EVALUATION SUMMARY

Bevacizumab
for treatment of recurrent glioblastoma multiforme

South Australian Medicines Evaluation Panel

Nov 2014

Government of South Australia
SA Health

Summary of SAMEP review

Receipt of High Cost Medicine (HCM) formulary application:	2nd October 2014
Date of SAMEP meeting:	5th November 2014

Name of medicine	Bevacizumab (Trade name: Avastin®)
Dosage form	Solution for intravenous infusion
Requested Statewide HCM Formulary Listing	Recurrent glioblastoma multiforme (GBM), with the following eligibility criteria: 1. Recurrent GBM after failure of standard treatment with surgery, radiotherapy and temozolomide; and 2. Not suitable for repeat surgery or radiotherapy or existing clinical trials; and 3. KPS[1] score > 60 4. Mini-mental[2] score > 26 5. No contra-indications for bevacizumab (e.g. recent surgery, active bleeding) Exclusion criteria: · Patients who received radiotherapy alone or temozolomide alone upfront unless they receive either on progression (majority of elderly patients) · After second surgery or re-irradiation unless progression documented · Those with poor performance status or poor cognitive function
Cost	100mg vial = $430 400mg vial = $1,720 The estimated costs for 16 weeks treatment and 25 weeks treatment are provided in the following two tables:

[1] KPS = Karnofski Performance Status is a measure of general well-being and activities of daily life in oncology patients, where 100 is "perfect" health and 0 is death (Karnofsky DA & Burchenal JH. (1949). "*The Clinical Evaluation of Chemotherapeutic Agents in Cancer*." In: MacLeod CM (Ed), Evaluation of Chemotherapeutic Agents. Columbia Univ Press. p 196).

2 Mini-mental score – tool to assess the cognitive performance of high grade glioma patients, with a score of 27-30 considered 'normal' and ≤ 26 considered abnormal. A loss of 3 points is considered a clinically significant deterioration (Brown PD, Jensen AW, et al (2006). *Detrimental effects of tumor progression on cognitive function of patients with high-grade glioma*. J Clin Oncol.(24)5427-33).

Table 1: 16 weeks treatment

Patient weight	5mg/kg every 2 weeks (9 doses)	10mg/kg every 2 weeks (9 doses)	15mg/kg every 3 weeks (6 doses)
50kg	$11,610	$23,220	$20,640
70kg	$15,480	$30,960	$28,380
100kg	$19,350	$38,700	$38,700

Table 2: 25 weeks treatment

Patient weight	5mg/kg every 2 weeks (13 doses)	10mg/kg every 2 weeks (13 doses)	15mg/kg every 3 weeks (9 doses)
50kg	$16,770	$33,540	$30,960
70kg	$22,360	$44,720	$42,570
100kg	$27,950	$55,900	$58,050

Note:

The formulary application has requested the dosing regimen of 5mg/kg every two weeks, however this is less than the dose approved by the TGA provided on the product information. Patients treated in SA to date have received 15mg/kg every three weeks. Justification for the lower dose was provided by the applicant (see under Clinical Pathway in Appendix 1).

SAMEP recommendations

Following the review of the current available evidence (appendix 1) and consideration of feedback from formal consultation with oncology clinical directors and prescribers who treat recurrent GBM, SAMEP recommend against listing of bevacizumab on the Statewide High Cost Medicines formulary as monotherapy for the treatment of recurrent glioblastoma multiforme (GBM) for the following reasons:

- While there is a clinical need for treatment for this patient group, the current data set shows no survival benefit with bevacizumab monotherapy.
- The Pharmaceutical Benefits Advisory Committee (PBAC) reviewed bevacizumab for recurrent GBM in November 2010, and it was rejected for listing on the PBS on basis of uncertain clinical benefit and an unacceptably high and uncertain incremental cost-effectiveness ratio. Since the PBAC review, the publication of the BELOB trial, an open-label, three arm, multi-centre phase II randomised study, has provided further evidence to support the outcome of the PBAC review in November 2010 [1]. Although the BELOB trial had limitations due to study design, there is evidence of no

improvement in overall survival with bevacizumab monotherapy compared to lomustine.

- There is uncertainty regarding the effect of bevacizumab on quality of life in recurrent GBM. This is an important outcome to patients in this setting particularly when the drug has no overall survival advantage. There is no evidence that bevacizumab is superior to best supportive care with respect to impact on quality of life.

    - While QoL was measured in the BELOB trial, QoL data were not reported in the available publication.

    - Anecdotal evidence of reduction in seizures in patients given bevacizumab, would be an easily measurable QoL indicator in these patients, however there is no published evidence correlating this.

