Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Bevacizumab

Proprietary Product Name: Avastin

Sponsor: Roche Products Pty Ltd

March 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indication
Decision:	Approved
Date of decision:	10 February 2010
Active ingredient:	Bevacizumab

Product name:	Avastin
Sponsor's name and address:	Roche Products Pty Ltd 4-10 Inman Road Dee Why NSW 2099
Dose form:	Solution for IV infusion
Strengths:	4 mL and 16 mL
Container:	Glass vials
Pack sizes:	100 mg pack containing one 4 mL single-dose vial 400 mg pack containing one 16 mL single-dose vial
Approved therapeutic use:	As a single agent, for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy
Route of administration:	Intravenous infusion
Dosage:	10 mg/kg given every 2 weeks or 15 mg/kg given every 3 weeks

Product background

The incidence of malignant gliomas is approximately 5 per 100,000 with about 12,000 new cases per year in the US. High grade malignant gliomas include Glioblastoma Multiforme (GBM – WHO Grade IV), Anaplastic Astrocytoma (AA – WHO Grade III) and Ananplastic Oligodendroglioma (AOD – WHO Grade III).

The mainstay of treatment has been surgery plus radiotherapy with/without chemotherapy. Temozolomide has increased median survival from 12.1 months with radiotherapy alone following surgery to 14.6 months with a 2-year survival of 26% (Stupp et al. 2005).[1] After the first recurrence, response to conventional chemotherapy is poor with 6-month progression-free survival (PFS) of 15%, the median overall survival of 25 weeks and an objective response rate of 5% (Wong et al.1999).[2]

A potentially significant advance in the treatment of high-grade glioma is the development of anti-angiogenic agents. A phase II trial was proposed by the National Cancer Institute (NCI) on the basis that malignant gliomas over-express several growth factors including vascular endothelial growth factor (VEGF). Bevacizumab, a humanised monoclonal antibody that targets VEGF to inhibit endothelial cell proliferation and tumour growth, has demonstrated activity as a single agent and in combination with chemotherapy in colorectal cancer, non small cell lung cancer, renal cell cancer, and breast cancer. Bevacizumab in combination with irinotecan was previously trialled in a phase II study (Vredenburgh et al. 2007) of patients with previously treated malignant glioma.[3] The results from this trial demonstrated 6-month PFS of 46% and objective response rate of 57%.

[1] Stupp R, Mason WP, van den Bent MT et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005; 352: 987-996.
[2] Wong ET, Hess KR, Gleason MJ et al. Outcomes and prognostic factors in recurrent glioma patients enrolled onto Phase II clinical trials. J Clin Oncol 1999; 17: 2572.
[3] Vredenburgh JJ, Desjardins A, Herndon JE et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007; 30: 722-4729.

The currently approved indications for bevacizumab are for the treatment of:

- Metastatic colorectal cancer
- Locally recurrent or metastatic breast cancer
- Advanced, metastatic or recurrent non-squamous Non Small Cell Lung Cancer (NSCLC)
- Advanced and/or metastatic renal cell cancer

The proposed indication is for:

- Relapsed high grade malignant glioma: Avastin as a single agent or in combination with irinotecan is indicated for the treatment of patients with high grade relapsed malignant glioma.

Regulatory status

A similar application has been approved in the US (5 May 2009), New Zealand (17 September 2009) and Switzerland (24 July 2009) as well as Albania, Dominican Republic, El Salvador, Hong Kong, India, Moldova and Ukraine. The approvals in the US and New Zealand are only for monotherapy and only for Grade IV disease. An application has been submitted in the European Union (EU) (12 Dec 2008) and Canada (Q1 2009).

Bevacizumab has been designated as an Orphan Drug in Australia for the indication of malignant glioma. According to information provided by the Australian Institute of health and Welfare (AIHW) the incidence of glioma in Australia is approximately 800 cases per annum.

Product information

The approved product information current at the time this AusPAR was prepared is at Attachment 1.

II. Quality findings

Drug product

Avastin is a clear to slightly opalescent, colourless to pale brown sterile solution for intravenous infusion. It is available in 100 mg and 400 mg single dose vials containing 4 ml and 16 ml, respectively of bevacizumab (25 mg/ml).

Quality summary and conclusions

There was no requirement for a quality evaluation in an application of this type.

III. Nonclinical findings

Nonclinical summary and conclusions

There was no requirement for a nonclinical evaluation in an application of this type.

IV. Clinical findings

Introduction

The sponsor has submitted two studies in support of an application for extension of indication to include bevacizumab alone or in combination with irinotecan for the treatment of patients with relapsed Grade IV malignant glioma. These were:

- the pivotal Study AVF3708g - a phase II study in patients with WHO Grade IV malignant glioma in first or second relapse, and
- Study NCI-06-C-0064E - an open-label, single site study of bevacizumab in the treatment of patients with recurrent high-grade malignant gliomas (WHO Grades III and IV).

The studies are summarised in Tables 1 and 1a. The two studies were supported by a literature based submission which contained data from over 230 patients described in 31 publications to support approval of bevacizumab for the treatment of Grade III gliomas.

Pharmacokinetics

There were no pharmacokinetic data provided in the application.

Pharmacodynamics

There were no pharmacodynamic data provided in the application.

Efficacy

Pivotal Study AVF3708g: A Phase II, multicentre, randomized, non-comparative, clinical trial to evaluate the efficacy and safety of bevacizumab alone or in combination with irinotecan for treatment of glioblastoma multiforme in first or second relapse. The objectives of the trial were:

Primary

- To evaluate 6-month progression-free survival (PFS) in patients with glioblastoma multiforme (GBM) in first and second relapse treated with bevacizumab or bevacizumab + irinotecan.
- To evaluate the objective response rate in patients with GBM in first or second relapse treated with bevacizumab or bevacizumab + irinotecan.

Secondary

- To characterize the safety of bevacizumab alone or in combination with irinotecan in patients with first or second relapse.
- To evaluate the efficacy of bevacizumab alone or in combination with irinotecan in patients with GBM in first or second relapse, as measured by the following:

1. PFS, as determined by the IRF[4]

[4] IRF _ Independent Radiology Facility – facility for review of radiology studies and relevant clinical information by a team of expert neuroradiologists and oncologists.

2. Duration of objective response, as determined by the IRF
3. Overall survival

The patients were recruited at 11 centres in the US. Eligible patients with histologically confirmed GBM in first or second relapse were randomized 1:1 into the bevacizumab alone arm (BV) and the bevacizumab + irinotecan arm (BV/CPT) using an interactive voice recognition system (IVRS). Selection criteria are summarised in Table 1.

Table 1: Summary of Study AVF3708g

Study design	Dose, Frequency, Duration	No. of patients	Results
Ph II, multicenter (11 US sites) randomized (1:1), non-comparative clinical trial of bevacizumab alone or in combination with irinotecan for treatment of GBM in first or second relapse. ***Objectives*** *Primary objective:* · 6-month PFS · Objective response rate (ORR) *Secondary objective:* · Safety · PFS by IRF · Duration of OR · OS ***Inclusion:*** Karnofsky ps >70% Life expectancy >12W Radiographic evidence of disease progression (min 1 cm in 1 diameter on MRI within 14 days of Tt 1st relapse is after: Prior radiotherapy + Temo 2nd relapse is after: Prior surgery & radiotherapy/+chemo ***Efficacy endpoint:***	<u>Bevacizumab:</u> 10 mg/Kg, IV once every 2 weeks. Max of 104 W <u>Irinotecan:</u> 340mg/m^2 over 90 min every 2W for pts on EIAEDs **or** 125mg/m^2 over 90 min every 2W for others. Max of 104W	Planned:160 Analysd:167 **ITT:** BV:85 BV/CPT:82 **PP:** BV:84; BV/CPT:79	***Efficacy*** *6M PFS* Arm 1: 42.6% Arm 2: 50.3% P<0.0001 **OR** Arm 1: 28.2% Arm 2: 37.8% P<0.0001 *Duration of response* Arm 1: 5.6 M Arm 2: 4.3 M *OS* Arm 1: 9.3 M Arm 2: 8.8 M ***Safety*** *Grade >3 AE* Arm 1: 39 (46.4%) (hypertension 8%; convulsions 6%) Arm 2: 52 (66%) (convulsions 14%; neutropenia 9%; fatigue 9%) *AE: Special interest* Hypertension, proteinuria, thromboembolic events, & GI perforation, rates similar to other

Study design	Dose, Frequency, Duration	No. of patients	Results
6-month PFS IRF assessment of ORR. Assessments on D0 & then D1 of each 6/52 cycle ***Safety endpoint:*** AEs, SAEs ***Statistics*** Historical controls were used (salvage chemotherapy) ***Primary endpoint:*** **PFS:** Stat.sig 6M PFS >15% in arms 1&2 **OR:** CR/PR on two consecutive times by IRF. Arm 1: Stat. sig ORR >5% Arm 2: Stat. sig ORR >10%			tumours *CNS: Haemorrhage* Arm 1: 2 (Grade 1) Arm 2: 3 (Grades 1, 2 & 4) *Wd healing probs* Arm 1: 5; Arm 2: 2 *Discontinuations* Bevacizumab: Arm 1: 4; Arm 2: 14 Irinotecan: Arm 2: 14

For patients in first relapse, prior treatment may have included radiotherapy and temozolomide. Prior surgery could be biopsy, partial resection or full resection. For patients in second relapse, prior treatment may have included surgery and radiotherapy only, or surgery, radiotherapy and chemotherapy. All the patients should have received temozolomide in their first-line treatment or in the treatment of relapse. All the patients received bevacizumab 10 mg/kg every 2 weeks. The initial dose of irinotecan was 340 mg/m^2 administered intravenously (IV) over 90 minutes every other week for patients in the BV/CPT arm (Arm 2) who were taking enzyme inducing anti-epileptic drugs (EIAEDs). For those not taking EIAEDs, the initial dose was 125 mg/m^2 IV over 90 minutes every other week.

