receiving corticosteroids at the start of treatment being able to decrease their requirement for corticosteroids by an average dose reduction of 59%,
- 25 patients (52%) having improved neurologic symptoms, including a number who were not progression-free at 6 months.

More recently, the results of a phase II study AVF3311s undertaken in a cooperative group setting to determine the efficacy and safety of Bv with irinotecan in relapsed glioblastoma demonstrated a PFS6 rate of 37%, with 21 of 57 patients progression-free at 6 months (Gilbert et al. 2009).

In conclusion, the results of studies AVF3708g, as well as study AVF3311s and the other investigator reported studies with bevacizumab in glioblastoma at relapse (presented in the Clinical Overview) all support the activity of bevacizumab at this dose in this indication. It is not possible to decide on the optimal schedule from the available data. The two-week and three-week schedules of bevacizumab have been accepted as equivalent. However, two- and three week schedules of irinotecan are probably not equivalent. The optimal schedule of irinotecan in this disease is still to be established.

The final published results of study NCI-06-C-0064E show somewhat shorter PFS and OS than in the pivotal study; median PFS 3.7 months and median OS 7.1 months vs median PFS 4.2/5.6 months (BV/BV+irinotecan) and median OS 9.3/8.9 months in the pivotal study. In addition the rate of PFS6 was smaller (29 %), than in the pivotal study (44%/58% (BV/BV+irinotecan)).

1. 2. 3. Clinical Safety

The safety of bevacizumab with or without irinotecan in patients with glioblastoma after relapse is derived from the pivotal Phase II, randomised, open-label trial (AVF3708g). In addition, further information on safety comes from NCI 06-C-0064E.

The methodology of safety assessments can be considered as standard and appropriate to evaluate safety in this patient population. Of note, specific events frequently observed in glioblastoma after relapse were collected as events of special interest, including seizure, haemorrhage and thromboembolism.

Patient exposure

In study AVF3708g, 84 patients in the Bevacizumab arm and 79 in the Bevacizumab+irinotecan arm received at least one dose of study medication during the planned treatment period. The number of Bevacizumab doses received (median 12 vs. 9) and the duration of Bevacizumab exposure (median 5.1 vs. 3.7 months) was increased in the Bevacizumab+irinotecan arm compared to the Bevacizumab alone arm. In the NCI-06-C-0064E study, 55 patients received at least one dose of Bevacizumab, and exposure was less than in study AVF3708g (median number of Bevacizumab doses 7, median duration of treatment of 2.8 months). In both studies, bevacizumab was administered at 10 mg/kg/q2w.

In the Bevacizumab+irinotecan arm of study AVF3708g, there was evidence that irinotecan was stopped in some patients a little earlier than bevacizumab (median number of doses of irinotecan 11, duration 4.9 months). At the time of the clinical cut-off for the analysis of AVF3708g, 22 patients (26%) in the Bevacizumab arm and 20 patients (24%) in the Bevacizumab+irinotecan arm were still continuing with bevacizumab treatment prior to progression. A total of 6 patients (7%) in the Bevacizumab arm, and 16 patients (20%) in the Bevacizumab+irinotecan arm had stopped bevacizumab for reasons other than PD or death, indicating that most patients were treated until progression or were still on trial treatment prior to progression.

Additionally, Bevacizumab+irinotecan was administered in the optional post-progression phase of study AVF3708g that was only open to patients initially randomised to the Bevacizumab alone arm. In total, 44 patients were enrolled in this phase of the study, with only 2 patients still being on treatment at the time of the clinical cut-off for the analysis.

The safety information in the target population for the present application is limited to 218 patients. This information is particularly relevant with regard to CNS complications and toxicity. However, there is a vast experience with Bevacizumab in other malignancies, including detailed information on adverse events.

Adverse events

In patients with glioblastoma treated with Bv or Bv+irinotecan after relapse:

- There were no unexpected toxicities with the use of bevacizumab in patients with this indication, the safety profile of bevacizumab being similar to that previously established in other cancer indications (mCRC, NSCLC, mBC, mRCC). In particular, there was no indication that Bv increased the following principal safety risks in this patient population:
 - clinically relevant intra-tumoral haemorrhage
 - thromboembolic events
 - seizures

- Deaths in both studies were mainly due to progressive disease. In total, 5.6% (7 out of 124 patients that died after receiving trial treatment) of the deaths were not directly attributed to the underlying

disease by the investigator. AEs that led to death were recorded as neutropenia infection (1), convulsion (1), pulmonary embolism (3, one associated with sudden death and one with cerebrovascular ischemia). Three of these patients had AEs that led to death that were considered to be possibly related to trial treatment by the investigator (neutropenia infection, convulsion, and one patient with both cerebrovascular ischemia and pulmonary embolism). The thromboembolic events are known risks in this patient population. The neutropenia infection and the convulsion events were also assessed by the investigator as possibly related to concomitant steroid use and immunosuppression, as well as underlying disease.

