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CADTH Reimbursement Review

CADTH Review Report

BEVACIZUMAB AND LOMUSTINE

(Non-Sponsored Review)

Therapeutic area: recurrent glioblastoma multiforme

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Abbreviations

AE	adverse event
CI	confidence interval
EORTC	European Organization for Research and Treatment of Cancer
HR	hazard ratio
HRQoL	health-related quality of life
ITT	intention-to-treat population
OL	open label
RANO	Response Assessment in Neuro-Oncology
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
VEGF	vascular endothelial growth factor
WDAE	withdrawal due to adverse event
WHO	World Health Organization

Executive Summary

An overview of the drug under review is provided in Table 1.

Table 1: Submitted for Review

Item	Description
Drug product	Bevacizumab (and biosimilar agents), 25 mg/ml solution for injection, IV infusion; used in combination with: Lomustine (CeeNu and generics), 10, 40 and 100 mg tablets, oral.
Health Canada Indication	Bevacizumab, in combination with lomustine, is indicated for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy.
Indication under consideration for reimbursement	As per Health Canada indication
Health Canada Approval Status	Approved
NOC date	April 29, 2022
Requester	Provincial Advisory Group

Introduction

Glioblastoma is a highly malignant and rapidly progressing brain tumour; prognosis is poor, as disease progression or reoccurrence is inevitable in most cases.[1,2] Survival rates range from 25-30% after 2 years, and are as low as 10-12% 5 years after diagnosis.[1,3] Glioblastoma has an average annual age-standardized incidence rate of 4.05 per 100,000 in Canada, and it is responsible for half of all malignant central nervous system tumours in the country.[4]

There is a lack of consensus regarding the management of patients upon relapse or disease progression, and evidence supporting the comparative efficacy of currently available treatments is limited.[1,2] Options for treatment of recurrent glioblastoma multiforme after chemoradiation can include repeat surgical resection, in some select-cases re-irradiation, second line systemic therapies, clinical trials and best supportive care. Second line systemic therapies such as bevacizumab, lomustine or temozolomide re-challenge may be initiated.[2] Current therapies are viewed as palliative and potential benefits should be weigh against toxicity and impact on quality of life.[2]

Glioblastoma is a highly vascularized tumour and is accompanied by abnormally high expression of vascular endothelial growth factor (VEGF).[3,5] Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to, and neutralises the biologic activity of, human VEGF, thereby reducing the vascularisation of tumours and inhibiting tumour growth.[6] Bevacizumab has a Health Canada-approved indication, in combination with lomustine, for the treatment of patients with glioblastoma multiforme after relapse or disease progression, following prior therapy.[6]

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to use bevacizumab in patients with recurrent glioblastoma multiforme, to slow down disease progression. The PAG requested that CADTH review bevacizumab in combination with lomustine for patients with recurrent glioblastoma multiforme and provide a reimbursement recommendation.

The clinical and pharmacoeconomic evidence for the review were provided through the CADTH Non-sponsored Reimbursement Review process. The review includes an appraisal of the clinical evidence and a comparison between the treatment costs associated with bevacizumab and lomustine and those comparators deemed to be appropriate based on feedback from clinical experts and public drug programs.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient groups who responded to CADTH's call for patient input and from clinical expert(s) consulted by CADTH for the purpose of this review.

Patient Input

No input was provided to CADTH for this review by any patient group.

Clinician input

Input from clinical experts consulted by CADTH

Two clinical specialists with expertise in the diagnosis and management of glioblastoma multiforme provided the input. The clinical experts noted that recurrent glioblastoma multiforme is highly refractory and challenging to treat with a median survival of 6-8 months, and often characterized by significant disability and dependence, with patients suffering from inexorable neurologic decline. The clinical experts identified that the current goal of recurrent glioblastoma multiforme treatment is to have a longer time free of neurologic deterioration, and patients being able to take fewer corticosteroids. These outcomes would translate to the patients being able to participate more fully in their lives, in whom symptoms are better palliated, reliance on corticosteroids is reduced and health-related quality of life (HRQoL) is often improved.

Clinical experts indicated that lomustine has an established used as a second-line systemic agent for recurrent glioblastoma multiforme, if temozolomide has failed. The clinical experts emphasized that bevacizumab is used in the recurrent setting, and can be considered akin to a supportive care agent rather than a direct anti-cancer therapy. Rather, bevacizumab (standard or alternate low dose regimen) is frequently used in the second line setting for recurrent glioblastoma multiforme to improve neurological deficits and to reduce peritumoural edema and prolong the time to neurologic deterioration. As such, clinical experts have indicated that bevacizumab is also used in instances where the tumour is refractory to lomustine.

As per the experts, patients with recurrent glioblastoma multiforme who are not eligible for surgical resection, re-irradiation or a clinical trial would be considered for treatment with the combination lomustine-bevacizumab. Patients with large volume recurrent tumours with significant mass effect/vasogenic edema, significant neurological symptoms, evidence of radionecrosis, and debilitating corticosteroid toxicities (as a steroid-sparing agent) could derive the most clinical benefit from the lomustine-bevacizumab combination or bevacizumab monotherapy. The clinical experts recommended that treatment with lomustine-bevacizumab should be based on tumour factors (histolgic confirmation of glioblastoma multiforme (WHO grade 4), volume of recurrent tumour, degree of associated vasogenic edema), patient performance status (including assessment of neurological deficits, functional independence, ECOG performance status, tolerability of corticosteroids, co-morbidities) and clinician's recommendation based on fitness for treatment. One clinical expert also noted that the activity of alkylating agents including lomustine may be most beneficial in patients with MGMT promoter methylation.

As per the experts, lomustine is discontinued if there is evidence of disease progression or intolerance (most often thrombocytopenia / myelotoxicity). Given its role as supportive care, the decision to discontinue bevacizumab at the time of disease progression is made on a case by case and focuses on tolerance of bevacizumab, perceived clinical benefit and the functional status of the patient. The drugs are prescribed and monitored under the supervision of a medical oncologist, with bevacizumab being administered in either a chemotherapy unit or Medical Day care unit.

Clinician group input

This section was prepared by CADTH based on the input provided by clinician groups. The full clinician group input is included in the Stakeholder Input section at the end of this report.

Clinician input was submitted by one clinician group, Ontario Health, Cancer Care Ontario (OH-CCO) CNS Cancer Drug Advisory Committee. Four members of the committee provided their input.

The clinician group noted the lack of standard of care treatment for patients with recurrent glioblastoma multiforme. Patients who have symptomatic recurrence such as those with mass-effect, edema, or are refractory to steroid, and those who are unsuitable for other interventions such as surgical resection, repeat radiation, or other clinical trials, would be suitable for treatment with the combination of lomustine and bevacizumab. Radiographic stability or improvement, decrease in steroid dependence, and neurologic

stability or improvement are the treatment goals, and are used as outcomes that indicate a patient is responding to treatment. Additionally, they noted the treatment toxicity assessment is conducted every 6 – 8 weeks, and radiographic imaging is conducted every 2-3 months. The decision to continue treatment is based on clinical benefit and response, patients' performance status, and patients not experiencing treatment-related toxicities such as unacceptable hematological toxicities (especially thrombocytopenia) from lomustine. Similar to the clinical experts, this clinician group also noted that patients could continue with bevacizumab, even if lomustine is discontinued.

Drug program input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. For the CADTH review of lomustine and bevacizumab combination, the drug plans provided questions pertaining to the initiation of therapy, criteria for and frequency of outcome assessment, criteria to determine disease progression, criteria for discontinuing either one of the drugs in the combination, rationale for continued use of bevacizumab if lomustine is discontinued, and expected percentage of patients that would switch to the combination if funded. These questions were addressed by the clinician experts consulted for the CADTH review. Clinician expert responses have been included in the Drug Program Input section (Table 4).

Clinical Evidence

Protocol Selected Studies

Description of studies

One published, open-label, multicentre, phase III RCT was included in the systematic review: the European Organization for Research and Treatment of Cancer (EORTC) 26101 study (n = 437)[7-10] evaluated the benefits of bevacizumab and lomustine, compared to lomustine monotherapy, for the treatment of patients with glioblastoma multiforme at unequivocal first progression after chemoradiotherapy. In the trial, bevacizumab was administered through IV infusion at a dose of 10 mg/kg every 2 weeks; when used as part of the combination therapy, lomustine was administered orally every 6 weeks at a dose of 90 mg/m^2, to be increased to 110 mg/m^2 in the absence of hematological toxicity, and at a dose of 110 mg/m^2 when used as monotherapy. Both study therapies were to be discontinued at further disease progression, and followed by investigator's choice of treatment.[7,9]

According to the clinical experts consulted by CADTH for this review, the study population that was deemed overall younger, and with a better performance status, than patients routinely seen in clinical practice. By having an open-label design, the study was susceptible to assessment and reporting biases for subjective efficacy and harms outcomes, and patient-reported outcomes, the impact or direction of which are uncertain. High treatment discontinuation rates were observed in both groups, which is not unexpected given the poor prognostic of the disease and AE profiles of the drugs; however, they remain a concern. In addition, there is a risk of bias due to missing outcome data, especially for HRQoL and neurocognitive function. The potential impact of discontinuations and missing outcome data on the results is uncertain.

Efficacy Results

The use of bevacizumab and lomustine did not result in benefits on the primary outcome of overall survival in Study EORTC 26101. Detailed results for each outcome are presented in Table 2. Improving survival in patients with cancer should remain the primary goal of therapy; however, in the very specific context of treating recurrent glioblastoma multiforme with bevacizumab plus lomustine (relative to lomustine monotherapy), the clinical experts consulted by CADTH did not consider overall survival as a realistic treatment goal, especially given the expected role of bevacizumab in the anti-cancer therapy as a targeted VEGF inhibitor. With a particularly poor survival prognosis and in the absence of treatment options providing any substantial survival benefits at this time, the clinical experts emphasized the relevance of progression-free survival as a more appropriate goal of therapy, which was assessed a key secondary outcome in the trial.

For progression-free survival, the use of bevacizumab and lomustine was associated with HRs in favour of the combination treatment versus lomustine monotherapy. The between-group difference of approximately 2.5 months in median progression-free survival observed in Study EORTC 26101 was considered clinically meaningful by both experts, especially in light of the limited life

expectancy after diagnosis. Therefore, the evidence suggests that the combination of bevacizumab and lomustine results in benefits in terms of progression-free survival for patients with recurrent glioblastoma multiforme.

Results also suggested potential benefits from bevacizumab and lomustine on other secondary outcomes, such as objective response rates assessed according to the RANO criteria, and deterioration-free survival, a measure encompassing HRQol, disease progression and death. However, there is uncertainty surrounding those findings. Only limited statistical analyses were reported for both outcomes, precluding proper assessment of the between-group differences and the precision of the estimates. Duration of response in each group was measured but not reported. In addition, deterioration-free survival was a composite outcome, for which results were mainly driven by progression-free survival, as emphasized by the authors of the publication. When taken alone, HRQoL findings from two established and validated tools were not conclusive, mainly due to large amount of missing data at longer follow-up lack of comparative effect estimates with confidence intervals, and the absence of known minimally important differences reported.

Combination therapy with bevacizumab and lomustine did not have a statistically significant impact on neurocognitive symptoms, per the investigators' conclusions, as data were not provided (unlabeled graphs) and no between-group effect estimates were reported. Also, the study did not assess the impact of bevacizumab and lomustine on corticosteroid dose-reduction, which the clinical experts identified as a particularly relevant outcome, especially in patients receiving high doses or who experience corticosteroid-related toxicity.

Harms Results

Nearly all patients experienced at least one AE throughout the study follow-up, and the proportions were similar between treatment groups. However, more patients receiving the combination therapy with bevacizumab and lomustine experienced grade 3 – 5 AEs and SAEs compared with patients in the monotherapy arm. The clinical experts consulted by CADTH indicated that it is common for patients under treatment for recurrent glioblastoma multiforme in clinical practice to experience numerous AEs, and that these may be considered tolerable by patients seeking treatment, considering the poor prognosis of the disease and limited number of therapeutic options. It should be noted that patients and clinicians in the trial were aware of the treatment strategy received, which may have introduced bias in the reporting of subjective harms.