Treatment was continued for 104 weeks in the absence of disease progression or discontinuation.

Response was determined using modified Macdonald criteria: complete response (CR), complete disappearance of tumour; partial response (PR), at least 50% decrease in the sum of products of the two largest perpendicular diameters of all measurable lesions. A complete response (CR) was determined if the magnetic resonance imaging (MRI) criteria for CR were met and the corticosteroid level was within physiological levels. A complete response (CR) can be determined only if the patient no longer requires corticosteroid treatment. A partial response (PR) was determined if the MRI criteria for PR were met and the corticosteroid dose at that time was the baseline corticosteroid dose. A baseline corticosteroid dose is defined as the highest corticosteroid daily dose during the first cycle (6 weeks) of treatment.

Patients in Arm 1, who experience disease progression may, at the discretion of the investigator, also receive irinotecan within 28 days of the date progression was documented by MRI scan. The patient would be discontinued from the study if there was severe toxicity or progression a second time.

Patients in Arm 2 (BV/CPT) who experience severe toxicity with one of the 2 agents may discontinue that agent and continue on a single agent for the balance of the 104 week treatment period in the absence of disease progression or discontinuation.

All the patients from both arms of the study, even if discontinued from the study, were followed up for survival until death, loss to follow-up, patient request for withdrawal or study termination by the sponsor. The study flowchart was described in Figure 1.

IRF oncology review: Independent review of MRIs were performed at the Independent Review facility (IRF) up to the time of the final analysis, by which time all the patients were expected to have at least 6 months follow-up. The review consisted primarily of the radiology studies, review of corticosteroid use, photographs and other relevant information from neuro-radiologists and oncologists. Corticosteroids, used for the management of tumour associated cerebral oedema and in the treatment of drug related nausea, can have an effect on blood-brain barrier permeability and hence on tumour measurements. Two listings of corticosteroid usage were obtained from the Case Report Form (CRF): one with all administered corticosteroids and the other with corticosteroids not given for chemoprophylaxis. In this study, efficacy was determined by the IRF using the modified Macdonald criteria, exclusive of corticosteroids given for chemoprophylaxis.

Analysis population: The primary efficacy analysis population was the ITT population defined as all the patients who were randomized, regardless of whether they received study treatment. The safety population were patients who had received at least one dose of study treatment.

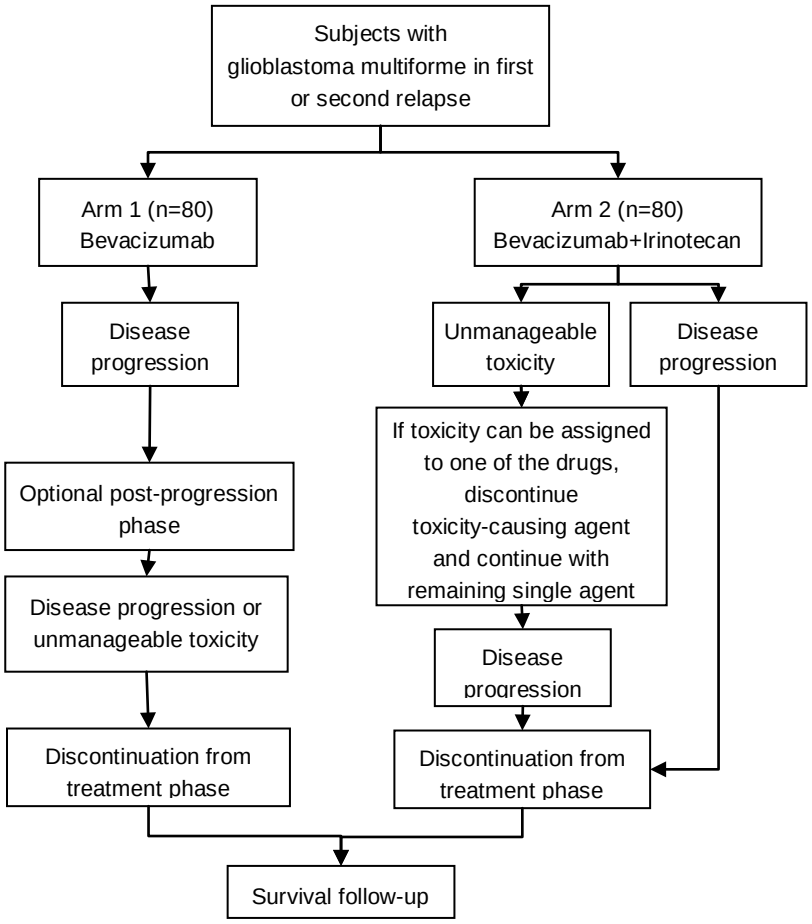
Efficacy endpoints

Primary efficacy endpoints

The primary efficacy endpoints were IRF assessments of 6-month PFS and objective response rate 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. Historical controls used to establish the null hypotheses for these endpoints was based on a study by Wong et al in 375 patients with recurrent glioma, drawn from 8 consecutive phase II chemotherapy trials. The study found the 6-month PFS was approximately 15%, overall survival, 25 weeks, and an objective response rate, 5%.

The Six-month PFS was defined as the percentage of patients who remained alive and progression free at 24 weeks. PFS was the time from randomisation to documented disease progression (as determined by the IRF using the modified Macdonald criteria), clear clinical progression in the absence of MRI determination of progression, or death from any cause, whichever occurred first. The date of MRI determination of progression, if conducted, was documented as the progression date for that patient.

Figure 1 Study Design



Note: Patients received study treatment (bevacizumab and/or irinotecan) for up to 104 weeks of treatment from Day 0 in the absence of disease progression or discontinuation. Independent review of MRIs occurred only for studies performed up to the time of the final analysis, when all randomized patients had been followed for at least 6 months.

The data were censored at the last tumour assessment date of those switching over to alternative anti-tumour therapy. For patients who experienced disease progression or died more than 42 days after the last dose of study treatment, the data were censored at the date of the last tumour assessment prior to the last dose of study treatment plus 42 days. The hypothesis tested at the 0.025 level of significance in this study was that the 6-month PFS following treatment with bevacizumab alone or in combination with irinotecan was statistically significantly > 15%.

The Objective response was defined as a CR or PR determined on two consecutive assessments > 4 weeks apart as determined by the IRF using the modified Macdonald criteria. The objective response rate was the percentage of patients enrolled in each treatment arm who were judged to have an objective response.

In Arm 1, the objective response rate to salvage chemotherapy was assumed to be approximately 5% (Wong et al). The hypothesis tested at the 0.025 level of significance was that treatment with bevacizumab alone was associated with an objective response rate that was statistically significantly > 5%.

In Arm 2, objective response rate to salvage chemotherapy was assumed to be 10%. The hypothesis tested at the 0.025 level of significance was that treatment with bevacizumab plus irinotecan was associated with an objective response rate that was statistically significantly > 10%.

Secondary efficacy endpoints

These were PFS as determined by IRF, duration of objective response as determined by IRF, and overall survival.

PFS (as determined by IRF) was the time from randomisation to documented disease progression as determined by the IRF, using the modified Macdonald criteria, clear clinical progression in the absence of MRI determination of progression, or death from any cause, whichever occurred first. The Kaplan-Meier method was used to estimate PFS for each arm. The data of patients who received alternate therapy before disease progression were censored at the last assessment date prior to receiving alternate therapy. The data for patients experiencing disease progression or death > 42 days after the last dose were censored at the date (+ 42 days) of the last tumour assessment prior to the last dose.

Duration of Objective Response (based on modified Macdonald criteria) was defined as the time from first tumour assessment that supported the patient's objective response to the time of disease progression, as determined by IRF, clear clinical progression in the absence of an MRI determination of progression, or death due to any cause, whichever occurred first.

Overall Survival for each treatment arm was defined as the time from randomisation to death from any cause.

The exploratory efficacy endpoints included 6-month progression-free survival, progression-free survival, and duration of objective response, as determined by the investigators. In addition, neurocognitive function was assessed using standard psychometric instruments known to be affected by brain tumours and treatments. These tests measured memory, visual-motor scanning speed and executive function.

Determination of sample size

In Arm 1 (BV), 6-month PFS of ≥ 28% would indicate that bevacizumab monotherapy has clinically meaningful activity in this population. 80 patients would provide ~80% power to detect a 13% increase in 6-month PFS, from 15% to 28% at the 2.5% two-sided significance level. The 97.5% confidence intervals (CI) were 17%, 39%.

An objective response rate (ORR) of ≥ 18% would indicate that bevacizumab monotherapy had clinically meaningful activity in this population. 80 patients would provide 92% power to detect a 13% increase in ORR from 5% to 18% at the 2.5% two-sided significance level. The 97.5% CI were 8%, 28%.

In Arm 2 (BV/CPT), 6-month PFS of ≥ 30% would indicate that bevacizumab + irinotecan has clinically meaningful activity in this population. 80 patients would provide 92% power to detect a 15% increase in 6-month PFS from 15% to 30% at the 2.5% two sided significance level. The 97.5% CI were 19%, 41%.