- More patients in the Bevcizumab+irinotecan arm (65.8%) than the Bevacizumab arm (46.4%) of study AVF3708g, experienced at least one Grade ≥ 3 AE. The difference was mainly due to the incidence of lymphopenia, neutropenia and leukopenia, fatigue, convulsion and AEs in the Gastrointestinal System Order Class. In part, this may reflect the longer safety follow-up of patients in this arm (6.1 vs. 4.3 months), but also the addition of the known toxicity profile of irinotecan.
- Within study AVF3708g, the use of Bevacizumab with irinotecan appeared to increase the number of patients that prematurely withdrew from Bevacizumab due to AEs (4.8% vs. 17.7%). However, despite this, exposure to Bevacizumab was longer in the combination arm (median 3.7 vs. 5.1 months). The incidence rate of premature withdrawal from Bevacizumab single-agent in study NCI-06-C-0064E (16%) was similar to that from the Bevacizumab+irinotecan arm of study AVF3708g.

In general, no new toxicities appeared in the pivotal and supportive studies.

Due to the lack of an internal control in the pivotal study AVF3708g, the MAH has not been able to clarify whether the described toxicity of Bv is comparable or worse than what would be expected from other therapies.

On the other hand the MAH has reviewed the safety data of study AVF3780 and the safety information for Bv across indications instead. In addition, the safety profile of Bv has been compared with supportive data from a second Phase II single-arm study (NCI 06-C.0064E) and published literature in approximately 860 BV-treated patients with relapsed GBM. Focus has also been put on events of special interest both in relation to the diagnosis and to the treatment with Bv.

No new safety signals have been identified. No additional risk has been identified in patients with recurrent GBM. Overall, the described safety profile of Bv in the sought indication seems to be 1) expectable from our previous experience with Bv, and last but not least 2) acceptable considering the gloomy prognosis, many co-morbidities and sequelae from other treatment modalities that are characteristic of patients with recurrent GBM.

Grade 3-5 Adverse Events

In study AVF3708g, Grade ≥ 3 AEs were reported in 39 patients (46.4%) in the Bevacizumab arm and in 52 patients (65.8%) in the Bevacizumab + irinotecan arm during the planned treatment period. Grade ≥ 3 AEs that occurred in $\geq 5\%$ of patients in either treatment arm are summarized in the table below. The most common of these AEs were hypertension (8.3%) and convulsion (6.0%) in the Bevacizumab arm; and convulsion (13.9%), neutropenia (8.9%) and fatigue (8.9%) in the Bevacizumab + irinotecan arm.

Study AVF3708g: Summary of Grade 3-5 Adverse Events with an Incidence of at least 5% in Either Treatment Arm during the Planned Treatment Period (Safety Population)

MedDRA Preferred Term	BV (n = 84)	BV/CPT-11 (n = 79)
Any Grade ≥ 3 adverse events	39 (46.4%)	52 (65.8%)
Aphasia	3 (3.6%)	6 (7.6%)
Confusional state	2 (2.4%)	4 (5.1%)
Convulsion	5 (6.0%)	11 (13.9%)
Deep vein thrombosis	2 (2.4%)	5 (6.3%)

Diarrhoea	1 (1.2%)	4 (5.1%)
Fatigue	3 (3.6%)	7 (8.9%)
Hypertension	7 (8.3%)	1 (1.3%)
Pneumonia	1 (1.2%)	4 (5.1%)
Pyramidal tract syndrome	1 (1.2%)	4 (5.1%)
Somnolence	1 (1.2%)	4 (5.1%)
Hypokalemia	3 (3.6%)	6 (7.6%)
Leukopenia	0 (0.0%)	5 (6.3%)
Lymphopenia	2 (2.4%)	6 (7.6%)
Neutropenia	1 (1.2%)	7 (8.9%)

BV = bevacizumab; CPT-11 = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities.

Deaths

In study AVF3708g, 38/84 patients (45.2%) in the Bevacizumab arm and 41/79 patients (51.9%) in the Bevacizumab + irinotecan arm died during the study or during follow-up, see table below. The majority of these deaths were considered by the investigator to be due to progressive disease.

Of the 5 deaths that were not due to progressive disease, 3 were attributed to AEs and occurred within 90 days of last Bevacizumab dose.