Five patients (1.8%) who received combination therapy with bevacizumab and lomustine, and one patient (0.7%) receiving lomustine monotherapy, died throughout the study of causes that were unrelated to disease progression, including myocardial infarction, large intestine perforation, sepsis, intracranial hemorrhage and lung infection.

Table 2: Summary of Key Results from Study EORTC 26101

Outcome	Bevacizumab / lomustine n = 288 (efficacy) n = 283 (safety)	Lomustine n = 149 (efficacy) n = 147 (safety)
Overall survival		
Number of events, n (%)	216 (75.0)	113 (75.8)
Median (95% CI), months	9.1 (8.1 – 10.1)	8.6 (7.6 – 10.4)
HR (95% CI); p-value	0.95 (0.74 – 1.21); p=0.65*	
Progression-free survival		
Local assessment, median (95% CI), months	4.2 (3.7 – 4.3)	1.5 (1.5 – 2.5)
HR (95% CI); p-value	0.49 (0.39 – 0.61); p<0.001*	
Central assessment, median (95% CI), months	3.8 (3.0 – 4.2)	1.5 (1.5 – 1.6)
HR (95% CI); p-value	0.59 (0.48 – 0.74); p<0.001*	
Objective response rate		
Number of patients	N = 260	N = 137
Number of events, n (%)	108 (41.5)	19 (13.9)
95% CI	35.5 – 47.8	8.6 – 20.8
Deterioration-free survival		
Median, weeks	12.4	6.7
p-value	p<0.001*	
Patients with harms outcomes		
AEs, n (%)	278 (98.2)	139 (94.6)
AEs – Grade 3 to 5, n (%)	180 (63.6)	56 (38.1)
SAEs, n (%)	109 (38.5)	14 (9.5)
Deaths, n (%)	5 (1.8)	1 (0.7)

AE = adverse event; CI = confidence interval; HR = hazard ratio; SAE = serious adverse event.

* It is not clear whether there was any multiplicity adjustment (not reported).

Source: Wick et al. 2017[7] (including supplementary appendix)[8]

Cost Information

As CADTH does not have access to an economic model to address the specified research question, the economic review included a comparison of the treatment costs of bevacizumab plus lomustine and those of comparators deemed to be appropriate based on clinical expert consultations and drug plan feedback.

Based on publicly available list prices, bevacizumab plus lomustine is expected to have a 28-day cost of $5,597 per patient when used as recommended in the bevacizumab product monograph for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy. Lomustine when used alone is expected to cost $45 per 28-day cycle and temozolomide is expected to cost between $741 and $1,037 per 28-day cycle. As such, the incremental cost of bevacizumab plus lomustine when compared to lomustine alone is $5,552 per patient, while the incremental cost compared to temozolomide is between $4,560 and $4,856 per patient.

Conclusions

Findings from Study EORTC 26101 did not show an overall survival benefit, but suggest that combination treatment with bevacizumab and lomustine may result in clinically meaningful prevention of disease progression versus lomustine monotherapy in patients with recurrent glioblastoma multiforme. The interpretation of neurocognitive function, corticosteroid-sparing and HRQoL was however limited by poor reporting and/or missing outcome data. The population in the study was deemed overall younger, and with a better performance status, than patients routinely seen in clinical practice. High proportions of patients experienced harms events, of which grade 3-5 AEs and treatment-related SAEs were numerically higher with the combination treatment than with monotherapy. Although the harms profile reported in the publications appeared consistent with what is currently seen in clinical practice according to the clinical experts consulted by CADTH, the use of bevacizumab in the study was associated with an increased toxicity, the implications of which is uncertain. As such, tolerability should be weighed against any potential gain expected from treatment on progression-free survival. Special consideration may also be given to the fact that there is a limited number of therapeutic options for patients with recurrent glioblastoma multiforme, all of which unfortunately having little impact on prognosis.

Results of the cost-comparison of per patient treatment costs demonstrate that, over a 28-day cycle, bevacizumab plus lomustine is $5,552 more costly than lomustine alone, and $4,560 to $4,856 more costly than temozolomide. As such, the reimbursement of bevacizumab plus lomustine for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy, is expected to increase overall treatment costs. No literature was identified comparing bevacizumab plus lomustine with temozolomide, therefore the comparative efficacy of these treatments is unknown. Based on the clinical review conclusions, bevacizumab and lomustine may provide a clinically meaningful benefit on progression-free survival compared to lomustine monotherapy. As such, bevacizumab and lomustine is associated with incremental costs and incremental benefit compared with lomustine monotherapy. A cost-effectiveness analysis would therefore be required to determine the cost-effectiveness of bevacizumab and lomustine compared with lomustine monotherapy. As a cost-effectiveness analysis was not available, the cost-effectiveness of bevacizumab plus lomustine compared with lomustine alone or temozolomide for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy, could not be determined. Other costs such as administration costs were not considered as part of the cost comparison. To consider this alongside the healthcare resource implications associated with comparative clinical benefits, a cost-effectiveness analysis comparing bevacizumab plus lomustine to lomustine alone or to temozolomide would be required.

Introduction

Disease Background

Gliomas are primary central nervous system tumours that arise from glial cells, which are supporting tissues of the brain.[1] Of all gliomas, glioblastoma multiforme is the most common; with an average annual age-standardized incidence rate of 4.05 per 100,000 in Canada, it is responsible for half of all malignant central nervous system tumours in the country.[4] Glioblastoma is also highly malignant; disease progression or reoccurrence is considered inevitable in most cases and may occur rapidly, and therefore, prognosis is poor.[1,2] There has been little improvement over the years in survival rates, which range from 25-30% after 2 years, and are as low as 10-12% 5 years after diagnosis.[1,3]

More specifically, glioblastoma multiforme is a highly vascularized tumour and its main growth mechanism is angiogenesis, a physiological process where new blood vessels form out of pre-existing ones.[3,5] This is accompanied by an upregulated vascular endothelial growth factor (VEGF) pathway, i.e., an abnormally high expression of VEGF.[3,5] Patients may present with a variety of neurological signs and symptoms, depending on the location and size of the tumour in the brain,[11] including headache, seizures, memory loss, motor weakness, visual symptoms, language deficit, cognitive and personality changes.[12] Large tumours may be associated with symptomatic peritumoral oedema and increased intracranial pressure.[2,12] All these symptoms, and any neurological deficits, will guide the diagnostic evaluation.[11] In terms of neuroimaging, contrast-enhanced magnetic resonance imaging (MRI) will be used for characterization of the tumor, along with a tissue diagnosis obtained at the time of surgical resection or through a biopsy in a variety of circumstances.[11]

Standards of Therapy

There is a lack of consensus regarding the management of patients upon relapse or disease progression.[1] Options for treatment of recurrent glioblastoma multiforme after chemoradiation can include repeat surgical resection, in some select-cases re-irradiation, second line systemic therapies, clinical trials and best supportive care. Second line systemic therapies such as bevacizumab, lomustine or temozolomide re-challenge may be initiated.[2] Evidence supporting the comparative efficacy of currently available treatments is extremely limited; any decision regarding therapy must be individualized, as there is no cure for recurrent glioblastoma multiforme.[2] At this time, therapy is considered palliative.[2] According to the clinical experts consulted by CADTH for this review, goals of therapy include longer time free of neurologic deterioration, prolonged progression-free survival, better symptom control, lesser reliance on corticosteroids, and improved HRQoL. Other treatment options may also include reoperation or reirradiation through various approaches, but only in a small proportion of patients.[2] No matter the choice of therapy, the potential benefits of any treatment should always be weighed against toxicity and the impact of treatment on quality of life.[2]

Drug

Bevacizumab is a recombinant humanised monoclonal antibody that selectively binds to, and neutralises the biologic activity of, human VEGF.[6] By doing so, bevacizumab reduces the vascularisation of tumours, thereby inhibiting tumour growth.[6]

Bevacizumab has a Health Canada-approved indication, in combination with lomustine, for the treatment of patients with glioblastoma multiforme after relapse or disease progression, following prior therapy.[6]

The Provincial Advisory Group (PAG) and clinical experts consulted by CADTH for this review indicated that there is an interest in clinical practice to use bevacizumab in patients with recurrent glioblastoma multiforme. The PAG requested that CADTH review bevacizumab in combination with lomustine for patients with recurrent glioblastoma multiforme and provide a reimbursement recommendation.

Stakeholder Perspectives

Patient Group Input

No input was provided to CADTH for this review by any patient group.

Clinician Input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by two clinical specialists with expertise in the diagnosis and management of glioblastoma multiforme.

Unmet Needs

The clinical experts noted that recurrent glioblastoma multiforme is highly refractory and challenging to treat. While clinical trials indicate that median survival is 6-8 months,[13,14] in clinical practice survival is likely shorter, as per the experts. The last few months of the patient's life are often characterized by significant disability and dependence, with patients suffering from inexorable neurologic decline.

The clinical experts noted that there is no evidence based standard therapy for recurrent glioblastoma multiforme. Patients may receive, on a case-by-case basis, repeat tumour resection and/or focal re-irradiation depending on their tumour location, performance status, and the time since their last surgery/radiation. The clinical experts noted that systemic therapies in recurrent glioblastoma multiforme includes re-challenge with temozolomide if patients have had an interval of time away from their first-line temozolomide (standard and metronomic daily dose). Other frequently used second line systemic chemotherapy includes lomustine, and one clinical expert noted that the evidence of lomustine efficacy is not based on randomized clinical trials, but rather on a combination of historical practice and indirect evidence (where lomustine looked superior to some failed newer agents in randomized trials where lomustine served as the control arm).[13] If available, bevacizumab (standard or alternate low dose regimen) is frequently used in the second line setting to control peritumoural edema and prolong the time to neurologic deterioration. The clinical experts noted that bevacizumab may also be used to treat radiation necrosis in patients who are re-irradiated. The clinical experts emphasized that bevacizumab should be considered akin to a supportive care agent rather than an anti-cancer therapy. Less frequently used treatment options include oral etoposide or in select patients best supportive care is considered the most appropriate treatment option.

The clinical experts noted the pressing need for new therapeutic options for recurrent glioblastoma multiforme that improves survival and delays neurologic deterioration while maintaining a high level of health-related quality of life.

Place in therapy

Both clinical experts indicated that lomustine has an established use as a second-line systemic agent for recurrent glioblastoma multiforme, if temozolomide has failed. Both clinical experts consider bevacizumab as a supportive care medication and to supplement lomustine. As such, they indicated that bevacizumab can also be used as monotherapy in instances where the tumour is refractory to lomustine.

Patient population

The clinical experts noted that patients who no longer respond to temozolomide, would be considered for treatment with lomustine as a second-line therapy in the recurrent setting.

The clinical experts noted that patients with recurrent glioblastoma >/= 3 months after chemoradiation with temozolomide, who may not be candidates for surgical resection, re-irradiation or a clinical trial, would be considered for treatment with the combination

lomustine-bevacizumab. Of these patients in the recurrent setting, the following patients could derive the most clinical benefit from the combination of bevacizumab and lomustine or bevacizumab monotherapy: those with large volume recurrent tumours with mass effect/vasogenic edema, evidence of radionecrosis, and debilitating corticosteroid toxicities (as a steroid-sparing agent). They did acknowledge that there is some variability in practice patterns regarding the role of bevacizumab. The clinical experts also noted that benefits including improvement in neurological symptoms, reduced reliance on corticosteroids with fewer steroid related toxicities and improved quality of life are based on clinical practice and to their knowledge are not as well-defined in evidence from clinical trials.

The clinical experts recommended that treatment with bevacizumab and lomustine should be based on tumour factors (pathology, volume of recurrent tumour, degree of associated vasogenic edema), patient performance status (ECOG performance status, tolerability of corticosteroids, co-morbidities) and clinician's recommendation based on fitness for treatment. One clinical expert also noted that the activity of lomustine may be most beneficial in patients with MGMT promoter methylation.

Assessing response to treatment

Both clinical experts highlighted that there is no expectation that the addition of bevacizumab to lomustine would improve overall survival. Rather, patients may have a more prolonged period free of neurologic deterioration, and potentially be able to take fewer corticosteroids with less steroid-related toxicities. It was emphasized that for patients living with recurrent glioblastoma multiforme and a prognosis of less than 6 to 9 months to live; rather than improvement in overall survival, the more important treatment goals should be prolonged progression free survival that can translate into meaningfully improved patient outcomes such as being able to participate more fully in their lives, better palliated symptoms, less reliance on corticosteroids, and improved HRQoL.