An ORR of ≥ 25% would indicate that bevacizumab + irinotecan had clinically meaningful activity in this population. 80 patients would provide 92% power to detect a 15% increase in ORR from 10% to 25% at the 2.5% two-sided significance level. The 97.5% CI were 14%, 36%.

Missing data

PFS: Data for patients without disease progression or death who were lost to follow up were censored at the time of the last tumour assessment when the patient was known to be progression free. Patients randomized but not treated were censored at the time of randomization plus 1 day. Those randomized and treated but discontinued before any assessments were similarly censored on the day of randomisation plus 1 day.

ORR: Patients randomized but not treated and those randomized and treated but discontinued before any assessments were counted as non-responders.

OS: Data of patients who were lost to follow-up were censored at the date when the patient was last known to be alive.

Results

As per the protocol, the final analyses were after all the patients had been followed for 6 months.

In all 160 patients were planned and 167 recruited between 30 June 2006 and 15 February 2007 from 11 study centres, and were randomised (BV: 85, BV/CPT: 82) into the study. All efficacy analyses were based on the ITT population.

In all 84 (98.8%) in the BV Arm and 79 (96.3%) in the BV/CPT Arm received at least one dose of study treatment and were evaluable for safety.

Forty four patients (51.8%) in the BV Arm received optional post-progression treatment of irinotecan plus bevacizumab. Patient disposition is summarised in Tables 2 and 3.

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 withbevacizumab.
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.

Table 3 Analysis Populations

Analysis Population	BV (n=85)	BV/CPT-11 (n=82)
Randomized [a]	85 (100.0%)	82 (100.0%)
Efficacy-evaluable	84 (98.8%)	79 (96.3%)
Safety-evaluable	84 (98.8%)	79 (96.3%)

Analysis Population	BV (n=85)	BV/CPT-11 (n=82)
Optional post-progression phase	44 (51.8%)	0 (0.0%)

BV=bevacizumab; CPT-11=irinotecan.

a. Analysis population for all efficacy analyses.

At the time of analysis, 83 patients (BV: 39 [45.9%], BV/CPT: 44 [53.7%]) had discontinued the study as a result of death. Four patients who did not meet the selection criteria were admitted to the study at the discretion of the sponsor, because the reasons for ineligibility were relatively minor and were not expected to have an impact on the final results.

The majority of patients in the two arms were 41-64 years of age and were mainly white males with a Karnofsky performance status of 70-80%. Most of the patients in the two arms of the study had an initial diagnosis of GBM. The remaining 13 patients who had an initial diagnosis of anaplastic astrocytoma or "other" progressed to GBM by the time of study entry. The distribution of medical and surgical problems in the two arms of the study was similar. The pattern of medication use at baseline in the two arms of the study was also similar. About half the patients in each arm were receiving corticosteroids at baseline.

Primary efficacy results

All the MRI scans, except for one in the BV Arm, were reviewed by the IRF.

Objective Response Rate (ORR): The primary analysis population for objective response rate included all the randomized patients. The objective response rates, 28.2% & 37.8% in arms 1 and 2 respectively, were significantly higher than the protocol defined rates for patients receiving salvage chemotherapy (5% and 10% respectively) (Table 4). There was 1 CR in the BV Arm and 2 CRs in the BV/CPT Arm.

Analyses of objective response, performed on 3 subsets of randomized patients, supported the findings (Table 5). The subsets were efficacy evaluable patients, patients with measurable disease at baseline as determined by IRF and patients with central pathology confirmed GBM at baseline.

The results of analyses of objective response rate by baseline characteristics and risk factors showed a consistent ORR of > 20%, except for the subgroups in the BV Arm, of patients in second relapse (n=16) and patients with an initial diagnosis that was non-GBM (n=7). The sponsor's explanation that the small sample sizes prevent any definitive conclusions from being drawn is reasonable.

Six-Month PFS as determined by the IRF: The 6-month PFS in the BV and the BV/CPT arms (42.6% and 50.3% respectively) were significantly higher than the protocol specified rates for patients receiving salvage chemotherapy (15% in both arms) (Table 6).

Six-month PFS of > 30% was achieved by all the subgroups in both arms of the study, except for patients in second relapse , patients with an initial diagnosis that was non-GBM, and patients > 65 years (n=11) in the BV Arm. The small sample size prevented any definite conclusions from being drawn.

Table 4 Objective Response, as Determined by the IRF (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Patients with objective response	24 (28.2%)	31 (37.8%)
Best objective response		
Complete response	1 (1.2%)	2 (2.4%)
Partial response	23 (27.1)	29 (35.4%)
97.5% CI for objective response	(18.5%, 40.3%)	(26.5%, 50.8%)
Difference in objective response rates relative to 5% objective response rate with salvage chemotherapy)	23.2%	
(97.5% CI)	(13.5%, 35.3%)	
p-value	<0.0001	
Difference in objective response rates (relative to 10% objective response rate with irinotecan alone)		27.8%
(97.5% CI)		(16.5%, 40.8%)
p-value		<0.0001

BV=bevacizumab; CI=confidence interval; CPT-11=irinotecan; IRF=Independent Radiology Facility

Table 5 Subset Analyses of Objective Response, as Determined by the IRF

	BV	BV/CPT-11
Randomized patients		
Number of patients	85	82
Patients with objective response	24 (28.2%)	31 (37.8%)
Efficacy-evaluable patients		
Number of patients	84	79
Patients with objective response	24 (28.6%)	31 (39.2%)
Randomized patients with measurable disease at baseline		
Number of patients	83	79
Patients with objective response	23 (27.7%)	31 (39.2%)

	BV	BV/CPT-11
Randomized patients with central pathology-confirmed GBM		
Number of patients	83	82
Patients with objective response	24 (28.9%)	31 (37.8%)

BV=bevacizumab; CPT-11=irinotecan; IRF=Independent Radiology Facility

Table 6 Six-Month Progression-Free Survival, as Determined by the IRF (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Patients with an event up to 6-month	44 (51.8%)	35 (42.7%)
Earliest contributing event		
Disease progression	38 (44.7%)	31 (37.8%)
Death	6 (7.1%)	4 (4.9%)
Patients without an event up to 6-month	41 (48.2%)	47 (57.3%)
Event-free at 6-month		
Event-free rate	42.6%	50.3%)
(97.5% CI)	(29.6, 55.5)	(36.8, 63.9)
Difference in rates (relative to 15% 6-month PFS with salvage chemotherapy)	27.6%	
(97.5% CI)	(14.6, 40.5)	
p-value	<0.0001	
Difference in rates (relative to 15% 6-month PFS with irinotecan alone)		35.3%
(97.5% CI)		(21.8, 48.9)
p-value		<0.0001

BV=bevacizumab; CI=confidence interval; CPT-11=irinotecan;
IRF=Independent Radiology Facility; PFS=progression-free survival.

Note: An event was defined as 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 occurs first.

Secondary efficacy results

PFS as determined by IRF: In all 72.9% in the BV Arm and 61% in the BV/CPT Arm had died or experienced disease progression at the time of the analysis. Median PFS was 4.2 months in the BV Arm and 5.6 months in the BV/CPT Arm (Table 7).

Table 7 Progression-Free Survival, as Determined by the IRF (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Patients with an event	62 (72.9%)	50 (61.0%)
Earliest contributing event		
Disease progression	56 (65.9%)	46 (56.1%)
Death	6 (7.1%)	4 (4.9%)
Patients without an event	23 (27.1%)	32 (39.0%)
Progression-free survival (months)		
Median	4.2	5.6
(95% CI)	(2.9, 5.8)	(4.4, 6.2)
25th–75th percentile	2.7–7.1	3.0–11.1
Minimum–maximum	0.0+–12.6+	0.0+–12.6+

BV=bevacizumab; CI=confidence interval; CPT-11=irinotecan;
IRF=Independent Radiology Facility; + indicates a censored value.

Duration of Objective Response as determined by the IRF: The median duration in the BV Arm was 5.6 months, and in the BV/CPT Arm, 4.3 months (Table 8).

Table 8 Duration of Objective Response, as Determined by the IRF (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Number of patients with an objective response	24	31
Patients with an event	19 (79.2%)	16 (51.6%)
Earliest contributing event		
Disease progression	19	16
Death		
Patients without an event	5 (20.8%)	15 (48.4%)
Duration of objective response (months)		

	BV (n=85)	BV/CPT-11 (n=82)
Median	5.6	4.3
(95% CI)	(3.0, 5.8)	(4.2, –)
25th–75th percentile	3.0–5.9	4.1–NR
Minimum–maximum	1.4+–11.1+	1.4+–9.7+

BV=bevacizumab; CI=confidence interval; CPT-11=irinotecan; IRF=Independent Radiology Facility; NR=not reached; + indicates a censored value; a dash indicates that the upper limit of the confidence interval could not be obtained.

Overall Survival: As at the cut-off date (15 September 2007) 45.9% (83 patients) in the BV Arm and 53.7% (44 patients) in the BV/CPT Arm had died. The median OS was 9.3 months in the BV Arm and 8.8 months in the BV/CPT Arm (Table 9).

Table 9 Overall Survival (Randomized Patients)

	BV (n=85)	BV/CPT-11 (n=82)
Patients who died	39 (45.9%)	44 (53.7%)
Patients not known to have died	46 (54.1%)	38 (46.3%)
Overall survival (months)		
Median	9.3	8.8
(95% CI)	(8.2, –)	(7.8, –)
25th–75th percentile	6.1–NR	5.7–NR
Minimum–maximum	0.7–13.0+	0.8–13.3+

BV=bevacizumab; CI=confidence interval; CPT-11=irinotecan; NR=not reached; + indicates a censored value; a dash indicates that the upper limit of the confidence interval could not be obtained.