- The ICER (as estimated by PBAC) is likely to be greater than $200,000, when compared to best supportive care. From the perspective of SA Health, it is not a cost-effective use of resources.

Additional issues noted by SAMEP:

- There are no placebo-controlled trials with bevacizumab in the recurrent GBM population i.e. the requested population in this application.

- There is no current standard of care for recurrent (progression following first-line therapy) GBM. Re-resection & re-irradiation, or various chemotherapeutic agents such as temozolomide, etoposide or carboplatin, or best supportive care / palliative care are the options. The median overall survival for recurrent GBM is estimated to be between 7-9 months [2]. Symptoms depend upon size, location and degree of infiltration of the tumour, and include headache, nausea, vomiting, seizures, visual disturbances, speech & language problems, and changes in cognitive and/or functioning ability.

- Safety – bevacizumab appears to be well tolerated with hypertension being the most common side effect, and easily managed. Intracranial haemorrhage is rare, but reported.

- Cost-share program: Prior to May 2014, a cost-share program offered by Roche specified that if patients paid for two doses, Roche would then fund all subsequent doses until disease progression. Since May 2014, the cost-share arrangement with Roche has been amended so that patients must pay for the first three months of treatment to be eligible for Roche paying subsequent doses until disease progression. SAMEP members noted that the median progression-free survival (PFS) in the bevacizumab arm of the BELOB trial was three months, therefore it is expected that many patients would never reach eligibility for compassionate supply under the new cost-share program.

- Dose: The cost-share arrangement offered by Roche does not include the dosing regimen proposed in the formulary application (5mg/kg every 2 weeks). The cost-share program is only offered at 10mg/kg every two weeks or 15mg/kg every three weeks.

The proposed dose of 5mg/kg is less expensive than the 10 -15mg/kg dose regimens recommended by the manufacturer. The review by Wong et al was cited by the applicant as the basis of the lower dose as the review reported no significant difference in 6-month PFS or 6-month overall survival between the 5mg/kg dose and higher doses, however the studies included in the review were of low quality, and the methods of combining trial results was not provided [3]. The trials included in the review that used 5mg/kg doses of bevacizumab, were using combination therapy with irinotecan, carboplatin, etoposide, lomustine or carmustine and therefore it is uncertain whether the 5mg/kg dosing schedule as monotherapy would be comparable.

- Although the proposed population is different to the first-line setting in which many of the current trials are investigating the use of bevacizumab, the results of the trials in that setting may also provide information on the possible benefits associated with bevacizumab therapy in GBM. The Cochrane review pooled the data from seven identified RCTs in both the first-line and recurrent GBM setting and found no differences in overall survival (Fixed effect pooled HR = 0.94; 95% CI: 0.86-1.02, p=0.16).

Appendix 1 Review of the evidence

Evaluation by other jurisdictions:

Pharmaceutical Benefits Advisory Committee (PBAC)	November 2010 → rejected on basis of uncertain clinical benefit and an unacceptably high and uncertain incremental cost-effectiveness ratio
Canadian Agency for Drugs and Technologies in Health (CADTH)	Bevacizumab has not been evaluated by CADTH for glioblastoma multiforme
Scottish Medicines Consortium (SMC)	Bevacizumab has not been evaluated by SMC for glioblastoma multiforme
National Institute for Health and Clinical Excellence (NICE)	Bevacizumab has not been evaluated by NICE for glioblastoma multiforme (Note - scoping for an appraisal was completed in November 2009, however the appraisal was suspended following the European Medicines Agency (EMA) refusal to recommend a licence extension for the treatment of glioblastoma).
Cochrane Collaboration	2014 → Khasraw M, et al., *Antiangiogenic therapy for high-grade glioma.* Cochrane Database of Systematic Reviews, 2014 [Available online: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008218.pub3/pdf]. [4]
EviQ – Cancer Institute of NSW (www.eviq.org.au)	April 2013 → published protocol for bevacizumab for recurrent glioblastoma multiforme [5]

Bevacizumab is approved by the FDA for use as monotherapy in recurrent glioblastoma in the United States.

Bevacizumab is not approved for treatment of glioblastoma in Europe, following the Committee for Medicinal Products for Human Use rejecting an application to extend the marketing authorisation in Europe to include glioblastoma in 2014 [6].