Discontinuing treatment

Both clinical experts suggested that the evidence of disease progression or intolerance (most often myelosuppression) will determine if the treatment with lomustine should be discontinued. Given its role as supportive care, the decision to discontinue bevacizumab at the time of disease progression is made on a case-by-case basis and focused on tolerance to bevacizumab, the functional status of the patient, and clinical benefit.

Prescribing conditions

As per the clinical experts, lomustine is prescribed and monitored under the supervision of a medical oncologist. Bevacizumab is administered in either a chemotherapy unit or Medical Day care unit, and presumably also under the supervision of the medical oncologist who is prescribing the lomustine.

Additional considerations

Other treatment options for recurrent glioblastoma multiforme include tumour treating fields which are currently not started often in the recurrent setting, but patients may remain on them at the time of progression. Other options include Gliadel wafers (but not widely available), ongoing clinical trials for new agents (if available), and palliative care.

The clinical experts noted that the FDA has approved bevacizumab as a supportive care medication. The experts recommended that the current review should also consider this drug as supportive care medication, and not as an anti-cancer drug (where there is expectation of improved survival).

Clinician group input

This section was prepared by CADTH based on the input provided by clinician groups. The full clinician group input is included in the Stakeholder Input section at the end of this report.

Clinician input was submitted by one clinician group: Ontario Health, Cancer Care Ontario (OH-CCO) CNS Cancer Drug Advisory Committee. The committee provides timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

Four members of the committee provided their input gathered jointly at a teleconference meeting and via emails.

Unmet Needs

The clinician group noted that currently there is no standard of care treatment for patients with recurrent glioblastoma multiforme. The clinical group indicated that, to their knowledge, current evidence supports the use of bevacizumab and lomustine in the setting of recurrent glioblastoma multiforme. However, they noted that patients need to have secondary insurance or go through a compassionate access program to access bevacizumab.

The clinician group noted the following goals of treatment for recurrent glioblastoma multiforme: palliation of neurological symptoms, improvement in neurological symptoms, improvement in quality of life, and steroid/dexamethasone sparing.

Patient population

The clinician group noted that treatment with bevacizumab and lomustine would be suitable for patients with symptomatic recurrence such as those with mass-effect, edema, or who are refractory to steroid; and who may not be suitable candidates for other treatment such as surgical resection, repeat radiation, or other clinical trials. The clinician group emphasized that while the review is for the combination of bevacizumab and lomustine, lomustine may be withheld in patients due to tolerability issues or clinical treatment resistance.

Assessing response to treatment

One clinician group indicated that radiographic stability or improvement, decrease in steroid dependence, and neurologic stability or improvement are used as outcomes that indicate a patient is responding to treatment. Additionally, they noted that the treatment toxicity assessment is conducted every 6 – 8 weeks, and radiographic imaging is conducted every 2 to 3 months. The decision to continue treatment is based on clinical benefit and response, patients' performance status, and reducing treatment-related toxicities.

Discontinuing treatment

The clinical group noted that unacceptable hematological toxicities (especially thrombocytopenia) are a reason to discontinue lomustine, however, patients could continue with bevacizumab. They noted unacceptable clinical progression as one of the reasons to discontinue bevacizumab and lomustine or bevacizumab only.

Prescribing conditions

The clinician group noted that bevacizumab would be administered in a hospital-based outpatient clinic, and lomustine can be administered at home.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's non-sponsored review processes by identifying issues that may impact their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 3.

Further, bevacizumab is funded for recurrent glioblastoma multiforme in some of the provincial drug plans. It was also noted that biosimilars for bevacizumab are now available in the Canadian market.

With regards to interventions, the drug plans noted that treatment of recurrent glioblastoma multiforme may also include temozolomide rechallenge. Nivolumab, which is one of the comparators in a clinical trial for recurrent glioblastoma multiforme,[15] is not currently approved by Health Canada as first-line treatment of glioblastoma multiforme or for recurrent glioblastoma multiforme.[16]

The drug plans noted the need to clarify if the inclusion and exclusion criteria, frequency of and criteria for assessment of outcomes, and criteria to determine progression in the pivotal trial EORTC 26101[7] are similar to those in clinical practice.

Table 3: Summary of Drug Plan Input and Clinical Expert Response

Drug Program Implementation Questions	Clinical Expert Response
What are the criteria for initiation of therapy, and does clinical practice align with the inclusion and exclusion criteria in the clinical trials?	As per the clinical experts, criteria to initiate therapy is recurrent glioblastoma >/= at least 3 months after chemoradiation with temozolomide. The clinical expert noted that the population included in the included clinical trial was overall younger, and had a better performance status, than patients seen in clinical practice.
What are the criteria for re-treatment with bevacizumab after disease progression?	As per the clinical experts, the decision to continue bevacizumab at the time of disease progression is made on a case-by-case basis. Clinical experts noted that the decision is based on patient tolerance to bevacizumab, the performance status and prognosis of the patient, and the clinical benefit of continued treatment, including reduced reliance on corticosteroids.
Is RANO criteria is used in clinical practice? What is the frequency of the assessments (including MRIs) for disease progression and outcomes in clinical practice?	As per the clinical experts, RANO criteria is used to standardize the approach to the interpretation of MRIs. Clinical assessments include laboratory monitoring at baseline and monthly thereafter, BP and urinalysis every 2 weekly prior to bevacizumab infusions, and MRIs generally performed every 2-3 months.
How is disease progression determined in clinical practice? What criteria are used?	As per the clinical experts,RANO criteria (radiographic response) combined with clinical assessment including a detailed neurological examination is used to determine disease progression.
What are the criteria to discontinue either one of the drugs in the combination? What is the rationale (if any) to continue on bevacizumab, if lomustine is discontinued?	As per the clinical experts, lomustine is discontinued if there is evidence of disease progression or intolerance (most often thrombocytopenia/ myelotoxicity). Given its role as supportive care, the decision to discontinue bevacizumab at the time of disease progression is made on a case by case and focus on (in)tolerance to bevacizumab, and the functional status of the patient. As per the clinical experts, bevacizumab should be considered akin to a supportive care agent rather than a direct anti-tumour therapy. Although it does not have demonstrated benefit in terms of overall survival, as per the experts, bevacizumab does have an impact on the tumour's vascular supply which can be associated with improvement in neurological symptoms. This may allow patients to participate more fully in their lives; with symptoms that are better palliated, reduced reliance on corticosteroids and HRQoL is often improved. The clinical experts considered these outcomes highly important, given that these patients have a prognosis of only <6-9 months.

HRQoL = health-related quality of life.; MRI = magnetic resonance imaging; RANO = Response Assessment in Neuro-Oncology

Industry Input

This section was prepared by CADTH based on the input provided by the manufacturer of bevacizumab.

The industry input was submitted by Amgen Canada Inc., one of the manufacturers of a biosimilar version of bevacizumab (MVASI) in Canada. Industry input was provided on the research protocol. They noted agreement with the research protocol posted on the CADTH website.

Amgen Canada Inc. noted evidence from the following studies on the use of combination of bevacizumab and lomustine in patients with glioblastoma multiforme after relapse or disease progression following prior therapy: the EORTC 26101 trial,[7] the randomized controlled Phase 2 BELOB Study,[17] a meta-analysis by Ren et al,[5] and a Cochrane network meta-analysis by McBain et al.[1]

Amgen Canada Inc. highlighted that most patients with glioblastoma multiforme experience progression/recurrence after initial therapy which consists of maximal tumour resection followed by chemoradiotherapy[18,19] (typically using temozolomide). Re-resection or re-irradiation remain options for relapsed or recurrent glioblastoma multiforme for only a select group of patients (e.g., young and fit).[18,19] A large subset of patients with relapsed or recurrent glioblastoma multiforme are given systemic therapy which consists of lomustine monotherapy, temozolomide rechallenge, PCV regimen (procarbazine, lomustine or carmustine, and vincristine), and etoposide monotherapy, as well as bevacizumab combined with lomustine, if approved for reimbursement.

Amgen Canada Inc. also commented on the administration of bevacizumab and related evaluations, which they consider to not be abnormally burdensome and not likely to impede adoption. It was noted that bevacizumab is administered via intravenous infusion once every 2 weeks until disease progression.[6] The infusion is initially delivered over 90 min reducing to 60 min and then to 30 min, depending on tolerability.[6] Further, it was noted that assessments generally involve blood tests at baseline and to be repeated after the first 3 doses; urinalysis and blood pressure evaluation at baseline and before each bevacizumab dose; and magnetic resonance imaging which is usually performed every 2 to 3 months while on therapy to identify relapse/progression.[7,19,20]

Clinical Evidence

The clinical evidence included in the review of bevacizumab and lomustine is presented in three sections. The first section, the Systematic Review, includes studies that were selected according to an a priori protocol. The second section would include indirect evidence selected from the literature that met the selection criteria specified in the review; however, no indirect evidence was considered relevant for inclusion in the review. The third section would include long-term extension studies and additional relevant studies that were considered to address important gaps in the evidence included in the systematic review; however, none were considered relevant for inclusion in the review.

Systematic Review (Protocol Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of bevacizumab and lomustine for the treatment of patients with glioblastoma multiforme after relapse or disease progression, following prior therapy.

Methods

Studies selected for inclusion in the systematic review included those meeting the selection criteria presented in Table 4. Outcomes included in the CADTH review protocol reflect outcomes considered to be important to patients, clinicians, and drug plans.

Table 4: Inclusion criteria for the systematic review

Patient Population	Adult patients with glioblastoma multiforme relapse or progression after prior therapy. Subgroups: • ECOG performance status • Number of recurrences • Previous therapies received
Intervention [a]	Bevacizumab (including biosimilars) 5-10 mg/kg IV infusion every 2 weeks. + Lomustine (CeeNU) every 6 weeks, according to the following dosing schedule: ○ 90 mg/m^2 orally (maximum 160 mg) for the first cycle; then can be escalated in the absence of hematological toxicity (Grade > 1 AEs) to ○ 110 mg/m^2 orally (maximum 200 mg) from second cycle onwards.
Comparators	• Lomustine (CeeNU) 110 mg/m^2 orally (maximum 200 mg) monotherapy every 6 weeks • Temozolomide (including generics) orally once daily for 5 days per 28-day cycle, according to the following dosage: ○ No prior chemotherapy: 200 mg/m^2 ○ Previous chemotherapy: 150 mg/m^2 for the first cycle to be increased, in the absence of hematological toxicity, to 200 mg/m^2 • Temozolomide (including generics) 50 mg/m^2 orally once daily continuously
Outcomes	***Efficacy outcomes:*** • Overall survival (OS) • Progression-free survival (PFS) • Objective response rate (ORR) • Duration of response (DOR) • Neurologic deterioration-free survival • Neurocognitive symptoms • Corticosteroid use • Health-related quality of life

	Harms outcomes:
	• AEs, SAEs, WDAEs, Mortality
	• Harms of special interest:
	  ○ Hematological toxicity (e.g., neutropenia, infections, wound healing complications, thrombocytopenia, serious bleeding or hemorrhage, thromboembolism);
	  ○ Neurologic toxicity (e.g., posterior reversible encephalopathy syndrome);
	  ○ Cardiac toxicity (e.g., hypertension, congestive heart failure);
	  ○ Other notable harms: gastrointestinal perforation, osteonecrosis of the jaw, proteinuria.

Study Design	Published and unpublished Phase II, III and IV RCTs.

AE=adverse events; ECOG = Eastern Cooperative Oncology Group; RCT=randomized controlled trial; SAE=serious adverse events; WDAE=withdrawal due to adverse events.
[a] The combination of bevacizumab and lomustine has a Health Canada indication for the treatment of glioblastoma multiforme, at the recommended dosages in the table.[6]

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[21]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multi-file search. Duplicates were removed using Ovid deduplication for multi-file searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparator, outcome, setting (PICOS) framework and research questions. The main search concepts were bevacizumab and glioblastoma. Clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, World Health Organization's International Clinical Trials Registry Platform (ICTRP) search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System (CTIS).

CADTH-developed search filters (https://searchfilters.cadth.ca/) were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. See Appendix 1 for the detailed search strategies.