Neutropenia infection (patient 20153 in the Bevacizumab arm) assessed by the investigator as related to Bevacizumab treatment but could also be attributed to concomitant steroid administration and immunosuppression.

Pulmonary embolism (patient 20404 in the Bevacizumab arm) was assessed by the investigator as unrelated to Bevacizumab treatment.

Convulsion (patient 20251 in the Bevacizumab + irinotecan arm) was assessed by the investigator as related to Bevacizumab and irinotecan treatment with the underlying disease as a possible etiological factor.

In the NCI 06-C-0064E study, 45/55 patients (81.8%) were known to have died as of the clinical cut off date of 3 June 2008. The majority of these deaths (43/45) were due to progressive disease. Of the two remaining deaths, one was attributed to clinical deterioration due to the underlying disease and the other to toxicity from study treatment.

Three patients are listed as having a Grade 5 AE of 'death' (NCI-CTCAE pre-selected term). The cause of death for 2 of these patients, however, is given as progressive disease. The remaining death was attributed to toxicity from study treatment:

- Patient 23: the cause of death was progressive disease (unrelated to study drug).
- Patient 44: the cause of death was progressive disease; the patient developed a Grade 4 pulmonary embolism and discontinued study drug 18 days before death.
- Patient 59: death was a result of a Grade 4 cerebrovascular ischemia and a Grade 4 pulmonary embolism and was assessed by the investigator as due to toxicity related to the study drug.

Serious Adverse Events

In study AVF3708g, 22 patients (26.2%) in the Bevacizumab arm and 34 patients (43.0%) in the Bevacizumab + irinotecan arm experienced a SAE during the planned treatment period. SAEs reported in $\geq 2\%$ of patients during the planned treatment period are summarized in the table below. The most common SAE reported was convulsion (6.0% in the Bevacizumab arm and 11.4% in the Bevacizumab + irinotecan arm).

Study AVF3708g: Summary of Serious Adverse Events with an Incidence of at Least 2% in Either Treatment Arm during the Planned Treatment Period (Safety Population)

MedDRA Preferred Term	BV (n = 84)	BV/CPT-11 (n = 79)
Any serious adverse events	22 (26.2%)	34 (43.0%)
Cellulitis	1 (1.2%)	3 (3.8%)
Cerebral hemorrhage	1 (1.2%)	2 (2.5%)
Convulsion	5 (6.0%)	9 (11.4%)
Diarrhea	0 (0.0%)	2 (2.5%)
Deep vein thrombosis	1 (1.2%)	2 (2.5%)
Hyperglycemia	2 (2.4%)	0 (0.0%)
Pneumonia	0 (0.0%)	3 (3.8%)

BV = bevacizumab; CPT-11 = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities.

In conclusion, the number of serious adverse events is quite high. They are experienced by more than half the patients.

The number of deaths is high as expected in this deadly disease. However, there are a number of deaths attributable to the treatment. It is impossible to estimate the real effect of Bevacizumab on the incidence of deaths because of the lack of a comparator arm.

Laboratory findings

Analysis of post-baseline laboratory abnormalities by NCI-CTCAE grade in study AVF3708g did not reveal any new safety signals associated with Bevacizumab treatment).

Safety in special populations

In study AVF3708g, the incidence of AEs during the planned treatment period was generally consistent across age (< 65 years vs. ≥ 65 years), race (White vs. non-White) and gender (male vs. female patients).

In the Bevacizumab arm, differences ≥ 10% in the incidence of Grade ≥ 3 AEs across subgroups were seen for:

Hypertension with a higher incidence in patients ≥ 65 years (18.2% vs. 6.8%).

In the Bevacizumab + irinotecan arm, differences ≥ 10% in the incidence of Grade ≥ 3 AEs across subgroups were seen for:

Neutropenia, fatigue and deep vein thrombosis with a higher incidence in patients ≥ 65 years (17.6% vs. 6.5%, 17.6% vs. 6.5%, and 17.6% vs. 3.2%, respectively).

Neutropenia with a higher incidence in female patients (17.4% vs. 5.4%).

However, due to the small number of patients in each of the different subgroups, these results should be interpreted with caution.

Only patients with adequate renal and hepatic function at baseline were eligible for this study, hence subgroup analyses stratified by these factors were not performed.

No further data are presented on special populations. This is acceptable, considering the type of patients that the indication is applied for.

Immunological events

No immunological events are reported. This is acceptable considering the large number of patients treated with Bevacizumab for other tumours.

Safety related to drug-drug interactions and other interactions

There is no new information specific to Bevacizumab.