SEARCH STRATEGY FOR ADDITIONAL EVIDENCE

Population	Patients with recurrent glioblastoma multiforme (where 'recurrent' is defined as: Relapse or disease progression after standard therapy with surgery, chemotherapy and radiation)
Intervention	Bevacizumab
Comparator	Other chemotherapy regimens (including temozolomide, etoposide, or carboplatin) Supportive care / palliative care
Outcome(s)	Health-related quality of life Progression-free survival Overall survival Adverse effects of treatment

Only one RCT investigating bevacizumab in recurrent GBM was identified in the Cochrane review by Khasraw et al, 2014. Therefore the search for additional evidence was expanded to include non-randomised studies:

Database searched: Medline

Selection criteria: All intervention studies

Search terms used:

1. clinical trial.mp.
2. clinical trial.pt.
3. 1 or 2
4. bevacizumab.mp.
5. Avastin.mp.
6. 4 or 5
7. exp Glioblastoma/
8. 3 and 6 and 7

Search conducted: 20 October 2014 - returned 75 citations. 28 of the 75 were in the recurrent GBM population (as opposed to newly diagnosed).

CLINICAL TRIALS

A search of ClinicalTrials.gov using the search terms "bevacizumab" AND "recurrent glioblastoma" (open studies, exclude unknown, interventional studies) identified 28 are actively recruiting studies (date of search 21 Oct 2014). 8 of the 28 were classified as randomised studies. Comparator arms in the various studies include nivolumab, ipilimumab, low dose bevacizumab + lomustine, intensity-modulated radiation therapy, Novo-TTF, temozolomide, bortezomib, vaccine therapy with bevacizumab, anti-endoglin monoclonal antibody TRC105, Rindopepimut (CDX-110) with GM-CSF, TPI 287(third generation taxane).

OVERVIEW OF RECURRENT GLIOBLASTOMA MULTIFORME (GBM)

Overview of Disease

Gliomas are malignant brain tumours that develop from the glial cells that support the nerve cells of the brain and spinal cord. They are graded (by the World Health Organisation classification) according to the proliferative potential, from grade 1 to grade 4. Grades 3 & 4 are considered high grade gliomas, and grade 4 gliomas are called glioblastoma multiforme (GBM). Gliomas account for almost 80% of primary malignant brain tumors [7].

Incidence

In 2009, 123 new cases of brain cancer were diagnosed in South Australia. Of the 123 new cases of brain cancer in SA in 2009, 74 (60%) were men and 49 (40%) were women [8].

If an estimated 80% of these cases are glioma, this would equate to approximately 99 new cases of glioma per annum in South Australia. The exact incidence of GBM is not known [9].

All gliomas are more common in men than in women, with a male:female ratio of approximately 3:2.[7, 10].

Symptoms

Symptoms of high-grade glioma depend upon size, location and degree of infiltration of the tumour. They include headache, nausea, vomiting, seizures, visual disturbances, speech & language problems, and changes in cognitive and/or functioning ability.

Treatment and prognosis

In Australia, the standard of care for *newly diagnosed* patients is maximal surgical resection followed by the "Stupp regimen" which includes adjuvant radiotherapy and temozolomide over 7 weeks, and subsequent temozolomide treatment for six months [11].

There is no current standard of care for recurrent (progression following first-line therapy) GBM. Re-resection & re-irradiation, or various chemotherapeutic agents such as temozolomide, etoposide or carboplatin, or best supportive care / palliative care are the options.

The prognosis for patients with recurrent GBM is poor, with a high propensity for tumour recurrence following first-line therapy. The median overall survival from initial diagnosis of GBM is estimated to be between 12-18 months. The natural history of *recurrent* GBM is largely undefined due to the heterogeneous nature of the disease and a lack of uniform definition and criteria for tumour recurrence. The median overall survival for recurrent GBM is estimated to be between 7-9 months [2].

Probable mechanism of action of bevacizumab

GBMs are highly vascular. Vascular endothelial growth factor (VEGF) is a protein involved in the regulation of new blood vessel formation, promoting survival of tumour blood vessels. Bevacizumab is an anti-VEGF antibody which binds to circulating VEGF_A preventing the formation of new blood vessels [4].

CLINICAL PATHWAY PROPOSED BY APPLICANT

Eligibility criteria:

1. Recurrent GBM after failure of standard treatment with surgery, radiotherapy and TMZ
2. Not suitable for repeat surgery or radiotherapy or existing clinical trials
3. KPS score >60
4. Mini-mental score > 26
4. No contra-indication for bevacizumab (e.g. recent surgery, active bleeding)

These strict criteria exclude the following patients:

- Patients who have received XRT alone or TMZ alone upfront unless they receive either on progression i.e. majority of the elderly
- After second surgery or re-irradiation unless progression documented
- Those with poor performance status or poor cognitive function

Dosing regimen: 5mg/kg intravenously every two weeks until disease progression of prohibitive toxicity.

Note: The Product Information for Avastin, registered with the TGA, recommends the following dose: 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an IV infusion. It is recommended that AVASTIN treatment be continued until progression of the underlying disease.