The initial search was completed on March 16, 2023. Regular alerts updated the search until the meeting of the CADTH Formulary Management Expert Committee (FMEC) on September 20, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature.[22] Included in this search were the websites of regulatory agencies (US Food and Drug Administration and European Medicines Agency). Google was used to search for additional internet-based materials. See Appendix 1 for more information on the grey literature search strategy.

These searches were supplemented by reviewing bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

A focused literature search for indirect treatment comparisons (ITCs) was run in MEDLINE on March 16, 2023. Retrieval was not limited by publication date or by language.

Two CADTH clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion.

Characteristics of Included Studies

One study (EORTC 26101) was identified from the literature for inclusion in the systematic review (Figure 1).[7-10] The included study is summarized in Table 5. A list of excluded studies is presented in

Appendix 2.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

Alt text: 420 citations were identified, 406 were excluded, while no electronic literature and no grey literature potentially relevant full text reports were retrieved for scrutiny. In total 2 reports are included in the review.

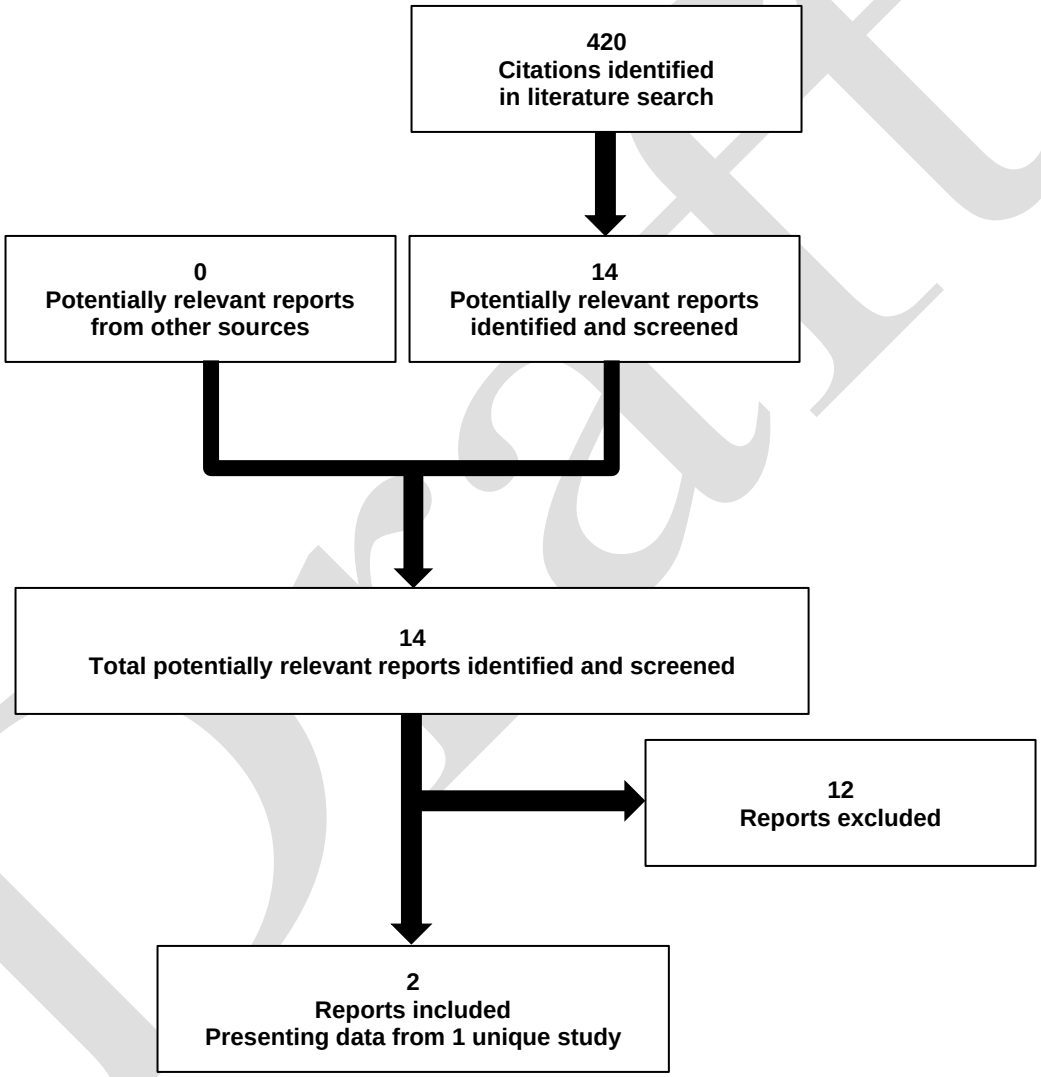

Table 5: Details of Included Study

Detail	EORTC 26101
Design & Population	
Study Design	Phase III open-label RCT
Locations	Multicentre; 38 sites in 8 countries
Patient enrolment dates	November 2011 to December 2014
Randomized (N)	437 patients
Inclusion Criteria	• Histologically confirmed glioblastoma multiforme. • Unequivocal first progression after chemoradiotherapy (≥ 3 months after end of radiotherapy). • WHO performance status ≤ 2.[a] • Adequate hematologic, renal, and hepatic function (per predefined study criteria).
Exclusion Criteria	• Patients who have undergone antiangiogenic treatment. • Use of enzyme-inducing antiepileptic drugs within 2 weeks prior to randomization.
Drugs	
Intervention	Combination of: **Bevacizumab** 10 mg/kg IV infusion every 2 weeks; with: **Lomustine** orally every 6 weeks; dose of 90 mg/m^2 for the first cycle (maximum dose, 160 mg), to be increased in the absence of hematological toxicity to 110 mg/m^2 (maximum dose, 200 mg) from the second cycle onwards.
Comparator(s)	**Lomustine** monotherapy, 110 mg/m^2 orally every 6 weeks (maximum dose, 200 mg)
Concomitant medications and treatments	Concomitant: • Radiotherapy with stereotactic radiosurgery / brachytherapy if recurrence histologically proven. • Corticosteroids in the smallest dose to control symptoms of cerebral edema and mass effect (to be reduced and/or discontinued if possible). • Non enzyme-inducing antiepileptic drugs and acetylsalicylic acid up to 325 mg/day allowed. At further progression: • Study drug regimen was discontinued; to be followed by investigator's choice of therapy.
Duration	
Follow-up	Approximately 3 years
Outcomes	
Primary end point	Overall survival, defined as time from randomization to death.
Secondary and exploratory end points	• Progression-free survival • Response rates (RANO criteria) • Corticosteroid use • AEs • Neurologic deterioration–free survival • HRQoL of patients and caregivers • Symptoms of neurocognitive deterioration
Notes	
Publications (included in the systematic review as source of information)	• Wick et al. 2017[7] • Wick et al. 2017 Supplementary appendix[8] • Le Rhun et al. 2023[9] • Le Rhun et al. 2023 Supplementary appendix[10]
Funding sources	The European Organization for Research and Treatment of Cancer

AEs = adverse events; HRQoL = health-related quality of life; RANO = Response Assessment in Neuro-Oncology; RCT = randomized controlled trial; SAEs = serious adverse events; WHO = World Health Organization.

[a] The WHO performance status is score on a scale of 0 to 5, as per the following: 0 = full activity; 1 = unable to carry out heavy physical work; 2 = up and about more than half the day but unable to work.[7]

Source: Wick et al. (2017)[7]

Study Design

One published, open-label, multicentre, phase III RCT was included in the systematic review: the European Organization for Research and Treatment of Cancer (EORTC) 26101 study (n = 437).[7-10] The study was initially designed as a phase II trial with four treatment groups, in order to evaluate the comparative efficacy of various treatment sequences with bevacizumab and/or lomustine in patients with recurrent glioblastoma multiforme; however, when findings from the BELOB trial[17] became available, the study was modified into a phase III trial before any endpoint had been evaluated.[7]

Indeed, BELOB was a hypothesis-generating open-label, multicentre phase II study (n = 153) assessing the efficacy and safety of lomustine monotherapy, bevacizumab monotherapy, and the combination of lomustine and bevacizumab, in patients with a first recurrence of glioblastoma multiforme.[17] At the time, findings were considered encouraging based on results from the primary outcome of 9-month overall survival observed in patients receiving the combination of bevacizumab and lomustine, meeting the prespecified criteria for assessment of the treatment in phase III studies. However, no statistical comparison between treatment groups was reported, therefore restricting the ability to draw any conclusion from the study. In the absence of comparative outcome data, the study was not included in the current systematic review.

Patients were randomized in the EORTC 26101 study in a 2:1 ratio to receive combination treatment with bevacizumab and lomustine, or lomustine monotherapy, each to be followed by the best investigator's choice of treatment at further progression.[7,9] Randomization was performed centrally using the minimization technique based on the variance method with 15% fully random assignment dependent on the preset threshold of four stratification factors:[8,9]

- institution;
- WHO performance status (0 versus > 0);
- use of corticosteroids at baseline (no versus yes); and
- largest lesion diameter (≤ 40 versus > 40 mm).

Patients and investigators were not blinded to treatment assignment; the rationale was not discussed in the published articles. In addition to local assessment, central imaging assessment was independently performed, and assessors were then blinded to treatment allocation.

The study was sponsored by the European Organization for Research and Treatment of Cancer.

Inclusion and Exclusion Criteria

Patients were eligible for the trial if they had histologically confirmed glioblastoma multiforme with unequivocal first progression after chemoradiotherapy (at least 3 months after the end of radiotherapy). For patients who had been operated for recurrence, residual measurable disease post-surgery was not required, although the surgery must have confirmed the recurrence and a post-surgical MRI must have been available within 48 hours of surgery. For patients who were not operated, recurrent disease was defined as at least 1 bi-dimensionally measurable contrast-enhancing lesion with clearly defined margins on MRI, with minimal diameters of 10 mm, visible on 2 or more axial slices 5 mm apart. Patients had to be on stable or decreasing doses of steroids for 7 days prior to baseline MRI scans. Patients also needed to have a WHO performance status ≤ 2, as well as adequate hematologic, renal, and hepatic function as per the predefined study criteria (absolute neutrophil count ≥1500/mm^3; platelet count ≥100,000/mm^3; serum creatinine level ≤1.5 times the upper limit of normal; total serum bilirubin level ≤1.5 times the upper limit of normal; liver function values <2.5 times the upper limit of normal). However, patients were not eligible for the trial if they had undergone antiangiogenic treatment or if they used enzyme-inducing antiepileptic drugs within 2 weeks prior to randomization.

Interventions

The intervention evaluated consisted of a combination therapy with bevacizumab 10 mg/kg IV infusion every 2 weeks and lomustine 90 to 110 mg/m^2 orally every 6 weeks, administered until further disease progression. Lomustine was started at a lower dose for the first cycle, then increased for the second cycle if there were no hematologic toxic effects of grade 1 or more. Patients randomized to the combination group in the study received a median of 3 cycles of lomustine (range 1 to 8) and 3 cycles of bevacizumab (range 1 to 16).[7]

The comparator was lomustine 110 mg/m^2 orally every 6 weeks (maximum dose, 200 mg) as monotherapy. Patients randomized to the lomustine monotherapy group in the study received a median of 1 cycle of lomustine (range, 1 to 8).[7]

Dose reductions or delays could be made for the likely causative agent (i.e., bevacizumab or lomustine); patients who required a delay of one of the protocol treatments for more than 2 weeks could not restart the treatment of interest. Bevacizumab and lomustine were to be continued until one or more of the withdrawal criteria were met, i.e., disease progression; patient refusal; intolerable toxicity precluding protocol therapy; patient's best interest; start of any other anti-cancer agent/modality. In both groups, at the time of documented disease progression, the trial regimen was followed by the investigator's choice of treatment. A total of 53% of patients in the bevacizumab and lomustine combination group, and 66% of patients in the lomustine monotherapy, received further treatment after disease progression. If one of the agents in the combination therapy was stopped for a reason other than progressive disease, the patient could continue on a single agent alone.

In both groups, concomitant radiotherapy with stereotactic radiosurgery or brachytherapy was allowed, as well as non enzyme-inducing antiepileptic drugs. Corticosteroids were to be used in the smallest dose to control symptoms of cerebral edema and mass effect and were to be reduced and/or discontinued if possible.