Discontinuation due to AES

In study AVF3708g, 4 patients (4.8%) in the Bevacizumab arm discontinued Bevacizumab due to an AE (all grades) during the planned treatment period. Any given AE leading to Bevacizumab discontinuation was reported in single patients only in this arm.

In the Bevacizumab + irinotecan arm, a total of 17 patients (21.5%) discontinued any component of study treatment due to an AE (all grades) during the planned treatment period. Fourteen patients (17.7%) discontinued Bevacizumab due to an AE; 7 of which (8.9%) were due to nervous system disorders (cerebral haemorrhage, cerebrovascular accident, convulsion, status epilepticus, RPLS). Single AEs leading to Bevacizumab discontinuation that occurred in $\geq 2\%$ of treated patients were cerebral haemorrhage (3.8%) and fatigue (2.5%).

Fourteen patients (17.7%) discontinued irinotecan due to an AE during the planned treatment period. The AEs leading to irinotecan discontinuation that occurred in $\geq 2\%$ of treated patients were fatigue (6.3%) and cerebral haemorrhage (2.5%).

In the NCI 06-C-0064E study, 9 patients (16.4%) discontinued Bevacizumab due to a Grade 3-5 AE. Six of these patients discontinued Bevacizumab due to venous thromboembolic events (3 with pulmonary embolism, 2 with deep vein thrombosis and 1 with thrombus). Of the remaining 3 patients that discontinued Bevacizumab, 1 discontinued due to vomiting; 1 due to an infection associated with Grade ≥ 2 lymphopenia; and 1 due to death, secondary to cerebrovascular ischemia and pulmonary embolism.

Treatment discontinuation due to adverse events was fairly common, but more often seen in the irinotecan treated patients. The influence of Bevacizumab is impossible to assess due to the lack of a comparator arm for this drug.

Adverse Events of Special Interest

The incidence of the AEs defined as of special interest for bevacizumab were specifically collected in AVF3708g only and were consistent with the previously established rates from patients with other types of cancer. Special attention is given below to those events of particular relevance to patients with recurrent glioblastoma, due to the inherent risks of this disease.

Seizure

In study AVF3708g, seizures occurred in 18% and 24% of the safety evaluable patients in the Bevacizumab and Bevacizumab+irinotecan arms, respectively. Of the 15 patients who experienced seizure in the Bevacizumab arm, 8 had a prior medical history of seizure. Similarly in the Bevacizumab + irinotecan arm, 14 of the 19 patients who experienced seizures had a prior medical history of seizure. Five patients (6.0%) in the Bevacizumab arm and 13 patients (16.5%) in the Bevacizumab + irinotecan arm had Grade 3-5 seizure AEs. Two patients experienced Grade 5 convulsion (one in each arm). In the NCI 06-C-0064E study, 5 patients (9.1%) had Grade ≥ 3 seizure AEs.

The occurrence of seizures is quite common in patients with glioblastoma, and it is part of the natural history of the disease. Comparison of incidence rates with expected rates in patients with glioblastoma after relapse are limited by the lack of a large series, and the inclusion of lower Grade gliomas in the published literature. However, available literature indicates that seizures can be expected to be experienced by 15-60% of patients with high-Grade glioma. Whether the number of patients with seizures in the studies presented is higher than would be expected is impossible to evaluate without a control group.

Wound Healing Complication

In study AVF3708g, 5 patients (6.0%) in the Bevacizumab arm and 2 patients (2.5%) in the Bevacizumab + irinotecan arm experienced wound-healing complications. Four of these patients (3 in the Bv arm and 1 in the Bevacizumab + irinotecan arm) experienced craniotomy wound-healing

complications. In the NCI 06-C-0064E study, 1 patient had a Grade 3 wound-healing complication, but no patient had a craniotomy wound-healing complication. Craniotomy wound healing complications have also been reported in other glioblastoma studies with bevacizumab.

For the purposes of historical comparison, data reported from the Glioma Outcomes Project indicated that patients with Grade 3 or 4 malignant gliomas who underwent a second operation had a peri-operative wound complication rate of 1.1%. In the initial surgery trial with carmustine-wafer, healing abnormalities occurred in 15.8% of carmustine-wafer treated patients and 11.7% of placebo recipients. In the setting of surgery for recurrent disease, healing abnormalities were reported as 14% in patients who received carmustine-wafers compared to 5% in those receiving placebo.

Wound healing complications are known to be associated with the treatment with Bevacizumab. The incidence in the studies presented here are not alarming, but the incidence of craniotomy healing complications is worrying because of the possible dire consequences of infection in this location.