The following justification for the proposed dosing regimen was provided in the application: "Three different dosing schedules have been used in GBM trials - 5mg/kg or 10mg/kg every 2 weeks or 15mg/kg every 3 weeks. A meta-analysis by Wong et al involving 548 patients identified that there was no dose-response difference seen between 5mg/kg and 10-15mg/kg doses".

Response assessment:

- MRI +/- MRS every 8 weekly
- Response assessed by using MacDonald's criteria or RANO criteria (see appendix 6)[12]. The referenced criteria use a comprehensive clinical-radiological assessment to categorise patients into four groups as in RECIST criteria. However, the use of clinical criteria (dose of steroid + clinical stability) in addition to imaging is unique to gliomas. Treatment with bevacizumab will be continued if the patient has complete response or partial response or stable disease as per the above criteria.
- Treatment will be ceased if progressive disease as per MacDonald's or RANO criteria is documented (as per table in Appendix 6 provided by the applicant, adapted from Weller et al, 2013 [12])

SUMMARY OF EVIDENCE FOR THE USE OF BEVACIZUMAB IN RECURRENT GLIOBLASTOMA MULTIFORME

Systematic Reviews & meta-analyses

Citation	Khasraw, M., et al., *Antiangiogenic therapy for high-grade glioma.* Cochrane Database of Systematic Reviews, 2014. **9**([Available online at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008218.pub3/pdf]).
Funding of review	Support for third party writing assistance was provided by F. Hoffman-La Roche ltd.
Review protocol & registration no.	Not provided
Study eligibility criteria:	
Patient population	High-grade gliomas
Intervention	Antiangiogenic therapy
Comparator(s)	Therapy without antiangiogenic therapy
Outcomes	1° outcome: Overall survival 2° outcomes: Progression-free survival, Quality of life, Adverse events
Study design(s) included	Only RCTs comparing antiangiogenic therapy versus a control treatment without antiangiogenic treatment included
Data sources	Cochrane Central Register of Controlled Trials, Medline & Embase Abstracts of conference proceedings Members of Cancer groups (EANO, SNO) & manufacturers of relevant drugs asked to provide details of outstanding clinical trials / unpublished trials
Data extraction	Two review authors independently assessed studies retrieved for eligibility, with consensus resolved by a third author. Data extraction performed independently by two reviewers and consensus resolved by a third reviewer.
No. of eligible studies included	7 eligible RCTs
Risk of bias in individual studies	4 of the 7 studies were only abstracts of conference proceedings – not possible to evaluate risk 3 of the 7 were determined low risk of bias as per the Cochrane risk of bias tool): · Allocation concealment - used computer-generated allocation · Blinding – participants & investigators blinded. Radiological review blinded. · Incomplete outcome data – minimal loss to follow-up, all used intention-to-treat analysis · Selective reporting – all trials pre-registered

No of patients included	2987
Synthesis of results	RevMan5
Results	Meta-analysis of all seven trials of antiangiogenic therapy found no observed differences in overall survival, with a fixed-effected pooled HR of 0.94 (95% CI: 0.86-1.20, p=0.16). Significant heterogeneity observed (I^2=0.61) due to differences in patient population, clinical setting & interventions.

Discussion

Of the 7 studies included in the Cochrane review above, only two studies were in the recurrent GBM population, and only one investigated bevacizumab (the BELOB trial) [1]. A meta-analysis of the two studies of antiangiogenic therapy in the recurrent setting showed no significant difference in overall survival (fixed effect HR 1.02, 95%CI: 0.84 – 1.24, p=0.86).

The BELOB trial was a phase II, three-arm, industry-funded open label trial comparing bevacizumab alone (10mg/kg every 2 weeks), oral lomustine alone (110mg/m^2 once every 6 weeks) or a combination of bevacizumab and lomustine [1]. The BELOB study did not report progression-free survival (PFS).

The Cochrane review concluded that current published data are inadequate to allow formal assessment and pooling of quality of life endpoints [4].

Systematic Reviews & meta-analyses cont.

Citation	Wong, E.T., et al., *Bevacizumab for recurrent glioblastoma multiforme: a meta-analysis.* Journal of the National Comprehensive Cancer Network, 2011. **9**(4): p. 403-7.
Funding of review	'A reason to ride' research fund (charitable cancer fund)
Review protocol & registration no.	(no registration no identified)
Study eligibility criteria:	
Patient population	Malignant glioma (recurrent glioblastoma)
Intervention	Bevacizumab in combination with irinotecan, bevacizumab alone, bevacizumab + stereotactic radiosurgery, bevacizumab + other chemotherapy (carboplatin, carmustine, etoposide, lomustine, liposomal doxorubicin) Dose range of bevacizumab in included studies: 5-15mg/kg
Comparator(s)	Not clear (Single arm, non-comparative studies included)
Outcomes	Overall survival; 6-month survival; 6-month progression free survival; time to progression; response (complete, partial or stable disease)
Study design(s) included	Study design of included trials not provided
Data sources & search process	Medline Plus/OVID for published studies (abstracts excluded). Search terms or criteria not provided.