Outcomes

A list of efficacy endpoints identified in the CADTH review protocol that were assessed in the clinical trial included in this review are provided in Table 6. Clinical and neurological evaluations, as well as MRI, were performed every week from Week 6 to Week 24, and were then carried out every 3 months. This would include assessments for the outcomes of overall survival, progression-free survival and objective response rate. Patients were evaluated for harms outcomes every two weeks.

Overall survival was the primary efficacy outcome in Study EORTC 26101 and was defined as time from randomization to death from any cause. Overall survival is widely recognized as the gold-standard goal of therapy in the treatment of cancer.[23]

Progression-free survival was a secondary outcome in Study EORTC 26101 and was defined as time from randomization to progression or death, whichever would occur first. Progression-free survival was assessed locally per investigator, as well as centrally for continuous quality control and independent blinded assessment, which was ensured by an Independent Review Committee for all assessments and interpretations of disease status performed locally.[7]

Progression was assessed via MRI according to the Response Assessment in Neuro-Oncology (RANO) criteria,[24] with an additional quantitative requirement for changes on fluid-attenuated inversion recovery (FLAIR) images or T2 weighted images (i.e., a 25% increase in the sum of the products of perpendicular diameters of areas with abnormalities on the images, compared to the nadir time, point would be considered progression).[8] If the evidence of progressive disease was equivocal, treatment could have been continued until the next assessment; however, if progressive disease was confirmed at the next assessment, the earlier date was used as the data of progression.[8]

Objective response rate, defined as the composite of complete and partial responses, was a secondary outcome in Study EORTC 26101. Response rates were assessed according to the RANO criteria. Duration of response was not reported.

Neurologic deterioration–free survival (i.e., time from randomization to documentation of neurologic deterioration or death, whichever would occur first) was a secondary outcome in Study EORTC 26101; however, this outcome was not defined, as no threshold of what would considered deterioration-free for each tool was specified, and no time-to-event results for this outcome was reported in the publications. Instead, the authors reported the neurocognitive function at various points of follow-up, resulting in change from baseline analyzes and between-group comparisons. Neurocognitive function was primarily assessed by comparing neurocognitive function scores from the following standardized psychometric instruments: the Hopkins Verbal Learning Test–Revised,[25] the Trail Making Test,[26] and the Controlled Oral Word Association.[27] Neurocognitive testing was performed at baseline and every 12 weeks, for a total of up to three follow-up assessments. Instruments were administered in a fixed order, and controlled for test-retest effects.[7]

The use of corticosteroids was a secondary outcome in Study EORTC 26101. It was assessed throughout follow-up as the proportions of patients initiating corticosteroid treatment and time to corticosteroid initiation.

HRQoL was a secondary outcome in Study EORTC 26101 and was assessed every three months using the EORTC Quality of Life Questionnaire–Core 30 and the EORTC brain-cancer module, which is a brain cancer specific HRQoL questionnaire with high internal consistency reliability, known groups validity and acceptable responsiveness to changes over time.[28] The publications did not specify whether the evaluation was self-reported, and if so, whether it was by patients or caregivers. Responses were aggregated and scored on a linear scale, where 0 corresponded to the lowest level of functioning or symptom, and 100 corresponded to the highest level of functioning or symptom. Scale scores were calculated using only items that were completed, assuming a completion level of at least half the items in the scale. In the trial, a difference of at least 10 points between treatment arms was considered clinically relevant; however, no justification for the use of this threshold was provided. Between-group analyses were performed at Week 36, as well within-group change from baseline to Week 36, for five prespecified scales (global health status, physical functioning, social functioning, motor dysfunction, and communication deficit).[7]

Results from two other outcome measures capturing HRQoL in Study EORTC 26101 were reported in the publications:

- Time to HRQoL deterioration, defined as time from randomization until the first of the two following events:
  - >10-point worsening from baseline in HRQoL score with no subsequent improvement;
  - or death.[8]
- Deterioration-free survival, defined as time from randomization until the first of the three following events:
  - >10-point worsening from baseline in HRQoL score with no subsequent improvement;
  - disease progression;
  - or death.[8]

Table 6: Summary of Outcomes of Interest Identified in the CADTH Review Protocol

Outcome Measure	Analysis in EORTC 26101
Overall survival	Primary
Progression-free survival	Secondary
Objective response rate	Secondary
Duration of response	NR*
Neurologic deterioration-free survival	NR*
Neurocognitive symptoms	Secondary
Corticosteroid use	Secondary
HRQoL	Secondary
AEs	Secondary
SAEs	Secondary
WDAEs	NR
Mortality	Secondary
Hematological toxicity	Secondary
Neurologic toxicity	NR
Cardiac toxicity	Secondary

AE = adverse event; HRQoL = health-related quality of life; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

* Measured but not reported.

Statistical analysis

The sample size calculation estimated that having at least 327 overall survival events (deaths) would enable the study to achieve 80% power, at a 1-sided log rank test at a significance level of 2.5%, to detect a hazard ratio of 0.72, assuming a rate of overall survival at 9 months of 40% in the monotherapy group.[7] Considering the 2:1 randomization scheme, 433 patients needed to be recruited based on the aforementioned assumptions (i.e., 289 patients in the bevacizumab and lomustine combination group and 144 patients in the lomustine monotherapy group).

The study was designed to test for superiority of the combination of bevacizumab and lomustine relative to lomustine monotherapy. The authors indicated that statistical analyses were performed as specified in the study protocol.[7] For safety analyses, the safety population consisted of randomized patients who started treatment.[7]

The primary outcome was overall survival, while progression-free survival was a key secondary outcome. For these time-to-event outcomes, survival probabilities were estimated with the use of the Kaplan–Meier technique, in the intention-to-treat population (in which patients were analyzed in the group to which they were allocated). A Cox proportional hazards model, adjusted for stratification factors used at randomization (except for institution), was used to generate estimates of treatment effect. No information was reported in the publications as to whether these analyses were adjusted for multiplicity. Differences between groups were assessed using a stratified 1-sided log-rank test at a 2.5% significance level and results were expressed using a hazard ratio (HR) with a 2-sided 95% confidence interval.[7] Overall survival was censored at the last follow-up date for patients alive or lost to follow-up; progression-free survival was censored at the last available date of disease assessment for patients alive and without disease progression.[7] If a patient received a second anti-tumoural therapy without prior documentation of disease progression, the patient was censored at the date of starting the new anti-tumoural therapy.[7]

Data for objective response rates were reported using numbers and percentages, accompanied with exact binomial 95% confidence intervals.[29] No information was available regarding the statistical assessment of neurocognitive symptoms.

The primary HRQoL outcomes or subscales for statistical considerations were global health status, cognitive functioning, and pain, with the objective of documenting HRQoL profile estimates and confidence intervals. Based on a standard deviation of 20 points in the global health status, 64 patients were required in each treatment arm for the study to achieve 80% power, at a 2-sided alpha set at 5%, to detect a clinically meaningful difference of 10 points. Under these assumptions, the study had sufficient power to show differences in HRQoL. Change from baseline in the scores were assessed with a repeated measurement modeling using a mixed effect procedure.[29] Both a patient-specific random effect model and a linear mixed model with time, treatment, and time-treatment interaction as fixed effects were to be fitted, the most suitable covariance structure being determined based on Akaike's Information Criterion.[29]

Critical Appraisal

Internal validity

Study Design, Intervention, and Comparators

Study EORTC 26101 was designed to evaluate the superiority of bevacizumab and lomustine over lomustine monotherapy in patients with glioblastoma multiforme. The trial was randomized but was not blinded. By having an OL design, Study EORTC 26101 was susceptible to assessment and reporting biases, as knowledge of treatment assignment could influence investigators' assessment of subjective efficacy and patient-reported outcomes, such as HRQoL and AEs. Ideally, anticancer drug trials should be blinded, when possible, with centralized review of tumour-based outcomes.[27] In EORTC 26101, comparison between investigator and central assessment of the tumours was reported for only the outcome of progression-free survival, where findings were overall consistent between assessments. It is not possible to determine the impact or direction of a potential bias that knowledge of treatment assignment may have had on other outcomes, such as HRQoL and AEs.

Upon further disease progression, the study drug regimen was discontinued and followed by the investigator's best choice of treatment. The various therapies received by patients after disease progression were reported in Wick et al.[7] There was an imbalance between treatment groups for the specific therapy received, including the fact that a larger proportion of patients in the lomustine monotherapy group received subsequent bevacizumab; however, the clinical experts consulted by CADTH highlighted that this is unlikely to have a substantial impact on the overall survival results, considering the limited efficacy of any treatment at this stage of the disease and the poor prognosis related to overall survival in glioblastoma multiforme.

Selection, Allocation, and Disposition of Patients

Patients were randomized at a ratio of 2:1 using appropriate methods to achieve prognostic balance and conceal allocation until group assignment. Reported baseline characteristics were equally balanced between treatment groups within treatment comparison.

High proportions of patients in both treatment groups discontinued treatment but remained in the study. In addition to high discontinuations due to disease progression, AEs led 14% of patients in the combination group to discontinue bevacizumab and 20% of patients in this group to discontinue lomustine; 10% of patients receiving monotherapy discontinued lomustine due to AEs. These high treatment discontinuation rates are expected given the poor prognosis of the disease and AE profiles of the drugs; however, they remain a concern as their potential impact on the results is uncertain.

Outcome Measures

The primary efficacy outcome in Study EORTC 26101 was overall survival, which is the preferred and most reliable endpoint in oncology trials.[23] Progression-free survival, which was measured as a secondary outcome in the trial, was considered relevant according to the clinical experts consulted by CADTH.

There is a risk of bias due to selective reporting, as some important outcomes in the systematic review protocol were measured in the trial but were not reported in the publications. In addition, there is also a risk of bias due to missing outcome data; for example, at Week 36, data were available for only 66% of patients for HRQoL, and for 61% pf patients for neurocognitive function. The impact and direction of these bias is uncertain.

Statistical Analysis

Study EORTC 26101 had sufficient power for the analysis of the primary outcome; statistical significance was also reached for the key secondary outcomes of progression-free survival and objective response rates.

The authors of the publication did not describe any methods for accounting for multiplicity of comparisons for the key outcomes in the study; therefore, there is the possibility of an increased risk of type 1 error (false positive conclusions) for statistically significant results.

The methods used for the analysis were appropriate for time-to-event outcomes (Cox proportional hazards regression adjusted for certain randomization stratification factors). The clinical experts consulted acknowledged that, except for institution, all covariates are considered clinically relevant (WHO performance status, use of corticosteroids at baseline and largest lesion diameter). Although no testing was reported with regard to the plausibility of the proportional hazards assumption, based on visual inspection of the Kaplan-Meier plots for overall survival, the curves followed a very similar trajectory (crossing around 12 to 15 months). For progression-free survival, the curves appeared to follow a relatively proportional trajectory and did not cross.

Between-group differences with confidence intervals were not reported for many of the outcomes in the trial. In addition, some data were only reported in unlabeled graphs. As such, interpretation of these outcomes data is limited.

External validity

Patient Selection

The inclusion and exclusion criteria were deemed clinically relevant and reasonable by CADTH's clinical experts. However, patients in the study differed from the population typically seen by the experts in clinical practice; they were younger and had a better performance status, as shown by the WHO performance status and by the proportions of patients using corticosteroids at baseline. This should be considered when generalizing the findings from the study to real-life patients.

Treatment Regimen and Length of Follow-Up

The administration of bevacizumab and lomustine in Study EORTC 26101 were in line with the Health Canada recommended dosages in oncology and what would be used in the reimbursement population. However, the experts noted that in clinical practice, it is not uncommon to use bevacizumab at a lower dose than the product monograph.

The median time between first progressive disease and treatment (i.e., 26 days) was considered representative of clinical practice by the clinical experts consulted by CADTH; however, they expressed concerns pertaining to the very wide range (up to 231 days), as such delay in receiving treatment would not be considered acceptable.

The duration of treatment in the trial, although noticeably short, was consistent with experience from clinical practice based on input from clinical experts; indeed, considering the aggressive nature of the disease, it is typical to see short treatment durations before disease progression.