Exploratory efficacy results:

The 6-month PFS, PFS, ORR and duration of objective response, as determined by the investigators, were in general in agreement with the results determined by the IRF.

Of the patients initially randomised to the BV Arm, 51.8% (44/85) had disease progression and transitioned into the optional post progression phase and received bevacizumab + irinotecan. There were no confirmed objective responses in this group (as determined by the investigators). Therefore, tumour assessments were not performed by the IRF.

In regard to neurocognitive function, since the study did not include a comparator arm, any attempt to quantify the results of the neurocognitive function was considered exploratory in nature.

Supporting Study NCI-06-C-0064E was an open label, non-randomized, single centre, single arm, Phase II study of bevacizumab in the treatment of patients with high-grade

gliomas (Table 1b). It was conducted by NCI according to the guidelines of NCIs Cancer Therapy Evaluation Program (CTEP). This study report contains the efficacy results based on a retrospective review by an Independent Review Facility (IRF). Safety analyses on Grades 3-5 adverse events and a summary of deaths are also included. The objectives of the study were:

Primary objectives

- To evaluate the anti-tumour activity of bevacizumab in patients with recurrent high-grade gliomas as determined by PFS.
- To evaluate the safety of treatment with bevacizumab of patients with high-grade gliomas.

Retrospective review

- To evaluate the Objective Response and the duration of Objective Response in patients with recurrent glioblastoma in Study NCI-06-C-0064E on the basis of an independent radiology review.

The patients were recruited at one institution in the US. Eligible patients were entered into two cohorts: glioblastoma cohort and anaplastic astrocytoma cohort. The glioblastoma cohort contained all the patients with high-grade recurrent glioblastoma multiforme or gliosarcoma. The anaplastic astrocytoma cohort included patients with high-grade recurrent anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic mixed oligoastrocytoma and malignant astrocytoma.

Table 1a: Summary of Study NCI-06-C-0064E

Study design	Dose, Frequency, Duration	No. of patients	Results
NCI study: Open-label, single site, Phase II study of bevacizumab in patients with recurrent high-grade gliomas: GBM & gliosarcomas. *Inclusion* >18y, histo. confirmed GBM, radiographic evidence of disease progression on MRI, interval of > 4W between radiotherapy & study entry (no limit for prior chemo). *Exclusion* Intracranial bleeding & anticoagulant therapy. **Objectives** PFS	bevacizumab 10 mg/kg every 2W on a 4W cycle. Other CA Tts were ceased.	56 patients – all had GBM Male: 53.6% Female: 46.4% White: 98.2% Asian: 1.8% Age: 18-40y: 14% 41-64y: 75% > 65: 11%	*Efficacy* **OR:** 11 (all PRs) **ORR:** 20% (95%CI: 11%, 31%) *Duration of response:* Median – 3.9m 95%CI: 2.4, 17.4 *Safety* **Exposure** **Doses per Patient:** mean: 8.9 median: 7 Duration of Tt Mean: 4.0 m Median: 2.8 m Range 0-22.5 m 25th-75th percentile: 1.4-

Study design	Dose, Frequency, Duration	No. of patients	Results
Safety **Design:** Two cohorts: recurrent GBM and recurrent AA. FDG-PET scan before first dose, a MRI perfusion scan within 48-96 h of 1st dose and then a MRI perfusion scan prior to each 4W cycle. An independent radiology review was conducted in a blinded manner.			4.4 m **AEs** Grade > 3: 65.5% (36 pts) had at least 1 event. Lymphopaenia: 16 Seizures: 5 Thromboembolism:7Hypophosphatemia:6 Hypertension:2 *Deaths* As at June 2003: 80.4% (45 pts) Malignancy: 77% Tt toxicity: 2%

The patients received bevacizumab 10 mg/kg IV every 2 weeks on a 4-week cycle. Other cancer chemotherapy, radiotherapy, immunotherapy, and investigational agents were excluded for the duration of the study. Patients who developed significant toxicity that was primarily caused by bevacizumab were discontinued from the study.

MRI perfusion scans were performed within 48-96 hours of the first dose of bevacizumab and thereafter prior to each 4-week cycle. An IRF was used to review the radiology scans, with IRF reviewers blinded to the investigator's assessments of efficacy outcomes. The first scan was not read by the IRF reviewers except in cases where no further follow-up scans were available for review. Tumour responses were determined by the IRF using the modified WHO response evaluation criteria (Macdonald criteria). Selection criteria are summarised in Table 1a.

The Efficacy population was the ITT population, and included all the patients who satisfied the selection criteria. The efficacy endpoints analysed were:

- Objective Response Rate - defined as a CR or PR determined on two consecutive assessments > 4 weeks apart, as determined by the IRF using the modified Macdonald criteria. Patients who were registered but did not receive treatment and those who received treatment but did not undergo a post-baseline tumour assessment were considered to be non-responders.
- Duration of Objective Response (based on modified Macdonald criteria) - defined as the time from first tumour assessment that supported the patient's objective response to the time of disease progression as determined by IRF, clear clinical progression in the absence of an MRI determination of progression, or death due to any cause, whichever occurred first. For patients who did not experience disease progression or death, the duration of response was censored at the date of the last tumour assessment. In the case of patients who experienced the first disease progression or death >56 days after the last dose, duration of objective response was censored at the

date of the last tumour assessment prior to the last study dose of study drug plus 56 days.

The Safety population included all those who received at least one dose of study drug.

This report presented the results of only the glioblastoma cohort (Grade IV glioma)

Of the 56 patients enrolled from January 2006 to September 2007, 55 received at least one dose of study drug. At the time of data cut-off (3 June 2008), 54 patients had discontinued from the study (Table 10). The majority of patients were Caucasian (98%) males (54%) aged 41-64 years with a Karnofsky performance status of 90% - 100%.

Table 10 Patient Disposition (Intent-to-Treat Patients)

	Bevacizumab (n=56)
Patients not treated	1 (1.8%)
Patients treated	55 (98.2%)
Patients not known to have discontinued from study	2 (3.6%)
Patients who discontinued from study	54 (96.4%)
Adverse event	11 (19.6%)
Disease progression before treatment [a]	1 (1.8%)
Disease progression during study [a]	40 (71.4%)
Patient request	2 (3.6%)

a. Disease progression was based on investigator assessment, not on IRF review.

Efficacy results

Objective response: In all 11 patients achieved a PR. There were no CRs. The objective response rate was 19.6% for the ITT population. The sensitivity analysis for the treated population (55 patients) determined an objective response rate of 20%.

Duration of Objective Response: The median duration of objective response was 3.9 months.

Exploratory analyses: The percent change in the smallest post-baseline sum of product of diameters (SPD) from baseline is an indicator of the best tumour shrinkage that was achieved by patients during the study. Of the 55 patients who were treated, 50 patients had tumour shrinkages and 14 had tumours that shrank by > 50%.

Other studies – literature review

The review included 31 clinical publications, reporting on 16 clinical trials containing patients with Grade III glioma, treated with bevacizumab monotherapy or bevacizumab in combination with irinotecan. Of the 16 clinical trials, 15 reported on efficacy and all 16 provided safety data. The number of studies of bevacizumab monotherapy in patients with malignant gliomas after relapse was small.

The literature searches were performed in Medline and EMBASE and the annual meeting abstracts of the American Society of Clinical Oncology (ASCO). The search produced 17 citations from Medline and EMBASE, 11 from ASCO abstracts and 3 from bibliography review of reviews. The patients in these citations were recruited from France, Spain, Israel, Denmark and the USA. The majority of these reported their experience of treatment with bevacizumab plus irinotecan, except for 2 which were of bevacizumab monotherapy.

Review of efficacy

The demographics and reported efficacy were discussed in 3 groups:

· Patients treated with bevacizumab plus irinotecan.

1. Separate efficacy data for Grade III patients.
2. Pooled efficacy data for both Grade III and Grade IV patients.

· Patients treated with bevacizumab alone.

Integrated analyses of data from the studies of Wong et al and Lamborn et al of patients with recurrent GBM and recurrent Grade III malignant glioma were used. The 6-month PFS in patients with recurrent Grade III malignant glioma was 31% (Wong et al) to 28% (Lamborn et al).

The standard dosing schedule for bevacizumab was 10 mg/kg given ever 2 weeks. A different dosing schedule using 5 mg/kg/week was used in some patient cohorts. Irinotecan dose schedules had dose alteration included to allow for concomitant medications. No cap on the duration of treatment was explicitly stated in the majority of citations.

Separate efficacy data for grade III patients (patient groups 1-4)

Patient groups 1 – 4 were studies of bevacizumab + irinotecan in combination in which efficacy data were available specifically for patients with Grade III glioma (Table 11).

The selection criteria in all 4 studies were similar. All the patients were treated with bevacizumab plus irinotecan. Progress was measured by MRI at 6 – 8 weekly intervals. The endpoints included 6-month PFS, response rates and overall survival. There was limited efficacy data from patient group 4. Patients in groups 1 and 2 were younger.