Risk of bias in individual studies	Assessment of risk of bias in individual studies not provided.
No. of eligible studies included	18 studies identified (15 included, 3 excluded). 2 excluded studies were on anaplastic gliomas, and 1 excluded as bevacizumab was used first-line and recurrence.
No of patients included	548
Summary measures	---
Synthesis of results	Method of combining results not provided
Risk of bias across studies	Assessment of risk of bias across studies not presented; measure of heterogeneity not provided.

Discussion:

Although the title of the above review implies a meta-analysis, the method of combining the studies is not described and no quantitative combined summary data are provided, including no forest plot or measure of heterogeneity (e.g. I^2) [3]. The study selection process, search terms used, and data extraction methods are not provided. [3]. The level of evidence limited by the level of evidence of the included studies, all of which are level III-2 (systematic review of level III-2 comparative studies, cohort studies, case-control studies) or lower.

Despite the limitations of the review and the lack of explanation as to how the studies were combined, the authors reported the median overall survival to be 9.3 months (95% CI: 7.9 – 10.6 months) [3]. The 6-month PFS rate was 45% (95% CI: 34-57%) and 6-month overall survival was 76% (95% CI: 69-84%). The review focussed on the possibility of using the lower dose of 5mg/kg as it was likely to be cost-saving, and the authors reported no significant difference to the higher dose, however the studies investigating the 5mg/kg dose of bevacizumab were investigating it's use as combination therapy [3].

Systematic Reviews & meta-analyses cont.

Citation	Zhang, G., S. Huang, and Z. Wang, *A meta-analysis of bevacizumab alone and in combination with irinotecan in the treatment of patients with recurrent glioblastoma multiforme.* Journal of Clinical Neuroscience, 2012. **19**(12): p. 1636-40.
Funding of review	Not provided
Review protocol & registration no.	---
Study eligibility criteria:	
Patient population	Histologically proven GBM, who had tumour progression measured by MRI
Intervention	bevacizumab alone, or in combination with irinotecan
Comparator(s)	Not stated
Outcomes	Overall survival, progression-free survival
Study design(s) included	Not stated
Data sources & search	Databases searched: Pubmed, Embase & Cochrane

process	controlled trials registry. Search terms provided, no language or date limitations Abstracts from meetings of the American Society of Clinical Oncology searched.
No. of eligible studies included	12 studies identified including 519 patients. 39 patients excluded as diagnosis not GBM, therefore 480 patients from 11 studies included
No of patients included	480
Risk of bias in individual studies	Assessment of risk of bias in individual studies not provided.
Summary measures	---
Synthesis of results	Results displayed in tabular format for each study (see table below) but method of combining results not provided.
Risk of bias across studies	Assessment of risk of bias across individual studies not provided. Heterogeneity across studies discussed but no measure provided.

Extracted from Zhang et al, 2012 [13]

Table 1
Patients with recurrent glioblastoma treated with bevacizumab only or in combination with irinotecan