Outcome Measures

Primary and secondary outcome measures of survival were considered relevant to clinical practice by the experts consulted by CADTH for this review, with focus being placed however on progression-free survival in this specific case for interpretation of the results. Indeed, the prognosis in recurrent glioblastoma multiforme is so poor that clinical experts consulted by CADTH did not consider overall survival as the most relevant outcome in the context of treatment with bevacizumab plus lomustine (relative to lomustine monotherapy), particularly given the expected anti-angiogenic role of bevacizumab in the anti-cancer therapy. Although improving survival in patients with cancer should remain the primary goal of therapy, in this very specific context (i.e., with a particularly poor survival prognosis and in the absence of treatment options providing any substantial survival benefits at this time) the clinical experts emphasized the relevance of progression-free survival as a more appropriate goal of therapy, which was assessed a key secondary outcome in the trial.

The clinical experts consulted by CADTH noted the relevance of assessing corticosteroid use. In clinical practice, most patients are expected to initiate corticosteroids at one point or another upon disease progression, and as a targeted VEGF inhibitor there is a rationale that the mechanism of action of bevacizumab may theoretically result in a potential steroid-sparing effect. However, the choice of outcome measure in the study does not inform on the ability of bevacizumab to reduce the use of corticosteroids in patients receiving high doses or who experience corticosteroid-related toxicity, which would be the most clinically relevant outcome measure.

Patient groups that provided input to this review identified the outcomes assessed and reported in EORTC 26101 as being important, including corticosteroid use, HRQoL, neurocognitive function and harms.

Results of the Included Study

Baseline Characteristics

Baseline characteristics were balanced between treatment groups in the EORTC 26101 study. Full details regarding baseline characteristics are provided in Wick et al[7] for the EORTC study.

More specifically, patients in the EORTC 26101 study had a median age of 58 years (range 21 to 82 years) and 61% of patients were male. The proportions of patients within each of the WHO performance status scores was as follows: 34% of patients had a performance status of 0, 55% had a performance status of 1, and 11% had a performance status of 2. A total of 49% of patients were using corticosteroids at baseline. The median time between first progressive disease and treatment was 26 days (range 1 to 231 days).

Patient Disposition

In the EORTC 26101 study (n = 437), 288 patients were randomly assigned to receive the combination of bevacizumab and lomustine, while 149 patients were randomized to lomustine monotherapy. High proportions of patients discontinued treatment, the most frequent reason for treatment discontinuation being disease progression, which is to be expected according to the clinical experts consulted by CADTH. Despite discontinuing study drug, most patients however continued follow-up in the study. More specifically, in the combination group, 79% of patients discontinued bevacizumab and 71% discontinued lomustine due to disease progression; in the monotherapy group, 83% of patients discontinued lomustine for such reason. AEs were the second reason for discontinuation and led 14% of patients in the combination group to discontinue bevacizumab and 20% of patients in this same treatment group to discontinue lomustine; 10% of patients receiving monotherapy discontinued lomustine due to AEs.

Efficacy Results

Only those efficacy outcomes identified in the review protocol are reported subsequently. Results are summarized in Table 7.

Overall Survival

The use of bevacizumab in combination with lomustine was associated with a HR of 0.95 (95% CI 0.74 – 1.21; P = 0.65) versus lomustine monotherapy. The median survival time was 9.1 months (95% CI 8.1 – 10.1) in the combination group and 8.6 months (95% CI 7.6 – 10.4) in the monotherapy group. In the Kaplan-Meier plot, provided in Wick et al.[7], the curves followed a similar pattern; they appeared to separate initially, but then crossed at approximately 12 months.

Progression-Free Survival

The use of bevacizumab in combination with lomustine was associated with a HR of 0.49 (95% CI 0.39 – 0.61) (P < 0.001) in favour of the combination treatment versus control, as per local investigator's assessment. The median survival time was 4.2 months (95% CI 3.7 – 4.3) in the combination group and 1.5 month (95% CI 1.5 – 2.5) in the monotherapy group. Results for central assessments were consistent with these findings; combination treatment was associated with a HR of 0.59 (95% CI 0.48 – 0.74) (P < 0.001) in favour of intervention versus control. The median survival time was 3.8 months (95% CI 3.0 – 4.2) in the combination group and 1.5 month (95% CI 1.5 – 1.6) in the monotherapy group. In the Kaplan-Meier plot, provided in Wick et al.[7], the curves appeared to separate as early as approximately one month, favouring the combination treatment. The curves remained separated throughout follow-up.

The clinical experts consulted by CADTH for this review emphasized the relevance of progression-free survival in the context of recurrent glioblastoma multiforme, a condition for which the between-group difference of approximately 2.5 months in median progression-free survival observed in Study EORTC 26101 was considered clinically meaningful. More specifically, the clinical experts highlighted the fact that progression-free survival is well correlated with clinical status in these patients in clinical practice.

Objective Response Rate

Response rates were assessed in Study EORTC 26101 according to the RANO criteria among patients who had measurable disease. An objective response (partial or complete response) was observed in 41.5% (95% CI 35.5 – 47.8) of patients in the bevacizumab and lomustine combination group and in 13.9% (95% CI 8.6 – 20.8) of patients in the lomustine monotherapy group. No statistical comparison was performed; however, the magnitude of the between-group difference (point estimate, 27.6%) was considered clinically meaningful by the clinical experts consulted by CADTH. Five (2%) patients in the combination therapy group and one (1%) in the monotherapy group experienced complete responses.

Duration of Response

No data was reported in the publications for the outcome of duration of response for Study EORTC 26101.

Neurologic Deterioration-Free Survival

No data was reported in the publications for the outcome of neurologic deterioration–free survival for Study EORTC 26101.

Neurocognitive Symptoms

Findings for neurocognitive symptoms are provided in the Wick et al Supplementary Appendix;[8] standardized mean scores (with 95% CI) are shown in unlabeled figures at baseline and at subsequent follow-up, by treatment arm, for each of the six prespecified subscales. Per the investigators, no statistically significant between-group difference was observed at any time point and for any of the testing instruments; however, between-group differences with confidence intervals were not reported at any time point for any instrument. Completion rates for the scales was 94.5% at baseline and went down to 61.4% after 36 weeks.[7]

Corticosteroid Use

The number of patients who did not receive corticosteroids at baseline was 144 patients in the bevacizumab and lomustine combination group and 78 patients in the lomustine monotherapy group; of these, 39% of patients in each treatment group initiated

corticosteroids throughout the study. The median time to initiation was 8.3 months (95% CI 6.8 – not reached) in the combination group and 8.6 months (95% CI 4.5 – 12.7) in the monotherapy group.

Health-Related Quality of Life

Except for social functioning, HRQoL scale scores at Week 36 were similar between treatment groups. No statistically or clinically significant difference (per the investigators) was observed. As for social functioning, the use of bevacizumab in combination with lomustine was associated with a lower level of functioning compared to lomustine monotherapy; the difference was considered clinically important by the investigators, however no between-group difference was reported. Completion rates for the HRQoL scales was 92.0% at baseline and went down to 66.3% after 36 weeks.[7]

According to the investigators, there were no statistically significant difference in within-group change from baseline, except for results obtained at Week 36 for the global health status and social functioning subscales, with data available from 35 patients in the combination group and 9 patients in the monotherapy group.[7] For global health status, the mean change from baseline was -5.6 versus 4.6 in the combination and monotherapy groups, respectively; for social functioning, the mean change from baseline was -1.1 versus 9.3 in the combination and monotherapy groups, respectively.[7] Between-group differences with confidence intervals were not reported.

With a median of 13.0 and 13.1 weeks in the monotherapy and combination treatment groups, respectively (P = 0.65), findings for time to HRQoL deterioration appeared similar in both treatment groups; however, no other statistical measure was reported (e.g., 95% CI, range or interquartile range), precluding any assessment of potential interindividual variation. Additionally, no HR was reported, nor any between group differences at relevant follow-up time points. When disease progression was captured, the use of bevacizumab and lomustine was associated with a statistically significant and clinically meaningful (per the investigators) benefit in deterioration-free survival compared with lomustine monotherapy, with a median of 12.4 weeks versus 6.7 weeks, respectively (p<0.001); again, no other statistical measure was reported, so that it is not possible to assess the precision of the results.

Table 7: Summary of Efficacy Outcomes for Study EORTC 26101 (ITT population)

Outcome	Bevacizumab / lomustine N = 288	Lomustine N = 149
Overall survival		
Number of events, n (%)	216 (75.0)	113 (75.8)
Median (95% CI), months	9.1 (8.1 – 10.1)	8.6 (7.6 – 10.4)
HR (95% CI); p-value	0.95 (0.74 – 1.21); p=0.65 [a]	
Survival at 9 months, % (95% CI)	51.2 (45.2 – 57.0)	47.5 (39.0 – 55.5)
Survival at 12 months, % (95% CI)	31.5 (25.7 – 37.6)	34.1 (25.8 – 42.6)
Progression-free survival		
Local assessment median (95% CI), months	4.2 (3.7 – 4.3)	1.5 (1.5 – 2.5)
HR (95% CI); p-value	0.49 (0.39 – 0.61); p<0.001 [a]	
Central assessment median (95% CI), months	3.8 (3.0 – 4.2)	1.5 (1.5 – 1.6)
HR (95% CI); p-value	0.59 (0.48 – 0.74); p<0.001 [a]	
Objective response rate (complete response + partial response)		
Number of patients	N = 260	N = 137
Number of events, n (%)	108 (41.5)	19 (13.9)
95% CI	35.5 – 47.8	8.6 – 20.8
Corticosteroid therapy initiated during study follow-up		
No corticosteroids at baseline	N = 144	N = 78
Patients starting corticosteroids, n (%)	56 (38.9)	30 (38.5)
Time to initiation in months, median (95% CI)	8.3 (6.8 – not reached)	8.6 (4.5 – 12.7)
p-value	p=0.33 [a]	
HRQoL – Scores for preselected scales at week 36 [b]		
Global health status, mean (SD)	62.1 (21.0)	66.7 (18.4)
p-value	p=0.1979 [a]	
Physical functioning, mean (SD)	71.7 (25.2)	75.9 (24.8)
p-value	p=0.2095 [a]	
Social functioning, mean (SD)	66.0 (30.3)	81.0 (25.2)
p-value	p=0.0011 [a]	
Motor dysfunction, mean (SD)	21.9 (23.9)	17.5 (22.1)
p-value	p=0.1754 [a]	
Communication deficit, mean (SD)	25.5 (28.6)	21.1 (29.3)
p-value	p=0.1950 [a]	
Deterioration-free survival [b]		
Median, weeks	12.4	6.7
p-value	p<0.001 [a]	
Time to deterioration in HRQoL [b]		
Median, weeks	13.1	13.0
p-value	p=0.65 [a]	

CI = confidence interval; HR = hazard ratio; ITT = intention to treat; SD = standard deviation.

[a] No information was provided in the publication or associated materials in order to determine whether there was any multiplicity adjustment; based on CADTH's best assessment, it appears there was none.
[b] These were subject to missing outcome data based on the completion rates reported in the publications; however, the sample size for each analysis was not reported.
Source: Wick et al. 2017[7] (including supplementary appendix)[8]

Harms Results

Only those harms identified in the review protocol are reported below. See Table 8 for detailed harms data.

Adverse events

The proportions of patients who experienced AEs were 98.2% in the bevacizumab and lomustine combination group and 94.6% in the lomustine monotherapy group. Grade 3 – 5 AEs were experienced by more patients in the combination therapy than in the monotherapy arm; more specifically, by 63.6% of patients who received bevacizumab and lomustine and by 38.1% of patients who received lomustine monotherapy.

Serious adverse events

The proportion of patients who experienced SAEs was higher in the bevacizumab and lomustine combination group, with 38.5% of patients reporting any treatment-related SAE, compared to 9.5% of patients in the lomustine monotherapy group.

Withdrawals due to adverse events

No data were reported for WDAEs as a harms outcome.

Mortality

Five (1.8%) patients who received combination therapy with bevacizumab and lomustine, and one (0.7%) patient receiving lomustine monotherapy, died throughout the study of causes that were unrelated to disease progression (those death captured under harms outcomes); details are provided in Table 8.