Thromboembolic Events (Arterial and Venous)

The incidence of venous thromboembolic events (VTEs) in study AVF3708g was 3.6% in the Bevacizumab arm and 10.1% in the Bevacizumab + irinotecan arm. All but one event were Grade ≥ 3 in severity. The incidence of deep vein thrombosis accounted for the difference between the treatment arms. In the NCI 06-C-0064E study, 7 patients (12.7%) developed Grade ≥ 3 VTEs, with pulmonary embolism being the most common (4 patients).

The incidence of arterial thromboembolic events (ATEs) in study AVF3708g was 4.8% in the Bv arm and 6.3% in the Bv + irinotecan arm. No Grade ≥ 4 ATEs were reported, but 2 patients in each arm had Grade 3 events (1 myocardial infarction, chest pain, cerebral ischemia, and 1 troponin increased – with Grade 2 myocardial ischemia). In the NCI 06-C-0064E study, only one Grade ≥ 3 ATE occurred, a CNS cerebrovascular ischemia (that together with pulmonary embolism resulted in death).

Clinically apparent deep vein thrombosis or pulmonary emboli that require anticoagulation drugs may occur in 20-30% of patients with primary brain tumours, although the Grade is not reported. In study AVF3708g, 14% of patients in the Bv arm and 29% in the Bv+irinotecan arm, received concomitant anticoagulants. The rate of VTEs in the AVF3708g and NCI study was consistent with the rate of symptomatic VTEs seen in non-bevacizumab studies in patients with glioblastomas – 9.7%.

Arterial and venous thromboembolic events are known to be associated with the treatment with Bevacizumab. The incidence in the studies presented here are not alarming, but they do underline, that the side effects of Bevacizumab are not trivial.

Cerebral Haemorrhage

In study AVF3708g, 2 patients (2.4%) in the Bevacizumab arm and 3 patients (3.8%) in the Bevacizumab+irinotecan arm experienced cerebral haemorrhage events. One of these was of Grade 4 severity (Bevacizumab+irinotecan arm), 3 were Grade 1 and 1 was Grade 2. In the NCI 06-C-0064E study, no Grade ≥ 3 cerebral haemorrhage events were reported).

Comparisons with the literature are confounded by small series and the inclusion of other pathologic conditions that may predispose a patient to haemorrhage. Although clinically non-relevant haemorrhage has been described in the literature, the rate of clinically relevant cerebral haemorrhage appears to be low in series published to date. In a retrospective clinico-pathological review of consecutive brain tumour cases, up to 29% of patients with mixed oligodendroglioma/astrocytoma experienced cerebral haemorrhage. In an autopsy series of 1800 primary and secondary brain tumours, instances of massive bleeding occurred in 2.4% of cases. Glioblastoma patients receiving anticoagulant agents that are maintained within the therapeutic range do not appear to have a greater risk of intracranial bleeding than those who do not need anticoagulant drugs.

The question of cerebral haemorrhage is a very important one. From the data presented the risk of bleeding is not very high, with only three cerebral haemorrhages, one of them grade 4. Patients with brain tumours, primary or secondary, have a considerable risk of bleeding in the tumour, and the figure presented for these 163 patients is rather low. This is probably attributable to the fact that AEs were only registered during the planned treatment period. More patients are likely to have experienced haemorrhages after the end of treatment and, in particular, after progression. Information on AEs after the planned treatment period would also be relevant. However, in the pivotal study, as there is no control arm, this information would be difficult to interpret, because the disease in itself increases the risk of intracerebral haemorrhage.

The MAH has reviewed all available safety data regarding the risk of cerebral haemorrhage during treatment with Bv in patients with brain metastases, both from randomized, controlled clinical trials, the MAH's global safety database, epidemiological data and recently published reports on the subject.

Overall, the risk of cerebral haemorrhage is seemingly not increased in bevacizumab treated patients with primary and secondary brain tumours. However, this statement is based on relatively limited data. Only more experience in these patients can reveal if there is an increased risk.

In March 2009 the CHMP approved the removal of a contraindication related to patients with brain metastases from the Avastin SPC.

Furthermore, the MAH has been asked to provide an update of the safety data from study AVF3708g, with specific focus on VTE, cerebral haemorrhage, wound-healing complications and infections. The MAH has presented safety data including 42 patients who continued to receive trial treatment after the initial cut-off. The updated safety analysis does not reveal new safety signals. The incidence of adverse events of special interest was consistent with that described in the AVF3708g CSR and similar to that observed in other Bv Phase III trials across indications as well as historical data of patients with glioblastoma.

Other Significant Events/Observations

One patient in the Bevacizumab+irinotecan arm of study AVF3708g had reversible posterior leukoencephalopathy syndrome. No Grade \geq 3 RPLS events were reported in the NCI 06-C-0064E study.