Table 11 Patient demographics of Patient Groups 1-4 (bevacizumab +irinotecan)

Pt group	KPS >80	Median Age	AA:AO/other Grade III (n)	Prior Rx
1	55 All>60 KPS	43	25 / 8 (**33**)	Median of 3
2	WHO 0=38% 1=41% 2=21%	46	13 / 7 (**20**)	<2 = 0% 2 = 4% ≥3 = 96%
3	42%	51	3 / 11 (**14**)	1st -line 43% 2nd line 29% ≥3rd line 28%

Pt group	KPS >80	Median Age	AA:AO/other Grade III (n)	Prior Rx
4	29%	52	5 / 23 (**28**)	NR
			95	

AA: Anaplastic Astrocytoma, AO: Anaplastic Oligoastrocytoma

The response rate ranged from 15% to 79% (Table 12). The lower response rate in group 2 may be because the patients in Group 2 had considerably more pre-treatments than the other groups. The CR rate was 4%. The overall pooled response rate for patient groups 1-3 was 52%. Stable disease was reported in 75% of the patients.

The 6-month PFS for patient groups 1-3 ranged from 33% - 79%.

For response rates and 6-month PFS, the poorer results were in the heavily pre-treated patient group (group 2) and the best results were in the least heavily pre-treated population (patient group 3).

The range of 12-month OS for the patient groups 1 to 3 was 45% to 78%.

Conclusion: Treatment with a combination of bevacizumab and irinotecan in 95 patients with Grade III glioma showed a response rate and 6-month PFS that was higher than in historical controls (Wong et al 1999).

Table 12 Summary of response data for Patient Groups 1-4 (bevacizumab +irinotecan)

Pt group	Number		Response Rates		
	n (all)	Grade III n (%)	CR	PR SD PD	ORR CR+PR
1	33	**33** (100%)	3/33	PR 17/33 SD11/33 PD 2/33	61%
2	52	**20** (38%)	1/20	PR 3/20 SD15/20 PD 1/20	15%
3	51	**14** (27%)	2/14	PR 9/14 SD 3/14 PD 0/14	79%
4	77	**28** (36%)	Grade III = 54% Grade III & IV = 36% (At 2 months)		

Pt group	Number		Response Rates		
	n (all)	Grade III n (%)	CR	PR SD PD	ORR CR+PR
		n = 95			

Pooled efficacy data for grades III and IV patients (patient groups 5-12)

Patient groups 5–12 were studies of bevacizumab in combination with irinotecan, where efficacy results were presented for a mixed population of Grade III and IV relapsed glioma patients. Patient groups 5-9 were from at least one full publication, while patient groups 10-12 were described in scientific congress abstract form, and were briefly summarised (Table 13).

Grade III disease was present in 28% of the patients in this group. The patients, except for two patient groups, were 5-13 years older than the historic controls. They also had a higher median number of treatments than the controls.

Table 13 Demographics of Patient Groups 5-12

Pt group (P or A)*	KPS >80 (All patients)	Median Age	Grade IV: Grade III (% Grade III) AA:AO+other	Prior treatment of study population
5 (P)	77	56	37 : 24 (**40%**) NR	Mean of 2 prior regimens + DXT
6 (P)	Median 80	50	33 / 22 (**40%**) 21:1	Median of 2 prior treatments
7 (P)	Median 80	46	12 / **15** (**56%**) NR	Median of 2 prior treatments
8 (P)	NR	58	17 / **4** (**20%**) 1 : 3	NR
9 (P)	50% : 50%	56	17 / **3** (**15%**) 1 : 2	80% 1 prior 15% 2 prior 5% ≥2 prior
10 (A)	NR	50	22 / **14** (**38%**)	50 % 5% ≥2 prior

Pt group (P or A)*	KPS >80 (All patients)	Median Age	Grade IV: Grade III (% Grade III) AA:AO+other	Prior treatment of study population
			NR	
11 (A)	Median 70	53	28 : **16** (**36%**) 11 : 5	Median of 2 prior treatments
12 (A)	NR	42	11 : **10** (**48%**) NR	Median of 3 prior treatments
			276 / **108** (**28%**)	

*: Publication or Abstract
AA: Anaplastic Astrocytoma, AO: Anaplastic Oligoastrocytoma

Pooled response rates were reported for all the groups except for group 10, which only reported PFS and OS. More than 5% of patients in the pooled analysis obtained a CR compared with < 1% in the 349 historic controls (Wong et al) (Table 14).

Table 14 Summary of response efficacy data for Patient Groups 5-12

Patient Group (A or P)	Number		Response Rates (combined Grade III and IV		
	n (all)	Grade III n (%)	CR	PR SD PD	ORR CR+PR (Grade III)
5 (P)	61	24 (40%) AA = 15 AO = 9	7/53	PR 32/55 SD 11/55 PD 3/55	NR
6 (P)	55	22 (40%) AG = 21 Other = 1	1/55	PR 25/55 SD 25/55 PD 3/55	NR
7 (P)	27	15 (55%) Gd III = 9 Gd I/II = 6	0/27	PR 12/27 SD 11/27 PD 4/27	NR
8 (P)	21	8 (NR)	Grade III CR 0/8	Grade III PR 4/8	Grade III 50%

Patient Group (A or P)	Number		Response Rates (combined Grade III and IV		
	n (all)	Grade III n (%)	CR	PR SD PD	ORR CR+PR (Grade III)
				SD 1/8 PD 3/8	
9 (P)	20	3 (15%) AA = 2 AO = 1	CR 2/19	PR 7/19 SD 2/19 PD 8/19	NR
11 (A)	44	16 (37%) AA = 11 AOD = 5	CR 4/44	PR 19/44 SD 12/44 PD 7/44	NR
12 (A)	21	10 (48%)	CR 1/27	PR 8/27 SD 11/27 PD 7/27	NR

*: Publication or Abstract
AA: Anaplastic Astrocytoma, AO: Anaplastic Oligoastrocytoma, AOD: Anaplastic Oligodendroglioma, AG: Anaplastic Glioma

Six-month PFS was reported separately for Grades III and IV in only 2 studies. The 6-month PFS for patients with Grade III disease was 32% in group 6 and 75% in group 7. In patients with Grade IV disease the corresponding results were 42% and 17%. The discrepancy in group 6 where the 6-month PFS was lower in Grade III patients than in Grade IV patients was explained as being due to the small sample size. The results for Grades III and IV combined, ranged from 25% to 44%. The data for patients in Groups 8 and 12 were not presented because there was no duration of response data available (Table 15).

Table 15 Summary of PFS and OS data for Patient Groups 5-12

Patient Group (A or P)	Number		Response Duration	
	N	Grade III n/(%)	6-month PFS	OS
5 (P)	61	24 (40%) AA = 15 AO = 9	All pts 44%	Median 9 month
6 (P)	55	22 (40%) AG = 21 Other = 1	Gd III=32% Gd IV=42%	III&IV 39%

Patient Group (A or P)	Number		Response Duration	
	N	Grade III n/(%)	6-month PFS	OS
7 (P)	27	15 (55%) Gd III = 9 Gd I/II = 4 (Bx GdIII) Gd I/II = 2	Grade III = 75% Grade IV = 17%	Grade I/II = 100% Grade III = 88% Grade IV = 75%
9 (P)	20	3 (15%) AA = 2 AO = 1	All pts 25%	All pts 55%
10 (A)	36	14 (47%) NR	All pts 25%	All pts 30 weeks
11 (A)	44	16 (37%) AA = 11 AOD = 5	Mean PFS 7.4 month	9.8 months

*: Publication or Abstract
AA: Anaplastic Astrocytoma, AO: Anaplastic Oligoastrocytoma, AOD: Anaplastic Oligodendroglioma, AG: Anaplastic Glioma

Conclusion: In the absence of any distinction between Grades III and IV efficacy results in this pooled data set, comparison of efficacy with historical controls, where the results were Grade specific, was not possible.

Efficacy conclusions

Bevacizumab used as single agent or in combination with irinotecan for the treatment of patients with relapsed glioblastoma resulted in a statistically significant increase in the IRF-assessed 6-month PFS in both treatment arms compared with historical controls (42.6% in the BV Arm and 50.3% in the BV/CPT Arm versus 15% in historical controls). There was a statistically significant increase in the IRF-assessed objective response rates in both treatment arms compared with historical controls (28.2% in the BV Arm and 37.8% in the BV/CPT Arm versus 5% and 10% in historical controls, respectively).

The duration of responses in both treatment arms was a median of 5.6 months (95% CI 3.0, 5.8) in the BV Arm and 4.3 months (95% CI 4.2, -) in the BV/CPT Arm. The median overall survival was 9.3 months (95% CI 8.2, -) in the BV Arm and 8.8 months (95% CI 7.8, -) in the BV/CPT Arm.

In Study NCI-06-C-0064E, the objective response rate, as determined by IRF, was 19.6% (11/56 patients, 95% CI 10.9, 31.3) and the median duration of response was 3.9 months (95% CI 2.4, 17.4).

The literature survey included 31 clinical publications, reporting on 16 trials, containing patients with Grade III glioma treated with bevacizumab monotherapy or bevacizumab in combination with irinotecan. Treatment with a combination of bevacizumab and irinotecan had a response rate and 6-month PFS that were higher than that in historical

controls. The limited number of trials of bevacizumab monotherapy prevented any efficacy conclusions from being reached.