Harms of Special Interest

Some results for harms of special interest were reported in Le Rhun et al. 2023[9] (including supplementary appendix).[10] This safety analysis included 78 additional patients in the lomustine monotherapy treatment group (N = 225), who were randomized only in phase II of Study EORTC 26101 and were assigned to receive lomustine monotherapy, to be followed by bevacizumab upon further disease progression.[9,10]

The proportions of patients who experienced thrombocytopenia in the bevacizumab and lomustine combination group, compared with lomustine monotherapy, were as follows: a grade 3 event was reported in 20.8% of patients versus 14.7%, respectively, while a grade 4 event was reported in 5.3% of patients versus 8.4%, respectively. As for intracranial haemorrhage, only two events were reported: one patient in the lomustine monotherapy group reported a grade 3 event and one patient in the bevacizumab and lomustine combination group reported a grade 5 event.

Table 8: Summary of Key Harms Outcomes in Study EORTC 26101 (Safety Population)

Outcome	Bevacizumab / lomustine N = 283	Lomustine N = 147
Patients with any AEs		
n (%)	278 (98.2)	139 (94.6)
Patients with any grade 3 – 5 AEs		
n (%)	180 (63.6)	56 (38.1)
Patients with any treatment-related SAEs		
n (%)	109 (38.5)	14 (9.5)
Deaths		
n (%)	5 (1.8)	1 (0.7)
Causes of death, n (%)		
Myocardial infarction	2 (0.7)	0
Large intestine perforation	1 (0.4)	0
Sepsis	1 (0.4)	0
Intracranial hemorrhage	1 (0.4)	0
Lung infection	0	1 (0.7)

AE = adverse event; SAE = serious adverse event.
Source: Wick et al. 2017[7] (including supplementary appendix)[8]

Indirect Evidence

A total of 81 references were identified from the ITC search. After title and abstract screening, 10 were included for full-text review. After full-text review, no ITCs were deemed eligible for this review.

Other Relevant Evidence

No long-term extension study, or additional relevant study was considered to address important gaps in the evidence included in the systematic review.

Economic Evidence

As this review is part of the CADTH non-sponsored reimbursement review program in which an application filed by a sponsor is absent, CADTH does not have access to an economic model for bevacizumab plus lomustine in this clinical condition. As a result, the economic review consisted of only a cost comparison for bevacizumab plus lomustine compared with lomustine alone or temozolomide.

CADTH Analyses

The comparators presented in Table 9 : CADTH Cost Comparison Table for Recurrent Glioblastoma have been deemed to be appropriate based on feedback from clinical experts and drug plans. Recommended doses were based on each product's respective product monographs, unless otherwise indicated, and validated by clinical experts. If discrepancies in dosing between the product monograph and Canadian clinical practice were noted, the dose specified by clinical experts was used. Based on wholesale list prices from IQVIA DeltaPA accessed August 2023, 100 mg and 400 mg vials of bevacizumab biosimilars are priced at $347 and $1,388, respectively.[30] Based on public list prices from the Ontario Drug Benefit Formulary accessed in August 2023, lomustine 4 mg and 10 mg tablets are priced at $7.89 and $13.60, respectively.[31] Pricing for comparator products was based on publicly available list prices.

When used as recommended in the bevacizumab product monograph, the per patient cost of bevacizumab plus lomustine for the treatment of relapsed or progressed glioblastoma is $5,597 per standardized 28-day cycle. When used alone, the cost per 28-day cycle of lomustine is $45, while that of temozolomide is $741 to $1,037. As such, results of the cost-comparison demonstrate that, over a 28-day cycle, bevacizumab plus lomustine is associated with an incremental cost of $5,552 per patient compared with lomustine monotherapy. Compared with temozolomide, over a 28-day cycle, bevacizumab plus lomustine is associated with incremental costs ranging from $4,560 to $4,856 per patient. Note that results may differ by jurisdiction should prices differ from those presented in Table 9 : CADTH Cost Comparison Table for Recurrent Glioblastoma.

Table 9 : CADTH Cost Comparison Table for Recurrent Glioblastoma

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average Cost per 28-days ($)
Bevacizumab (biosimilars)	25 mg/mL 4 mL (100 mg) 16 mL (400 mg)		347.0000[a] 1,388.0000[a]	10 mg/kg on Day 1 and every 14 days[bc]	198.29	5,552
Lomustine (CeeNU)	10 mg 40 mg	Capsule	7.8900 13.6025	90 mg/m^2 BSA (max: 160 mg) on Day 1 for the first cycle and every 42 days. Dose can be escalated to 110 mg/m^2 (max: 200 mg) from second cycle onward[b]	1.62[d] based on a 200 mg dose	45[d]
Bevacizumab-Lomustine Regimen Cost					**199.91**	**5,597**
Lomustine monotherapy						
Lomustine (CeeNU)	10 mg 40 mg	Capsule	7.8900 13.6025	110 to 130 mg/m^2 BSA on Day 1 every 42 days[e]	1.62[d]	45[d]
Temozolomide						
Temozolomide (generics) cyclical use	5 mg 20 mg 100 mg 140 mg	Capsule	1.9500 7.8000 39.0015 54.6025	200 mg/m^2 BSA on Days 1 to 5 every 28 days[f]	26.46	741

Treatment	Strength / concentration	Form	Price ($)	Recommended dosage	Average daily cost ($)	Average Cost per 28-days ($)
	250 mg		97.5010			
Temozolomide (generics) continuous use	5 mg 20 mg 100 mg 140 mg 250 mg	Capsule	1.9500 7.8000 39.0015 54.6025 97.5010	50 mg/m^2 BSA daily[f]	37.05	1,037

BSA = body surface area.

Note: All prices are from the Ontario Drug Benefit Formulary (accessed August 2023) unless otherwise indicated, and do not include dispensing fees.[31]

Note: All dose calculations assume an 80 kg patient with a body surface area of 1.9 m^2, derived from mean BMI reported in a study on body weight and high-grade glioma survival and CDC growth curves.[32,33]

[a] Delta PA wholesale list price, accessed May 2023.[30]

[b] As listed in the MVASI (bevacizumab) product monograph.[34] This dosing is also reported in the Cancer Care Ontario Regimen formulary but is currently unfunded.[35] This lomustine dose was also evaluated in the EORTC 26101 trial.[7] Dose escalation of lomustine to 110 mg/m^2 is recommended only in the absence of Grade >1 hematological toxicity in the first cycle.[34]

[c] According to the literature and clinical expert feedback elicited by CADTH, lower doses of bevacizumab than recommended in the product monograph are also used in clinical practice.[5,36,37] When dosed at 5 mg/kg every 21 days, the cost of bevacizumab is $66.10 per day or $1,851 per standardized 28-day cycle, while the cost of the regimen including lomustine would be $67.39 to $67.71 per day or $1,887 to $1,896 per standardized 28-day cycle.

[d] Daily cost and cost per 28-days for lomustine assume all patients receive 200 mg per administration, based on a dose of 110 mg/m^2 up to a maximum of 200 mg. The daily cost of a 130 mg/m^2 dose with no maximum assumed would be $2.15 ($60 per 28-day cycle).

[e] The product-monograph recommended dosing of lomustine when used alone is 130 mg/m^2,[38,39] however, according to clinical expert opinion solicited by CADTH for this review, 110 mg/m^2 is frequently used with or without bevacizumab.

[f] The listed temozolomide regimen options are specifically funded by Cancer Care Ontario for glioblastoma multiforme with documented evidence of recurrence or progression after standard therapy.[39] In patients using cyclical dosing who have previously received chemotherapy, the initial cycle should consist of 150 mg/m^2, escalating to 200 mg/m^2 in cycle 2 in the absence of hematologic toxicity and ≥ grade 3 of other toxicities in cycle 1.

Issues for Consideration

- The use of bevacizumab for patients with relapsed or progressed glioblastoma may potentially allow for a reduction in steroid dependency,[40] though this was not evaluated in the EORTC 26101 trial.[7] According to clinical expert feedback elicited by CADTH, the ability to taper high-dose steroid use (e.g., dexamethasone) would improve patient quality of life and reduce costs associated with steroid use. A cost-effectiveness analysis would be required to incorporate the costs and benefits associated with high-dose steroid use reductions.
- While the dose used in the EORTC 26101 trial[7] and product-monograph recommended dose of bevacizumab when used in combination with lomustine for glioblastoma is 10 mg/kg once every 2 weeks,[34] alternate dosing of 5 mg/kg every 3 weeks has been reported in the literature[5,36,37] and, according to clinical expert opinion elicited by CADTH, is also used in Canadian clinical practice. At this dose, the cost of bevacizumab would be $66.10 per day or $1,851 per standardized 28-day cycle, assuming IQVIA-reported wholesale list prices and an 80 kg patient, while the cost of the regimen including lomustine would be $67.71 per day or $1,896 per standardized 28-day cycle.
- CeeNU (lomustine) is anticipated to be discontinued in early 2025.[41] Despite being available in Canada since 1974,[38] CeeNU is currently the only lomustine product available in Canada and as such, it is unclear whether lomustine will continue to be available after this discontinuation.
- No Canadian cost-effectiveness studies were identified based on a literature search conducted on June 27, 2023.

Discussion

Summary of Available Evidence

One published, open-label, multicentre, phase III RCT was reviewed: Study EORTC 26101 (n = 437)[7-10] evaluated the benefits of bevacizumab and lomustine, compared to lomustine monotherapy, for the treatment of patients with glioblastoma multiforme at unequivocal first progression after chemoradiotherapy. In the trial, bevacizumab was administered through IV infusion at a dose of 10 mg/kg every 2 weeks; when used as part of the combination therapy, lomustine was administered orally every 6 weeks at a dose of 90 mg/m^2, to be increased to 110 mg/m^2 in the absence of hematological toxicity, and at a dose of 110 mg/m^2 when used as monotherapy. Both study therapies were to be discontinued at further disease progression, and followed by investigator's choice of treatment.[7,9]

Findings from Study EORTC 26101 were obtained in a population that was deemed overall younger, and with a better performance status, than patients routinely seen in clinical practice. This should be considered when generalizing the findings from the study to real-life patients. By having an open-label design, the study was susceptible to assessment and reporting biases for subjective efficacy and harms outcomes, and patient-reported outcomes, the impact or direction of which are uncertain. There is however an exception for progression-free survival, which was also centrally reviewed by assessors who were blinded to treatment assignment. High treatment discontinuation rates were observed in both groups, which is expected given the poor prognosis of the disease and AE profiles of the drugs; however, they remain a concern. In addition, there is a risk of bias due to missing outcome data, especially for HRQoL and neurocognitive function. The potential impact of discontinuations and missing outcome data on the results is uncertain.

Interpretation of Results

Efficacy

The use of bevacizumab and lomustine did not show an overall survival benefit. Improving survival in patients with cancer should remain the primary goal of therapy; however, in the very specific context of treating recurrent glioblastoma multiforme with bevacizumab plus lomustine (relative to lomustine monotherapy), the clinical experts consulted by CADTH did not consider overall survival as a realistic treatment goal unfortunately, especially given the expected role of bevacizumab in the anti-cancer therapy as a targeted VEGF inhibitor. With a particularly poor survival prognosis and in the absence of treatment options providing any substantial survival benefits at this time, the clinical experts emphasized the relevance of progression-free survival as a more appropriate goal of therapy, which was assessed a key secondary outcome in the trial.

As such, the use of bevacizumab and lomustine was associated with HRs in favour of the combination treatment versus lomustine monotherapy for progression-free survival. The between-group difference of approximately 2.5 months in median progression-free survival observed in Study EORTC 26101 was considered clinically meaningful by both experts, especially in light of the limited life expectancy after diagnosis. Progression-free survival was not subject to confounding from the treatments received upon disease progression, nor subject to assessment bias due to central review by assessors blinded to treatment assignment. Therefore, the evidence suggests that the combination of bevacizumab and lomustine results in benefits in terms of progression-free survival for patients with recurrent glioblastoma multiforme.

Results also suggested potential benefits from bevacizumab and lomustine on other secondary outcomes, such as objective response rates assessed according to the RANO criteria, and deterioration-free survival, a measure encompassing HRQol, disease progression and death. However, there is uncertainty surrounding those findings. Only limited statistical analyses were reported for both outcomes, precluding proper assessment of the between-group differences and the precision of the estimates. Duration of response in each group was measured but not reported. In addition, deterioration-free survival was a composite outcome, for which results were mainly driven by progression-free survival, as emphasized by the authors of the publication. When taken alone, HRQoL findings from two established and validated tools were not conclusive, mainly due to the large amount of missing data at longer follow-up, the lack of comparative effect estimates with confidence intervals, and the absence of known minimally important differences reported.