Safety data from NCI-06-C-0064E

As reported in the publication and summarised in Table 4, the most frequently observed severe adverse events (defined as Grade \geq 3) possibly or probably related to bevacizumab according to the investigator's assessment of causality, were thromboembolic events (these occurred in six of the 48 patients - 12.5%). Three of these events were pulmonary emboli and one was a cerebral vascular event. The second most frequent bevacizumab-related adverse event was hypertension. All cases were ultimately controlled with antihypertensive medication, and no patient required removal from study due to hypertension. Overall, six patients (12.5%) were removed from study for bevacizumab-associated adverse events (five thromboembolic events, one bowel perforation). Two additional patients were removed due to non-bevacizumab-related adverse events (one seizure, one opportunistic infection). No patients had intracranial hemorrhage. No other safety data were reported in the publication.

Table 4 Bevacizumab-Related Adverse Events (Investigator Assessment)

Toxicity	No. of Events			
	Grade 1	Grade 2	Grade 3	Grade 4
Thromboembolic event			2	4
Hypertension		4	2	
Hypophosphatemia		1	2	
Thrombocytopenia		2	1	
Hepatic dysfunction			1	
Proteinuria	1			
Bowel perforation			1	

Source = [\[8889\]](#)

No new safety signals were found in this study.

Overall conclusion on safety

The adverse events observed with bevacizumab alone were consistent with previous reports. The combination of bevacizumab and irinotecan did not have a major impact on the known safety profiles of either bevacizumab or irinotecan individually. Without a direct comparison it is difficult to assess the rate of treatment related adverse events for bevacizumab. Nevertheless, the overall safety profile of bevacizumab in glioblastoma seems comparable to the known safety profile of bevacizumab in other indications. In addition, the rate of complications of special interest for glioblastoma patients, is comparable for bevacizumab treated patients and historical controls. Considering the experience with bevacizumab across indications, the safety profile seems acceptably defined. However, adverse events of special interest for glioblastoma patients should be closely monitored.

The MAH recognizes that the safety data in some of the historic controls (including 3 large pooled analyses by Wong et al, 1999, Ballman et al. 2007 and Lamborn et al. 2008) were limited. Therefore, the MAH performed a more comprehensive and critical evaluation of the safety profile of Bevacizumab in the pivotal study compared to other available, contemporary regimens. Confounding factors were discussed in detail. The updated safety analysis did not reveal new safety signals. The incidence of adverse events of special interest was consistent with that described

Pharmacovigilance/RMP

The MAH provided an updated Risk Management Plan with the application for an extension of indication for Avastin (bevacizumab). No new safety concerns specific for the applied indication have been identified.

Discussion at the SAG-Oncology

The SAG-O was consulted on the following questions:

- Does the SAG believe that an actively controlled study is necessary to decide on the benefit / risk of treating relapsed glioblastoma patients with bevacizumab and is such a study feasible?

The SAG agreed that the MAH has not submitted sufficient evidence of efficacy of bevacizumab in the applied indication. However, the phase II data presented are very encouraging and warrant further investigation of the efficacy and safety of bevacizumab in glioblastoma. The best way to provide convincing clinical evidence of efficacy and safety is through randomised controlled trials in the claimed

indication and using an appropriate clinical endpoint such as overall survival, as well as a number of secondary endpoints that are conventionally studied in this setting, in particular patient-reported outcomes. It is acknowledged that randomised trials are difficult to conduct in this rare disease setting, but this should not prevent such trials to be conducted successfully. Although many neuro-oncologists are hopeful and may already use bevacizumab for some of their patients, for example through compassionate use programmes or similar programmes, this is not unusual with new agents that show promising activity and *per se* does not undermine the feasibility of randomised trials using a parallel control without bevacizumab, in the proposed indication. However the definition of this control is not unequivocal in the absence of recognized therapeutic options.

Besides safety and efficacy, an aspect that should also be addressed is further optimising the dose of bevacizumab in this indication.

According to a minority view, however, the window of opportunity for conducting randomised controlled trial with this agent in this indication is no longer available as sufficient evidence of efficacy has been generated (see also minority view in answer to question No. 2).

- Would Bevacizumab therapy with the currently described safety profile, a steroid-stabilizing or even sparing effect, a stabilizing (or improving) effect on neurocognition and performance, and a demonstration of an ORR in the area of 30% (monotherapy), a PFS6 of about 40% and no clear - but at best - a modest prolongation of the OS, be considered as sufficient evidence of clinical benefit to patients with recurrent GBM compared to existing therapies?