Year[ref]	No. patients	Median age (years; min, max)	Bevacizumab dose (mg/kg)	Combined with irinotecan	Treatment cycle (weeks)	CR (%)	PR (%)	SD (%)	OR (%)[A]	TTP (months)	DT (%)	PFS-6 (%)	Median PFS (months)	OS-6 (%)	Median OS (months)
2009[19]	85	54 (23, 78)	10	No	2	1.2	27.1	N/A	28.3	N/A	4.8	42.6	4.2 (2.9–5.8)	74.1	9.2 (8.2–10.7)
2009[19]	82	57 (23, 79)	10	Yes	2	2.4	35.4	N/A	37.8	N/A	17.7	50.3	5.6 (4.4–6.2)	69.5	8.7 (7.8–10.9)
2008[17]	17	56 (38, 74)	5	Yes	2	10.5	36.8	10.5	47.3	4.7	5.9	25	4.2 (0.7–10.5)	55	7 (1.7–16)
2009[20]	37	53 (30, 74)	10	Yes	2	5.4	62.2	16.2	67.6	N/A	16.2	63.7	7.6 (4.8–10.5)	78	11.5 (8.3,15.6)
2007[16]	35	48 (18, 66)	10,15	Yes	2,3	N/A	57	43	57	4.6	31.4	46	6 (4.5–9)	77	10.5 (8.75–15)
2010[21]	50	64 (36, 70)	10	No	2	0	42	0	42	1	0	42	10	76	8.5 (2–17)
2009[22]	48	53 (21, 69)	10	No	2	2	33	20	35	N/A	12.5	29	4 (3–6.5)	57	7.75 (5.25–13.5)
2008[23]	13	53 (32, 76)	5,10	Yes	2	0	77	23	77	6	15.4	N/A	N/A	N/A	6.75
2009[24]	57	57	10	Yes	2	N/A	N/A	N/A	N/A	N/A	N/A	37	N/A	N/A	N/A
2008[25]	12	46 (5, 69)	10	Yes	4	0	44	41	44	N/A	50	17	3.8	75	7.1
2007[26]	17	58 (26, 78)	10	Yes	2	0	19	48	19	2.4	N/A	N/A	N/A	65	N/A
2009[18]	27	46 (26, 67)	10	Yes	2	14.8	14.8	44.4	29.6	N/A	14.8	40	5.5 (4–7)	54	7 (3.25–10.75)

CR = complete response, DT = discontinued treatment, max = maximum, min = minimum, N/A = not available, OR = objective response, OS-6 = 6-month overall surviv
OS = overall survival, PFS-6 = 6-month progression-free survival, PR = partial response, SD = stable disease, TTP = time to progression.
[A] OR (%) = CR (%) + PR (%).

Discussion

As with the review by Wong et al, this study by Zhang et al implied a meta-analysis in the study title, however the individual study results are provided separately but the method of combining the studies is not described and no quantitative combined summary data are provided, including no forest plot or measure of heterogeneity (e.g. I^2) [13].

Despite the limitations of the design of the included studies, the authors concluded that there was no significant difference in overall survival between bevacizumab alone, compared to combination with irinotecan. The reported mean overall survival for bevacizumab alone was 8.6 months, compared to 8.9 months for bevacizumab plus irinotecan [13].

Randomised controlled trial

Citation	Taal W, Oosterkamp HM, Walenkamp AME, Dubbink HJ, Beerepoot LV, Hanse MCJ, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncology. [Research Support, Non-U.S. Gov't]. 2014 Aug;15(9):943-53.			
Funding of study	Roche (Nederland) & KWK Kankerbestrijding (Dutch Cancer Society)			
Design	Open-label, three arm, multi-centre phase II randomised study			
Trial Identification number	NTR1929 (www.trialregister.nl)			
Duration of treatment	Lomustine arm - maximum of 6 treatment cycles (36 weeks) Bevacizumab arm - until disease progression Combination arm -not specified			
Patient population	*Inclusion criteria*: · Histologically proven glioblastoma, with progression after previous chemo-radiotherapy with temozolomide · At least one bi-dimensionally measurable target lesion of at least 10mm · Had not received previous chemotherapy for recurrent disease · Had not received previous treatment with anti-VEGF or nitroureas · On stable or decreasing dose of steroids for 7 days from baseline MRI scan · Had not received radiotherapy within 3 months of diagnosis of progression · Had not received chemotherapy in the previous 4 weeks · ≥ 18 years of age · WHO performance status of 0-2 · Adequate bone marrow, renal and hepatic function *Exclusion criteria*: · Uncontrolled hypertension (Systolic > 150mmHg or diastolic > 100mmHg · Arterial or venous thrombosis in previous 6 months · Evidence of recent haemorrhage on brain MRI · Substantial cardiac disease (eg MI in previous 6 months, or unstable angina) · Use of therapeutic doses of oral or parenteral anticoagulants or thrombolytic drugs			
Interventions	Bevacizumab 10mg/kg every 2 weeks until disease progression	Lomustine 110mg/m^2 every 6 weeks for 6 cycles	Bevacizumab 10mg/kg every 2 weeks + lomustine 110mg/m^2	Bevacizumab 10mg/kg every 2 weeks + lomustine 90mg/m^2
No. of patients in treatment arm	50	46	8	44
Withdrawals from treatment arm	50 (100%): · 3 early progression · 45 progression · 2 toxicity	46 (100%): · 1 withdrew consent · 5 early progression · 37 progression	7 (88%): · 7 progression	42 (95%): · 2 withdrew consent · 2 early progression · 30 progression · 3 toxicity · 2 died