Safety

Pivotal study AVF3708g

All the patients who received at least one dose of study treatment were included in the safety analyses, that is, 84 patients in the BV Arm and 79 patients in the BV/CPT Arm. The median number of doses received was 9 in the BV Arm and 12 in the BV/CPT Arm. The median dose in both arms was 10 mg/Kg. All the patients in the BV/CPT Arm received at least one dose of irinotecan. The median number of doses received was 11. The irinotecan dosing was dependent on whether enzyme inducing anti-epileptic drugs (EIAEDs) were used. Adverse events that were included in the planned treatment period were those that occurred up to 30 days from the last treatment in the BV Arm and BV/CPT Arm. In patients receiving the optional post-progression treatment of irinotecan, adverse events occurring on or after the first treatment with irinotecan and up to 30 days after the last treatment with either bevacizumab or irinotecan (whichever was the last to occur) were included in the optional post-progression phase analysis.

The median duration of safety observation in the planned treatment period was 4.3 months in the BV Arm and 6.1 months in the BV/CPT Arm. For patients in the optional post-progression phase of treatment which included irinotecan, the duration of safety observation was from the first administration of irinotecan. The number of doses of bevacizumab and irinotecan received was a median of 3 and the length of treatment was also similar (Medians of 1 and 1.1 months, respectively).

Adverse events

In all, 98.8% (83 patients) in the BV Arm, and 100% (79 patients) in the BV/CPT Arm reported an adverse event. Of these, 46% of the patients in the BV Arm and 66% of those in the BV/CPT Arm reported Grade ≥3 adverse events.

The most common adverse events were fatigue (45.2%), headache (37%) and hypertension (30%) in the BV Arm and fatigue (75%), diarrhoea (75%) and nausea (67%) in the BV/CPT Arm. The commonest Grade ≥3 adverse events were hypertension, and convulsion in the BV Arm and convulsion, neutropenia, and fatigue in the BV/CPT Arm (Table 16).

In the optional post-progression phase, 98% of the patients reported an adverse event. Of these, 52% reported a Grade ≥3 adverse event. The commonest Grade ≥3 adverse events were lymphopenia (7%), diarrhoea (7%), fatigue (7%) and headache (9%).

Table 16 Incidence of Grade ³ 3 Adverse Events Occurring in ³ 5% of Patients in Either Treatment Arm during the Planned Treatment Period (Safety-Evaluable Patients)

MedDRA Preferred Term	BV (n=84)	BV/CPT-11 (n=79)
Any Grade ³ 3 adverse events	39 (46.4%)	52 (65.8%)
Aphasia	3 (3.6%)	6 (7.6%)
Confusional state	2 (2.4%)	4 (5.1%)

MedDRA Preferred Term	BV (n=84)	BV/CPT-11 (n=79)
Convulsion	5 (6.0%)	11 (13.9%)
Deep vein thrombosis	2 (2.4%)	5 (6.3%)
Diarrhea	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.

Deaths: Among treated patients, 45% of patients in the BV Arm and 52% of those in the BV/CPT Arm died. All but 5 of the deaths were due to disease progression. Adverse events were the cause of death in 3 of the 5 deaths not due to disease progression. These events were neutropenic infection and pulmonary embolism in the BV Arm and convulsions in the BV/CPT Arm.

Serious Adverse Events (SAEs): Among treated patients, 26% of patients in the BV Arm and 43% of patients in the BV/CPT Arm experienced a SAE. The commonest SAE in both arms was convulsion (Table 17).

In the optional post-progression phase, 13 patients (29.5%) experienced a SAE. These were unstable angina, large intestine perforation, pyrexia, wound infection, wound dehiscence, muscular weakness, intracranial tumour haemorrhage, hydrocephalus, convulsions, cerebral haemorrhage, headaches, pulmonary embolism, hypoxia and deep vein thrombosis.

Adverse events leading to treatment discontinuation: In all 4 patients (4.8%) in the BV Arm discontinued treatment because of an adverse event. None of these adverse events had an incidence >2%. In the BV/CPT Arm 14 patients (17.7%) discontinued bevacizumab treatment because of adverse events. Fatigue (2.5%) and cerebral haemorrhage (3.8%) were the commonest adverse events that caused treatment discontinuation.

In the optional post-progression phase, 9 patients (20.9%) discontinued bevacizumab and 7 (15.9%) discontinued irinotecan because of an adverse event. No adverse event was responsible for more than one discontinuation.

Table 17 Incidence of Serious Adverse Events Occurring in ³ 2% of Treated Patients in Either Treatment Arm during the Planned Treatment Period (Safety-Evaluable Patients)

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.

Significant adverse events

Haemorrhage: There were fewer haemorrhages reported in the BV Arm than in the BV/CPT Arm (27.4% vs 40.5%). Cerebral haemorrhage was reported by 1 patient in the BV Arm and 3 patients in the BV/CPT Arm. All the cerebral haemorrhages were of Grade 1/2 intensity except for one in the BV/CPT Arm which was Grade 4. In the optional post-progression phase, 12 patients (27.3%) experienced haemorrhagic events. Cerebral haemorrhage was reported in 3 patients. Of these one was reported as a Grade 3 haemorrhage. One of the patients with a Grade 1 cerebral haemorrhage developed a Grade 3 haemorrhage 61 days after the last study treatment.

Hypertension: In all 30 patients in the BV Arm (35.7%) and 21 patients in the BV/CPT Arm (26.6%) experienced hypertension. Of these, there were 7 patients in the BV Arm and 1 patient in the BV/CPT Arm who reported Grade 3 hypertension. There were no Grade 4 hypertension events reported. Two patients experienced hypertension (Grade 2) in the optional post-progression phase.

Proteinuria: A total of 4 patients in the BV Arm and 2 patients in the BV/CPT Arm experienced proteinuria. Of these 1 patient in the BV/CPT Arm reported Grade 3 proteinuria.

Venous thromboembolic events: There were more venous thromboembolic events reported in the BV/CPT Arm. One patient in the BV Arm had Grade 5 pulmonary embolism, which led to death.

In the optional post-progression phase 1 patient had a Grade 4 pulmonary embolism. Another also experienced Grade 4 pulmonary embolism and then 2.5 months later Grade 3 deep vein thrombosis.

Arterial thromboembolic events: These included angina unstable, cerebral ischaemia, cerebrovascular accident, chest pain, myocardial infarction, myocardial ischaemia, and troponin increased. In all 4 patients in the BV Arm and 5 patients in the BV/CPT experienced an arterial thromboembolic event. There were 2 Grade 3 events in each arm.

There were no Grade 4 events. One patient experienced an arterial thromboembolic event (Grade 3 angina unstable) in the optional post-progression phase.

Gastrointestinal perforation: Only the BV/CPT Arm reported gastrointestinal perforation in 2 patients (2.5%). Both events were classified as Grade 3. One patient (2.3%) in the optional post-progression phase experienced a Grade 4 large intestine perforation.

Wound healing complications: In all 5 patients (6%) in the BV Arm and 2 patients in the BV/CPT Arm (2.5%) experienced wound healing complications during the planned treatment phase. The incidence of impaired wound healing was 3.6% in the BV Arm and 1.3% in the BV/CPT Arm. In all 5 were classified as Grade 3. In the optional post-progression phase, 3 patients experienced wound healing complications of which 1 was classified as Grade 3.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): The only report of RPLS events was a Grade 1 event in the BV/CPT Arm. There were no RPLS events in the optional post-progression phase.

Seizure: A total of 15 patients in the BV Arm and 19 patients in the BV/CPT Arm experienced a seizure during the planned treatment phase. Of these 2 were classified Grade 5. In the optional post-progression phase, 6 patients experienced a seizure. Three of these were classified Grade 3. Of the 6, four patients had a prior medical history of seizures.

Infection: In all 8 patients in the BV Arm and 11 patients in the BV/CPT Arm experienced a Grade ≥3 infection event during the planned treatment period. Of the infection events in the BV Arm, one was classified Grade 5 (neutropenic infection) which led to death. In the optional post-progression phase, two patients experienced Grade 3 infections (wound infection and peritonitis). There were no Grade ≥4 infections.

Clinical laboratory evaluations

There were 6 Grade ≥3 abnormalities in the BV Arm and 10 Grade ≥3 abnormalities in the BV/CLT Arm.

Supporting study NCI-06-C-0064E

In all 55 patients received at least one dose of bevacizumab. The median number of doses received per patient was 7 and the median length of bevacizumab treatment was 2.8 months.

Adverse events: Of the 55 patients, 36 experienced a Grade ≥3 AE. The commonest was lymphopenia (25.5%). The other Grade ≥3 AEs were: 7 patients with venous thromboembolic events (9%), 2 patients with hypertension (3.6%), 1 patient with an arterial thromboembolic event (1.8%), and 1 patient with gastrointestinal perforation (1.8%). There were no instances of congestive heart failure or intracranial events reported.

The commonest AE leading to discontinuation were venous thromboembolic events. The others were vomiting, neck pain, death, infection, and hyperglycaemia.

Deaths: Of the 56 patients enrolled in the study, 45 were known to have died as of 3 June 2008. Disease progression was the commonest cause (76.8%). One patient died of pulmonary emboli and CVA and another had a venous thromboembolic event, followed by sudden death. The other causes were toxicity from treatment (1.8%), and other clinical deterioration (1.8%).

Literature review

The literature review found that the reporting of safety of bevacizumab, as monotherapy or in combination with irinotecan in the treatment of Grade III patients, was limited. The publications tend to report only CTC Grades 3-5 adverse events because of word-count limitations.

Duration of exposure was not reported in almost half the citations. Duration of exposure where reported ranged from 9 -24 weeks. The adverse events of special interest were haemorrhage, cerebral haemorrhage, hypertension, proteinuria, venous thromboembolic events, arterial thromboembolic events, GI perforation, wound healing complications, reversible posterior leukoencephalopathy syndrome, congestive heart failure, infections, and convulsions.