The data submitted are from exploratory phase II studies. These studies allow concluding that bevacizumab has activity in the applied indication, as measured by the radiological endpoint of objective response according to the criteria used in the study. However, the validity of response rate as a surrogate for overall survival or other important clinical endpoints has not been established in this disease and for this agent. The responder analysis presented by the MAH does not establish the validity of response as a predictor for survival as this may just be a prognostic indicator independent of treatment. Furthermore, one needs to be particularly cautious in interpreting response data for this class of agents that can interfere with contrast enhancement. There are doubts on whether contrast-enhancement MRI is a suitable method to monitor bevacizumab effects on richly vascularized tumours like GBM, as this may merely be an indication of the decreased blood flow, without altering the tumour cell content. Thus, objective response and other endpoints that include a radiological component, are not considered to be reliable to assess clinical benefit with this type of agent. Notwithstanding these weaknesses, the objective response rate results observed are not considered dramatic, and one cannot reasonably assume that this activity should translate in a clinical benefit.

Concerning other endpoints that are claimed to measure clinical benefit, the endpoints of progression-free survival and overall survival are difficult to interpret in the absence of a randomised comparison against an adequate control. Furthermore, the progression-free survival suffers of the same drawbacks described for response. The historical comparisons presented may be promising but are not enough to establish efficacy. The results observed are not considered dramatic, and the results from historical comparisons cannot be considered as reliable.

Concerning the claimed effect of maintaining or improving neuro-cognitive function, the longitudinal analyses presented are difficult to interpret due to missing data. Lastly, the claimed steroid-sparing effect and the effect on performance status are difficult to interpret as it is unclear if rigorous methodology has been used in order to avoid bias.

According to a minority view, however, the data presented so far all point in the same direction and are convincing, particularly looking at the long duration of some responses and the relatively early onset. Taken all together the data presented allow assuming that the product can be of clinical benefit to some patients, particularly if responding to treatment after the first few cycles.

Overall Discussion and Benefit-Risk Assessment

The MAH has emphasized that little progress has been obtained in the management of relapsed GBM for several decades and that the currently available therapies have proved disappointing with RRs rarely exceeding 10% and typically fewer than 30% of patients being progression-free at 6 months. Ever since temozolomide became the treatment of choice as adjuvant chemotherapy for newly diagnosed patients with GBM, there has been no established “gold standard” when it comes to the systemic treatment of recurrent malignant GBM. Consequently, a control arm for study AVF3708g was not deemed feasible by the study investigators, especially in view of the promising results of bevacizumab activity in GBM in early, available phase II data. Furthermore, the MAH puts focus on the fact that the design and methodology of this phase II study were robust and appropriate: It included a central pathology review, response assessment by use of MRI at serial 6-week intervals, and an independent radiological review of tumour responses.

The data submitted are from exploratory phase II studies. These studies allow concluding that bevacizumab has activity in the applied indication, as measured by the radiological endpoint of objective response according to the criteria used in the study. However, the validity of response rate as a surrogate for overall survival or other important clinical endpoints has not been established in this disease and for this agent. The responder analysis presented by the MAH does not establish the validity of response as a predictor for survival as this may just be a prognostic indicator independent of treatment. Furthermore, one needs to be particularly cautious in interpreting response data for this class of agents that can interfere with contrast enhancement. Thus, objective response and other endpoints that include a radiological component, are not considered to be reliable to assess clinical benefit with this type of agent. Notwithstanding these weaknesses, the objective response rate results observed are not considered dramatic, and one cannot reasonably assume that this activity should translate in a clinical benefit. Whether bevacizumab is truly superior in terms of overall survival, PFS6 or patient reported outcomes to other available therapies is unknown due to the lack of directly comparative trials. The results of study NCI 06-C-0064E provide some support for the anti-tumour activity of bevacizumab in patients with relapsed glioblastoma

The feasibility to conduct an actively controlled study in relapsed grade IV glioblastoma was discussed at the Oral Explanation. The MAH believes that an actively controlled trial would be challenging and is not necessary as the benefit of bevacizumab is already established. The improvements seen in objective response rate, progression free survival, steroid use, performance and neurocognitive function represent an important and clinically meaningful benefit for the patients. The customised surrogate endpoints seen with MRI imaging are relevant and valid in the context of this anti-VEGF therapy and they translate into clinical benefit.

It should be noted that two large, randomized, placebo-controlled phase III trials are currently assessing the efficacy and safety of bevacizumab in patients with newly diagnosed GBM.

There are currently no comparative trials running in the relapsed high grade (IV) glioma.