		· 3 other reason		· 3 other reason
Primary efficacy outcome(s)	9-month overall survival			
Secondary outcome(s)	Median PFS PFS at 6 months PFS at 12 months Proportion of patients who achieved an objective response Association of outcome with MGMT promotor methylation status			
Blinding of patients	No			
Blinding of outcome assessors	No			
Allocation concealment	Yes			
Outcomes:	Bevacizumab 10mg/kg every 2 weeks until disease progression	Lomustine 110mg/m^2 every 6 weeks for 6 cycles	Bevacizumab 10mg/kg every 2 weeks + lomustine 110mg/m^2	Bevacizumab 10mg/kg every 2 weeks + lomustine 90mg/m^2
9-month overall survival	38%	43%	87%	59%
Median PFS (months)	3 (95% CI: 3-4)	1 (95% CI:1-3)	11 (95% CI:1-27)	4 (95% CI:3-8)
6-month PFS	16% (95% CI:7-27)	13% (95% CI: 5-24)	50% (95% CI: 15-77)	41% (95% CI: 26-55)
12-month PFS	Not provided			
Proportion of patients who achieved an objective response	18/48 (38%)	2/41 (5%)	5/8 (63%)	14/41 (34%)

Discussion

The BELOB trial above is the only well-controlled randomised trial investigating bevacizumab for the treatment of recurrent GBM [1]. 148 were included in the analysis with no patients lost to follow-up. The median number of treatment cycles was one for the lomustine group, two in the bevacizumab group, three in the bevacizumab + 90mg/m^2 lomustine group and six in the bevacizumab + 110mg/m^2 lomustine group. Most patients (129/148, 87%) discontinued treatment for early progression or progression. Hypertension was the most common adverse event in the bevacizumab group (26% of patients)[1].

Outcomes were assessed with MRI scans after every cycle for the first four treatment cycles, and thereafter following every other cycle. Salvage therapy was given to each of the treatment groups on disease progression[1]. Response and disease progression was assessed with the RANO criteria. Clear disease progression at 6 weeks was defined as early progression and treatment was discontinued. Health-related Quality of Life (HR-QoL) was assessed but not reported in this publication but the authors stated that results of HR-QoL will be reported separately in the future [1].

The authors concluded that the results of the trial do not support a significant role for single-agent bevacizumab in recurrent glioblastoma, but that a phase 3 trial of the combination treatment with lomustine 90mg/m^2 is warranted [1].

Other studies

Single-agent bevacizumab was approved for marketing by the FDA in the USA based upon submission of the following two studies:

- The BRAIN study: Friedman, H.S., et al., *Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma.* Journal of Clinical Oncology, 2009. **27**(28): p. 4733-40

- The National Cancer Institute (NCI) study: Kreisl, T.N., et al., *Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma.* Journal of Clinical Oncology, 2009. **27**(5): p. 740-5.

The BRAIN study evaluated the efficacy of bevacizumab alone (10mg/kg every 2 weeks) or in combination with irinotecan in 167 patients [14]. The estimated 6-month PFS rates were 42.6% (97.5% CI: 29.6 - 55.5%) in the bevacizumab group and 50.3% (97.5% CI: 36.8 – 63.9%) in the bevacizumab + irinotecan group. Median overall survival was 9.2 months in the bevacizumab group and 8.7 months for the bevacizumab + irionotecan group [14]. 39 patients (46.4%) experienced grade 3 or higher adverse events, including hypertension (8.3%) & convulsions (6%) in the bevacizumab monotherapy group, and convulsion (13.9%), neutropenia (8.9%) & fatigue (8.9%) in the combination group. Intracranial haemorrhage occurred in two patients (2.4%) in the bevacizumab monotherapy group, and in three patients (3.8%) in the combination therapy group [14].

The NCI study included 48 adults (median age 53 years) with recurrent GBM following radiotherapy and temozolomide [15]. All patients were treated with bevacizumab monotherapy 10mg/kg every two weeks. 26 patients (54%) were receiving corticosteroids at baseline. On progression, patients received combination therapy with bevacizumab + irinotecan. The primary endpoint was 6-month PFS, which was reported to be 29% (95% CI: 18-48%). The median PFS was 16 weeks (95% CI: 12-26 weeks), the 6-month overall survival rate was 57% (95% CI: 44-75%) and the median overall survival was 31 weeks (95% CI: 21-54 weeks) [15]. The most frequently reported adverse event were thromboembolic events, occurring in 6 patients (12.5%) and hypertension (12.5%) [15]. Of the patients who were on corticosteroids at baseline, 15 (58%) were able to reduce their dose while in the study, with an average reduction in steroid dose of 59% [15]. It was not reported if any patients not taking steroids at baseline were commenced on steroids during the study.