The under reporting of events and inconsistent causality reporting that was seen in the citations made interpretation of safety difficult. The data presented in the 16 citations suggest however, that the adverse event profile was in keeping with the known adverse events of bevacizumab.

Conclusion

Adverse events were reported in > 99% of the patients enrolled in study AVF3708g. Grade ≥3 adverse events were reported by 46.4% of patients in the BV Arm versus 65.8% of patients in the BV/CPT Arm. The commonest Grade ≥3 adverse events in the BV Arm were hypertension and convulsion, and in the BV/CPT Arm, convulsion, neutropenia and fatigue.

The adverse events of special interest in the bevacizumab alone Arm were haemorrhage, including CNS haemorrhage (27.4%), hypertension (35.7%), gastrointestinal perforation (2.5%), thromboembolic events (venous: 3.6% and arterial: 4.8%), infection (Grade ≥3: 9.5%), seizures (17.9%), proteinuria (4.8%) and wound healing complications (6%).

There were fewer reports of haemorrhage, including CNS haemorrhage, gastrointestinal perforation, thromboembolic events (venous and arterial), infection, RPLS, seizures and laboratory abnormalities in the BV Arm than in the BV/CPT Arm. There were slightly more wound healing complications in the BV Arm than in the BV/CPT Arm. The number of discontinuations due to adverse events was greater in the BV/CPT Arm than in the BV Arm. About half the patient population in both arms died. All but 5 of the deaths were due to disease progression. Adverse events were the cause of death in 3 of the 5 deaths not due to disease progression.

In Study NCI-06-C-0064E, the reported adverse events were lymphopenia, venous thromboembolic events, hypophosphatemia, hypertension, seizure, arterial thromboembolic events, gastrointestinal perforation and wound healing complication. These were all in keeping with the known safety profile of bevacizumab.

The safety data from the 16 citations from the literature review were of limited value because of its brevity and the inconsistent causality reporting.

Clinical summary and conclusions

The sponsor seeks approval for Avastin (bevacizumab) as a single agent, or in combination with irinotecan for the treatment of patients with relapsed high grade malignant glioma. Efficacy and safety data from two historically-controlled studies were submitted in support of Grade IV glioma. The sponsor also submitted a clinical overview of 16 clinical trials described in 31 publications retrieved from a systematic literature review in support of Grade III glioma.

The pivotal study AVF3708g is an open-label, multicenter, non-comparative, parallel group trial to evaluate the efficacy and safety of bevacizumab monotherapy and of bevacizumab plus irinotecan in patients with previously treated glioblastoma. A total of 167 patients were enrolled: 85 in the bevacizumab alone Arm, 82 in the bevacizumab plus irinotecan Arm. The primary efficacy endpoints were objective response rate as determined by an independent review facility and the 6-month PFS. Tumour assessment was based on the modified WHO response criteria taking into account corticosteroid dosing.

There was a statistically significant increase in the IRF-assessed objective response rates in both treatment arms compared with historical controls (28.2% in the BV Arm and 37.8% in the BV/CPT Arm versus 5% and 10%, respectively, in historical controls). Similarly, there was a statistically significant increase in the IRF-assessed 6-month PFS in both treatment arms compared with historical controls (42.6% in the BV Arm and 50.3% in the BV/CPT Arm versus 15% in historical controls).

The duration of responses was a median of 5.6 months (95% CI 3.0, 5.8) in the BV Arm and 4.3 months (95% CI 4.2, -) in the BV/CPT Arm. The median overall survival was 9.3 months (95% CI 8.2, -) in the BV Arm and 8.8 months (95% CI 7.8, -) in the BV/CPT Arm.

NCI 06-C-0064E was a single arm, single site, NCI-sponsored study of bevacizumab for the treatment of patients with previously treated Grade IV gliomas. The study enrolled 56 patients with high grade glioma. Objective response as determined by independent review was 19.6% (95% CI 10.9 %, 31.3%). Median duration of response was 3.9 months (95% CI 2.4, 17.4) among the responders.

The systematic literature review confirmed improvement in response rate, 6-month PFS and OS compared to historical controls in patients with Grade III gliomas. The reduction in steroid use, as described by the sponsor, supports the improvement in the efficacy parameters.

The IRF assessments were based on MRI measurements. Due to the hallmark histology of pseudopalisading necrosis of GBM, tumour size cannot be accurately measured by MRI because of the irregular configuration. This difficulty is even greater for relapsed gliomas after prior surgery and radiation therapy, the target population for this application. Neither objective response rate nor objective progression can be satisfactorily assessed. However, it was considered that a response rate of sufficient magnitude was likely to be associated with clinical benefit as the magnitude of response rate would outweigh the uncertainties associated with interpreting MRI scans.

Adverse events were reported in > 99% of the patients enrolled in study AVF3708g. The incidence of serious adverse events (Grade ≥3) was greater in the BV/CPT Arm than in the BV Arm. The commonest Grade ≥3 adverse events in the BV Arm were hypertension and convulsion and in the BV/CPT Arm, convulsion, neutropenia and fatigue. The adverse events of special interest in the bevacizumab alone Arm were haemorrhage, including CNS haemorrhage (27.4%), hypertension (35.7%), gastrointestinal perforation (2.5%), thromboembolic events (venous: 3.6% and arterial: 4.8%), infection (Grade ≥3: 9.5%), seizures (17.9%), proteinuria (4.8%) and wound healing complications (6%). There were fewer reports of haemorrhage, including CNS haemorrhage, infection, gastrointestinal perforation, thromboembolic events, RPLS, seizures and laboratory abnormalities in the BV Arm than in the BV/CPT Arm. There were more discontinuations due to adverse events in the BV/CPT Arm. About half the patient population in both arms died. All but 5 of the deaths were due to disease progression. Adverse events were the cause of death in 3 of the 5 deaths not due to disease progression.

In Study NCI-06-C-0064E, the reported adverse events were lymphopenia, venous thromboembolic events, hypophosphatemia, hypertension, seizure, arterial thromboembolic events, gastrointestinal perforation and wound healing complication.

The safety data from the 16 citations from the literature review were of limited value because of their brevity and the inconsistent causality reporting.

The adverse event profile in the submitted studies was in keeping with the known profile. Events of special concern were CNS haemorrhage, wound healing complications and venous thromboembolism, which are inherent in patients with GBM and associated surgery/radiotherapy.

The submitted data has demonstrated that bevacizumab was beneficial in the treatment of these extremely treatment-resistant tumours. The combination of irinotecan with bevacizumab for the treatment of high-grade glioma however is questionable. In study AVF3708g, there was no statistical difference in efficacy between the treatment arms and a higher incidence of severe adverse events in the combination therapy Arm. It can be concluded that irinotecan does not add significant efficacy to bevacizumab and at the expense of added toxicity.

Recommendation of the clinical evaluator

On the basis of the submitted data, the clinical evaluator recommended that Avastin (bevacizumab), as a single agent, be approved for the treatment of patients with relapsed high grade malignant glioma.

The application for the use of Avastin (bevacizumab) in combination with irinotecan for the treatment of relapsed high grade glioma should be rejected.

V. Pharmacovigilance findings

A Risk Management Plan was submitted with the application but it was not a requirement at the time of submission and was therefore not evaluated.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in an application of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in an application of this type.

Clinical

The clinical evaluator has recommended approval of the application, but only for use of bevacizumab as monotherapy.

Two separate sets of clinical data have been submitted:

For Grade IV glioma the data submitted were one pivotal phase II trial (**study AVF 3708g**) and one supportive phase II trial (**NCI-06-C-0064E**);

For Grade III glioma the sponsor has submitted a literature-based submission, which included 31 publications from 16 separate clinical trials.

Efficacy – grade IV glioma

Study AVF 3708g enrolled 167 subjects with glioblastoma multiforme (GBM) in first or second relapse. All patients were required to have had prior therapy with temozolomide. Subjects were randomised to receive either:

- Bevacizumab 10 mg/kg IV every 2 weeks; or
- Bevacizumab 10 mg/kg IV every 2 weeks with irinotecan 125 or 340 mg/m2 every 2 weeks.

The higher dose of irinotecan was used in those patients who were on enzyme-inducing anti-epileptic agents (EIAEA's) as the drug is metabolised by CYP3A4.

The primary endpoints were response rate and progression-free survival (PFS) at 6 months. Although patients were randomised to the two treatment arms, the trial was not designed to compare the efficacy of the two treatments. Rather, each of the two treatments was to be compared with published pooled historical data from previous phase II studies of various chemotherapy agents.

Study NCI-06-C-0064E was an open uncontrolled study which enrolled 56 subjects with relapsed GBM or gliosarcoma. All were treated with bevacizumab monotherapy 10 mg/kg IV every 2 weeks. The primary endpoint was response rate.

Results of these two studies are summarised in Table 18. The table also includes historical data from the Wong et al paper, as well as the results from the trials which were the basis of TGA approval of temozolomide for relapsed GBM in 1999.