The robustness of the endpoints was discussed. The MAH stated that PFS6 and ORR are robust, valid and predict clinical benefits for GBM patients. Challenges with MRI-imaging under treatment with a VEGF-inhibitor were addressed by using rigorous methodology of tumour assessment according the modified McDonald criteria, independent review and confirmation by the NCI study. The CHMP considered that endpoints that are claimed to measure clinical benefit, are difficult to interpret in the absence of a randomised comparison against an adequate control. Furthermore, the progression-free survival suffers of the same drawbacks described for response. The historical comparisons presented may be promising but are not enough to establish efficacy. The results observed are not considered dramatic, and the results from historical comparisons cannot be considered as reliable. Concerning the claimed effect of maintaining or improving neurocognitive function, the longitudinal analyses presented are difficult to interpret due to missing data. Lastly, the claimed steroid-sparing effect and the effect on performance status are difficult to interpret as it is unclear if rigorous methodology has been used in order to avoid bias.

The overall safety profile of bevacizumab in glioblastoma seems comparable to the known safety profile of bevacizumab in other indications.

In summary, the MAH has submitted data from exploratory phase II studies. These are compared with historical or contemporary external controls. The results indicate that bevacizumab may be a promising treatment in relapsed glioblastoma with an overall response rate in the area of 30% (as monotherapy), a Progression Free Survival at 6 months of about 40% and at best a modest prolongation of the Overall Survival while the safety profile is consistent with what is currently known for bevacizumab. These data need cautious interpretation in view of concerns related to the uncontrolled nature of the trial, the validity of response rate as a surrogate for overall survival and possible issues when applying MRI response criteria in the setting of VEGF inhibition.

Although the phase II data presented are encouraging and warrant further investigation of the efficacy and safety of bevacizumab in glioblastoma, the CHMP considered that the MAH has not submitted sufficient evidence of efficacy of bevacizumab in the applied indication as a randomised controlled trial has not been performed.

It is acknowledged that randomised trials are difficult to conduct in this rare disease setting, however the CHMP considers that such a trial is feasible and necessary to confirm clinical benefit of bevacizumab.

For the reasons stated above the CHMP concluded that the benefit-risk of Avastin (bevacizumab) alone or in combination with irinotecan in the treatment of patients with glioblastoma (WHO Grade IV malignant glioma) after relapse, cannot be determined.

Some members of the CHMP expressed a divergent position as follows:

Although the results are derived from exploratory phase II studies, the steroid-sparing and stabilizing (or improving) effect on neurocognition and performance, an overall response rate in the area of 30% (monotherapy), a Progression Free Survival at 6 months of about 40% and a modest prolongation of the Overall Survival in the context of a well known safety profile can be considered as sufficient evidence of clinical benefit to patients with recurrent GBM with a poor prognosis and in view of the high unmet medical need in this clinical setting.

It is not reasonable to expect the MAH to conduct a randomised controlled trial with this agent in this indication as the window of opportunity is no longer available as sufficient evidence of efficacy has been already generated.

According to a minority view, however, the data presented so far all point in the same direction and are convincing, particularly looking at the long duration of some responses and the relatively early onset. Taken all together the data presented allow assuming that the product can be of clinical benefit to some patients, particularly if responding to treatment after the first few cycles. Therefore, members of the CHMP expressed a divergent position as follows:

“- Although the results are derived from exploratory phase II studies, the steroid-sparing and stabilizing (or improving) effect on neurocognition and performance, an overall response rate in the area of 30% (monotherapy), a Progression Free Survival at 6 months of about 40% and a modest prolongation of the Overall Survival in the context of a well known safety profile can be considered as sufficient evidence of clinical benefit to patients with recurrent GBM with a poor prognosis and in view of the high unmet medical need in this clinical setting.

-It is not reasonable to expect the MAH to conduct a randomised controlled trial with this agent in this indication as the window of opportunity is no longer available as sufficient evidence of efficacy has been already generated.”

II. CONCLUSION

On 19 November 2009 the CHMP considered this Type II variation and agreed that the changes to the terms of the Marketing Authorisation should be refused on the following grounds:

- The main evidence of efficacy is based on data from exploratory trials. The results in terms of objective response rate cannot be considered dramatic and the validity of objective response rate as a surrogate endpoint for clinical benefit has not been established.
- The results presented in terms of overall survival and progression-free survival, are difficult to interpret due to the lack of a randomised concurrent control.
- The MAH has not submitted sufficient evidence of efficacy of bevacizumab in the applied indication. In the absence of an established efficacy, the CHMP was of the opinion that a positive benefit-risk for the indication for Avastin, *“as a single agent, or in combination with irinotecan, in the treatment of patients with glioblastoma after relapse”* has not been established.