OVERVIEW OF EVIDENCE

Study Design and Quality

There are no placebo-controlled randomised trials in this patient population. At the time of the PBAC review in November 2010, there were no direct comparative trial data available, and historical control data was used for that submission. In 2014, the BELOB trial, a phase II randomised controlled trial was published and was the only randomised trial in the recurrent GBM population that was identified in the Cochrane systematic review published in 2014 [4]. The Cochrane review by Khasraw et al is the highest quality evidence, however it investigated all anti-angiogenic therapy (not only bevacizumab) in all high grade gliomas (newly diagnosed or recurrent grade 3 or 4 gliomas).

Effectiveness

Overall survival & Progression-free survival

Results from the BELOB trial, the only well controlled randomised study comparing bevacizumab in recurrent GBM, showed no improvement in 9-month overall survival in the bevacizumab only arm compared to the other groups:

Treatment arm	9-month overall survival	Median PFS (months)	6-month PFS
Bevacizumab 10mg/kg every 2 weeks until disease progression	38% (95% CI: 25-51%)	3 (95% CI: 3-4)	16% (95% CI:7-27)
Lomustine 110mg/m^2 every 6 weeks for 6 cycles	43% (95% CI: 29-57%)	1 (95% CI:1-3)	13% (95% CI: 5-24)
Bevacizumab 10mg/kg every 2 weeks + lomustine 110mg/m^2	87% (95% CI: 39-98%)	11 (95% CI:1-27)	50% (95% CI: 15-77)
Bevacizumab 10mg/kg every 2 weeks + lomustine 90mg/m^2	59% (95% CI: 43-72%)	4 (95% CI:3-8)	41% (95% CI: 26-55)

Quality of life

There are no published clinical trial data on the effect of bevacizumab on QoL in this patient group. A narrative review of the impact of therapy on quality of life in glioblastoma multiforme was submitted with the formulary application [16]. Main points noted in the publication by Henriksson et al:

- Loss of neurologic function and inability to perform daily activities is likely to reduce the quality of life (QoL) of patients with glioblastoma multiforme.
- To determine the effect of a treatment on the QoL of a patient with GBM, it is necessary to determine the QoL of the patient at baseline. A review of the literature published in 2009 noted that due to different measurement tools used, and different times of measurement of baseline QoL (e.g. after surgery but before radiotherapy, after radiotherapy, before chemotherapy) it is not possible to directly compare results of different trials [17].
- Due to the absence of well-powered randomised trials investigating bevacizumab for treatment of glioblastoma multiforme, there is no robust data determining the impact of bevacizumab on QoL, compared to alternative treatment or best supportive care.
- Measurement of health-related quality of life (HR-QoL) is complicated by the fact that patients with impaired neurocognitive function may not be able to complete multidimensional HR-QoL questionnaires. Multi-dimensional HR-QoL tools may not be sensitive to detect changes in QoL in patients with GBM and more disease-specific tools may be more sensitive. In addition, it is likely that missing data due to non-completion of questionnaires is from patients with more advanced disease, and potentially poorer HR-QoL.

- Toxicity of chemotherapeutic agents may reduce the QoL of GBM patients due to adverse effects. Corticosteroid use may also negatively impact QoL due to adverse effects, however the possible steroid-sparing effect of bevacizumab is difficult to quantify based on current available data.

The recently published BELOB trial reported that they measured HR-QoL, however the results of QOL are not yet published [1].

A review of seven randomised trials in glioma which reported HR-QoL showed no statistically significant differences in HR-QoL between the arms of the trials (the trials included comparisons between supportive care, radiotherapy, chemotherapy, placebo, but none investigating bevacizumab). [17]

Safety

Adverse effects of antiangiogenesis are considered a 'class effect' and include bleeding, hypertension, delayed wound healing, gastrointestinal perforation and thromboembolic events (stroke, MI, TIA, angina) [4].

Adverse effects reported in the phase II BRAIN study showed hypertension (8.3%) and convulsions (6%) were the most commonly reported adverse events in the bevacizumab alone arm of the study. Intracranial haemorrhage occurred in 2 patients (2.4%) in the bevacizumab-alone arm, compared to three patients (3.8%) in the bevacizumab plus irinotecan arm [14]. In the BELOB trial, hypertension was significantly more commonly reported in patients who received bevacizumab monotherapy compared to patients who did not receive bevacizumab (26% compared to 7% respectively)

Infusion-related reactions including shortness of breath, flushing, hypo/hypertension, hypersensitivity occurs in <3% of patients, therefore the manufacturer recommends administering the initial dose over 90 minutes and ceasing the infusion if reaction occurs, and treating symptomatically. If well tolerated, subsequent doses can be administered over 60 minutes (Australian Medicines Handbook).

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