Table 18 – Efficacy results for relapsed Grade IV glioma - compared with historical data

Study	N	Response Rate	Median Duration Of Response	PFS at 6 m	Median PFS (1)	Median OS(1)
HISTORICAL DATA						
Pooled Historical data (2)	150	6 %	-	15 %	2.1 m (9 wks)	5.8 m (25 wks)
Temozolomide (3)						
trial 1	60	7 %	-	20 %	3.5 m	7.7 m
trial 2	138	8 %	-	19 %	2.1 m	5.4 m
STUDY AVF 3708g						
Bevacizumab monotherapy	85	28.2 %	5.6 m	42.6 %	4.2 m	9.3 m
Bevacizumab with irinotecan	82	37.8 %	4.3 m	50.3 %	5.6 m	8.8 m
STUDY NCI 06-C-0064E						
Bevacizumab monotherapy	56	19.6 %	3.4 m	-	-	-

(1) – Where result for median PFS or OS was reported in terms of weeks, this has been converted to months, with actual week value in brackets.
(2) - Wong et al 1999
(3) – Temodal product information

Comparison of the results across trials clearly suggests that bevacizumab treatment (either as monotherapy or in combination with irinotecan) results in improved response rates and 6-month PFS compared to the pooled historical data or the previous data with temozolomide. The differences between the bevacizumab arms and the historical data were statistically significant for these two endpoints.

Results for median PFS and median overall survival (OS) were also numerically superior.

Although the study was not designed to compare the two treatment arms, the efficacy results did not suggest any marked advantage of the bevacizumab + irinotecan combination over bevacizumab monotherapy.

Efficacy – grade III glioma

The literature review included 31 publications arising from 16 separate clinical trials. There were a total of six studies of bevacizumab which contained efficacy data specifically for the Grade III glioma population. The remaining studies all presented data for mixed populations of Grade III and Grade IV patients and hence efficacy data specific to the grade III population in question could not be analysed. Only one of the studies was a prospectively conducted clinical trial, the others being retrospective analyses of patients treated at the authors' institutions. All were small studies.

The results of the six studies are summarised in Table 19. The table also includes historical data from the Wong et al paper, as well as the results from the trial which was the basis of TGA approval of temozolomide for relapsed Grade III disease (anaplastic astrocytoma) in 1999.

Table 19 – Results of published studies (relapsed Grade III glioma) – compared with historical data.

				PROGRESSION-FREE SURVIVAL (PFS)				OVERALL SURVIVAL (OS)		
	Study	N	Response Rate	PFS at 6 m	PFS at 12 m	PFS at 24 m	Median PFS (1)	OS at 6 m	OS at 12 m	Median OS(1)
HISTORICAL DATA										
	Wong et al 1999	150	14 %	31 %	20 %	10 %	13 wks	-	47 %	47 wks
	Temozolomide (2)	162	35 %	46 %	24 %	-	23 wks (5.4 m)	75 %	56 %	59 wks (13.6 m)
BEVACIZUMAB WITH IRINOTECAN										
1	Desjardins 2008	33	61 %	55 %	39 %	11 %	30 wks	79 %	55 %	65 wks

				PROGRESSION-FREE SURVIVAL (PFS)				OVERALL SURVIVAL (OS)		
	Study	N	Response Rate	PFS at 6 m	PFS at 12 m	PFS at 24 m	Median PFS (1)	OS at 6 m	OS at 12 m	Median OS(1)
2	Poulsen 2008	20	15%	33 %	-	-	22 wks	-	45 %	32 wks
3	Zuniga 2009	14	79 %	79 %	64 %	-	58 wks (13.4 m)	86 %	78 %	Not reached
4	Guiu 2008	28	54 %	-	-	-	-	-	-	-
7	Kang 2008	9	-	75 %	-	-	41 wks (9.5 m)	88 %	-	55 wks (12.6 m)
BEVACIZUMAB MONOTHERAPY										
13	Chamberlain 2009	25	64%	60 %	20 %	-	30 wks (7 m)	76 %	36 %	39 wks (9 m)

(1) Where result for median PFS or OS was reported in terms of months, this has been converted to weeks, with actual month value in brackets.
(2) Temodal PI

The results of bevacizumab treatment were variable, with response rates varying from 15 – 79%, and 6-month PFS from 33 – 79%. Using cross-trial comparison, in most of the studies efficacy appeared to be superior to that documented in the Wong et al paper, or the study with temozolomide. However, study 2 did not suggest any increased efficacy.

Using cross-trial comparison, there did not appear to be any marked advantage of the bevacizumab + irinotecan combination over bevacizumab monotherapy.

Safety

Study AVF 3708g indicated that the bevacizumab + irinotecan combination was associated with an increased incidence of toxicity compared to bevacizumab monotherapy, as illustrated by the table 20:

Table 20: Comparison of Selected Adverse Events

	BV + IRN	BV
Grade III or higher adverse events	66 %	46%
Serious adverse events	43 %	26 %
Any haemorrhage	41 %	27 %

	BV + IRN	BV
Cerebral haemorrhage	4 %	1 %
Venous thrombosis	10 %	4 %
Any seizure	24 %	18 %
Neutropenia	34 %	8 %

The remainder of the studies submitted with the application were open uncontrolled studies, and only limited safety data were reported in the published trials. The evaluator considered that the adverse event profile observed in these studies was in keeping with the known adverse events of bevacizumab.

Risk-benefit analysis

Grade IV glioma

Lack of randomised controlled trial data

The application is based on two Phase II trials with efficacy assessed using comparisons to historical data. The EMEA guideline on anticancer agents which has been adopted by the TGA generally requires provision of Phase III data (comparing the drug to an established comparator) to obtain marketing approval. The previously approved submissions for temozolomide and carmustine implants for relapsed Grade IV disease were based on randomised controlled trials.

However, ADEC and the TGA have previously approved oncology applications based on Phase II data in situations where a) the condition is rare, or b) the condition is a life-threatening one for which no other therapy is available, and the evidence for efficacy is convincing. Bevacizumab has been designated as an Orphan Drug for treatment of malignant glioma due to the rarity of the condition. Temozolomide is approved for relapsed GBM. However, the drug is now used as part of standard first-line therapy in combination with surgery and radiotherapy, and therefore would not be used for relapsed disease. A trial comparing bevacizumab vs temozolomide in the relapsed disease setting is therefore unlikely to have been feasible. It could be argued that a trial comparing bevacizumab to carmustine implants could have been conducted, however, many patients would not be considered suitable for repeat surgery.

On balance, due to the rarity of the condition and the lack of established comparators, the Delegate considered it would be reasonable to base an approval on Phase II data.

Combination with irinotecan

The safety data from study AVF 3708g demonstrate that the combination is associated with significantly increased toxicity compared with bevacizumab monotherapy. For approval of the combination, convincing evidence of a significant efficacy benefit for the combination over monotherapy would be required. No such evidence is available and the Delegate therefore agreed with the clinical evaluator that any approval should be restricted to monotherapy.

Overall risk-benefit

The pivotal study suggested greater efficacy for bevacizumab compared to historical data with chemotherapy. The safety profile of monotherapy was consistent with that previously observed with the drug. The incidence of cerebral haemorrhage was low with

monotherapy. Given the poor prognosis for patients with relapsed Grade IV tumours and the lack of alternative treatments, the Delegate considered that the submitted evidence is sufficient to establish a favourable risk-benefit ratio. It was therefore proposed to approve the application for monotherapy in patients with Grade IV disease.

Approval for grade III glioma

Lack of randomised controlled trial data

Temozolomide is not approved as part of first-line therapy for Grade III disease. It is registered for relapsed Grade III disease (anaplastic astrocytoma). A randomised controlled trial comparing bevacizumab with temozolomide in relapsed disease may therefore have been appropriate. However Grade III disease is even more rare than Grade IV disease and it may not therefore be reasonable to expect Phase III data for this subgroup. Temozolomide was approved for relapsed Grade III disease on the basis of an open uncontrolled trial.

Combination with irinotecan

For the same reasons given in above, the Delegate agreed with the clinical evaluator that any approval for Grade III disease should be restricted to monotherapy.

Overall risk-benefit

If approval for Grade III disease was to be restricted to monotherapy, the only evidence on which to base a risk-benefit assessment would be the study of Chamberlain et al.[5] This was a retrospective analysis on only 25 patients. This would be an inadequate dataset on which to base an approval. The Delegate therefore proposed to reject that part of the application relating to Grade III glioma.

The Delegate proposed to approve the application, but restrict the approval to monotherapy for Grade IV glioma.

The Australian Drug Evaluation Committee (ADEC), having considered the evaluations, the Delegate's overview and the sponsor's responses to these documents, agreed with the Delegate's proposal.

ADEC recommended approval of the submission to include the recommended revised indication:

> *Avastin(bevacizumab) as a single agent, is indicated for the treatment of patients with Grade IV glioma with relapse or disease progression after standard therapy including chemotherapy*

In making this resolution, the Committee noted that bevacizumab has been designated an Orphan Drug for the indication of malignant glioma. Although the application was based on two phase II trials with efficacy assessed using comparisons to historical data, the ADEC concurred with the Delegate that due to rarity of the condition and the lack of established comparators, it was reasonable to base approval on phase II data. Additionally, the pivotal study suggested greater efficacy for bevacizumab compared to historical data with chemotherapy and presented a favourable risk benefit ratio. The Committee noted the safety data from study AVF3708g which demonstrated that the combination with irinotecan was associated with significant toxicity compared with bevacizumab monotherapy, and therefore agreed with the clinical evaluator and the Delegate that approval be restricted to monotherapy.

[5] Chamberlain et al. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. Neurology 2006;67:2089

Outcome

Based on review of quality, safety and efficacy data, TGA approved the registration of Avastin containing bevacizumab 100mg/4mL and 400mg/16mL for the new indication:

as a single agent, for the treatment of patients with Grade IV glioma after relapse or disease progression after standard therapy, including chemotherapy

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

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