The combination therapy with bevacizumab and lomustine also did not seem to have a significant impact on neurocognitive symptoms, per the investigators' conclusions, as data were not provided (unlabeled graphs) and no between-group effect estimates were reported. Finally, the study did not inform on the corticosteroid-sparing ability of bevacizumab, especially in patients receiving high doses or who experience corticosteroid-related toxicity. Corticosteroid use was assessed in the trial as therapy initiation, which was not considered clinically relevant by the clinical experts, as the vast majority of patients, no matter the choice of treatment, are expected to initiate corticosteroids at one point or another upon disease progression.

Harms

High proportions of patients experienced at least one AE throughout the study follow-up, and the proportions were similar between treatment groups. However, more patients receiving the combination therapy with bevacizumab and lomustine experienced grade 3 – 5 AEs and SAEs that were unrelated to disease progression compared with patients in the monotherapy arm. There were too few events to draw a strong conclusion regarding mortality due to AEs. The clinical experts consulted by CADTH indicated that it is common for patients under treatment for recurrent glioblastoma multiforme in clinical practice to experience numerous AEs, and that these may be considered tolerable by patients seeking treatment, considering the poor prognosis of the disease and limited number of therapeutic options. It should be noted that patients and clinicians in the trial were aware of the treatment strategy received, which may have introduced bias in the reporting of subjective harms.

Cost Information

Based on publicly available list prices, bevacizumab plus lomustine is expected to have a 28-day per patient cost of $5,588 to $5,597 when used as recommended in the bevacizumab product monograph for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy, whereas lomustine when used alone is expected to have a 28-day per patient cost of $51 to $60. As such, the incremental cost of bevacizumab plus lomustine compared to lomustine alone is $$5,552, while the incremental cost compared to temozolomide is $4,560 to $4,856. These incremental costs are based on publicly available list prices and may not reflect actual prices paid by Canadian public drug plans.

Conclusions

Findings from Study EORTC 26101 did not show an overall survival benefit, but suggest that combination treatment with bevacizumab and lomustine may result in clinically meaningful prevention of disease progression versus lomustine monotherapy in patients with recurrent glioblastoma multiforme. The interpretation of neurocognitive function, corticosteroid-sparing and HRQoL was however limited by poor reporting and/or missing outcome data. The population in the study was deemed overall younger, and with a better performance status, than patients routinely seen in clinical practice. High proportions of patients experienced harms events, of which grade 3-5 AEs and treatment-related SAEs were numerically higher with the combination treatment than with monotherapy. Although the harms profile reported in the publications appeared consistent with what is currently seen in clinical practice according to the clinical experts consulted by CADTH, the use of bevacizumab in the study was associated with an increased toxicity, the implications of which is uncertain. As such, tolerability should be weighed against any potential gain expected from treatment on progression-free survival. Special consideration may also be given to the fact that there is a limited number of therapeutic options for patients with recurrent glioblastoma multiforme, all of which unfortunately having little impact on prognosis.

Results of the cost-comparison of treatment costs demonstrate that, over a 28-day cycle, bevacizumab plus lomustine is $5,552 more costly than lomustine alone, and $4,560 to $4,856 more costly than temozolomide, per patient. As such, the reimbursement of bevacizumab plus lomustine for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy, is expected to increase overall treatment costs. No literature was identified comparing bevacizumab plus lomustine with temozolomide, therefore the comparative efficacy of these treatments is unknown. Based on the clinical review conclusions, bevacizumab and lomustine may provide a clinically meaningful benefit on progression-free survival compared to lomustine monotherapy. As such, bevacizumab and lomustine is associated with incremental costs and incremental benefit compared with lomustine monotherapy. A cost-effectiveness analysis would therefore be required to determine the cost-effectiveness of bevacizumab and lomustine compared with lomustine monotherapy. As a cost-effectiveness analysis was not submitted, the cost-effectiveness of bevacizumab plus lomustine for the treatment of patients with glioblastoma after relapse or disease progression, following prior therapy, could not be determined. Other costs such as administration costs were not considered as part of the cost comparison. To consider this alongside the healthcare resource implications associated with comparative clinical benefits, a cost-effectiveness analysis comparing bevacizumab plus lomustine to lomustine alone or to temozolomide would be required.

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Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Date of search: March 16, 2023

Alerts: Bi-weekly search updates until project completion

Search filters applied: Randomized controlled trials; controlled clinical trials

Limits: Conference abstracts: excluded

Table 10: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*****	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.mp	Mapped term

Syntax	Description
.rn	Registry number
.nm	Name of substance word (MEDLINE)
.yr	Publication year
.jw	Journal title word (MEDLINE)
.jx	Journal title word (Embase)
freq=#	Requires terms to occur # number of times in the specified fields
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily
cctr	Ovid database code; Cochrane Central Register of Controlled Trials

Multi-Database Strategy

1	Bevacizumab/
2	(abevmy*or abp 215 or abp215 or ainex* or altuzan* or alymsys* or ankeda* or ask b1202 or askb1202 or avastin* or avegra* or aybintio* or ba 1101 or ba1101 or bambevi* or bat 1706 or bat1706 or "bcd 021" or bcd021 or bevacizumab* or bevatas* or bevax* or bevz 92 or bevz92 or bewacyzumab* or bi 695502 or bi695502 or "bow 030" or bow030 or boyounuo* or "bp 01" or bp01 or bryxta* or bxt 2316 or bxt2316 or byvasda* or cbt 124 or cbt124 or chs 305 or chs 5217 or chs5217 or cizumab* or ct p16 or ctp16 or equidacent* or fkb 238 or fkb238 or gb 222 or gb222 or "gbs 004" or gbs004 or hanbeitai* or hd 204 or hd204 or "hlx 04" or hlx04 or hot 1010 or hot1010 or ibi 305 or ibi305 or "idb 0072" or idb0072 or intp 24 or intp24 or ipique* or jhl 1149 or jhl1149 or js 501 or js501 or "jy 028" or jy028 or krabeva* or kyomarc* or lextemy* or lumiere* or "ly 01008" or ly01008 or mabionvegf or "mb 02" or mb02 or mil 60 or mil60 or mvasi* or myl 14020 or myl 1402o or myl14020 or myl1402o or nsc 704865 or nsc704865 or onbevzi* or ons 1045 or ons 5010 or ons1045 or ons5010 or oyavas* or "pf 06439535" or pf 6439535 or pf06439535 or pf6439535 or pmc 901 or pmc901 or pobevcy* or pro 169 or pro169 or pusintin* or ql 1101 or ql1101 or r 435 or "r tpr 023" or r435 or rg 435 or rg435 or rhuMAb-VEGF or ro 4876646 or ro4876646 or "rph 001" or rph001 or rtpr023 or sb 8 or sb8 or sct 510 or sct510 or stc 103 or stc103 or stivant* or "tab 008" or "tab 014" or tab008 or tab014 or tot 102 or tot102 or "trs 003" or trs003 or tx 16 or tx16 or versavo* or zirabev* or zrc 113 or zrc113 or zybev* or 2S9ZZM9Q9V).ti,ab,kf,ot,rn,nm.
3	or/1-2
4	Lomustine/
5	(belustine* or CCNU or cecenu* or ceenu* or cinu* or gleostine* or lomeblastin* or lomustin* or lucostin* or lucostine* or nsc 79037 or nsc79037 or 7BRF0Z81KG).ti,ab,kf,ot,rn,nm.
6	or/4-5
7	exp chemoradiotherapy/ or consolidation chemotherapy/ or induction chemotherapy/ or maintenance chemotherapy/
8	(chemotherap* or chemoradiotherap* or radiochemotherap* or multichemotherap* or poly-chemotherap* or polychemo or polychemotherap* or carcinochemotherap*).ti,ab,kf.
9	(adjuvant drug adj3 therap*).ti,ab,kf.
10	or/7-9

11	6 or 10
12	3 and 11
13	exp Glioma/ or exp Glioblastoma/
14	(astrocytom* or xanthoastrocytoma* or gliobastom* or glyoblastom* or glioma* or GBM or glia* tumor* or glia* tumour* or glio blastom* or gliosarcoma* or oligodendroglioma* or medulloblastoma* or oligoastrocytoma* or oligodendrocyte* or astroblastoma* or ependymocyt* or ependymyoma* or ependymoma* or ganglioglioma* or ependymoma* or subependymoma*).ti,ab,kf.
15	or/13-14
16	12 and 15
17	16 use medall
18	*Bevacizumab/
19	(abevmy*or abp 215 or abp215 or ainex* or altuzan* or alymsys* or ankeda* or ask b1202 or askb1202 or avastin* or avegra* or aybintio* or ba 1101 or ba1101 or bambevi* or bat 1706 or bat1706 or "bcd 021" or bcd021 or bevacizumab* or bevatas* or bevax* or bevz 92 or bevz92 or bewacyzumab* or bi 695502 or bi695502 or "bow 030" or bow030 or boyounuo* or "bp 01" or bp01 or bryxta* or bxt 2316 or bxt2316 or byvasda* or cbt 124 or cbt124 or chs 305 or chs 5217 or chs5217 or cizumab* or ct p16 or ctp16 or equidacent* or fkb 238 or fkb238 or gb 222 or gb222 or "gbs 004" or gbs004 or hanbeitai* or hd 204 or hd204 or "hlx 04" or hlx04 or hot 1010 or hot1010 or ibi 305 or ibi305 or "idb 0072" or idb0072 or intp 24 or intp24 or ipique* or jhl 1149 or jhl1149 or js 501 or js501 or "jy 028" or jy028 or krabeva* or kyomarc* or lextemy* or lumiere* or "ly 01008" or ly01008 or mabionvegf or "mb 02" or mb02 or mil 60 or mil60 or mvasi* or myl 14020 or myl 1402o or myl14020 or myl1402o or nsc 704865 or nsc704865 or onbevzi* or ons 1045 or ons 5010 or ons1045 or ons5010 or oyavas* or "pf 06439535" or pf 6439535 or pf06439535 or pf6439535 or pmc 901 or pmc901 or pobevcy* or pro 169 or pro169 or pusintin* or ql 1101 or ql1101 or r 435 or "r tpr 023" or r435 or rg 435 or rg435 or rhuMAb-VEGF or ro 4876646 or ro4876646 or "rph 001" or rph001 or rtpr023 or sb 8 or sb8 or sct 510 or sct510 or stc 103 or stc103 or stivant* or "tab 008" or "tab 014" or tab008 or tab014 or tot 102 or tot102 or "trs 003" or trs003 or tx 16 or tx16 or versavo* or zirabev* or zrc 113 or zrc113 or zybev*).ti,ab,kf,dq.
20	or/18-19
21	*Lomustine/
22	(belustine* or CCNU or cecenu* or ceenu* or cinu* or gleostine* or lomeblastin* or lomustin* or lucostin* or lucostine* or nsc 79037 or nsc79037).ti,ab,kf,dq.
23	or/21-22
24	exp chemotherapy/
25	(chemotherap* or chemoradiotherap* or radiochemotherap* or multichemotherap* or poly-chemotherap* or polychemo or polychemotherap* or carcinochemotherap*).ti,ab,kf,dq.
26	(adjuvant drug adj3 therap*).ti,ab,kf,dq.
27	or/24-26
28	23 or 27
29	20 and 28
30	exp Glioma/ or exp Glioblastoma/
31	(astrocytom* or xanthoastrocytoma* or gliobastom* or glyoblastom* or glioma* or GBM or glia* tumor* or glia* tumour* or glio blastom* or gliosarcoma* or oligodendroglioma* or medulloblastoma* or oligoastrocytoma* or oligodendrocyte* or astroblastoma* or ependymocyt* or ependymyoma* or ependymoma* or ganglioglioma* or ependymoma* or subependymoma*).ti,ab,kf,dq.
32	or/30-31
33	29 and 32
34	33 use oemezd
35	34 not (conference abstract or conference review).pt.
36	17 or 35

37	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
38	Randomized Controlled Trial/
39	exp Randomized Controlled Trials as Topic/
40	"Randomized Controlled Trial (topic)"/
41	Controlled Clinical Trial/
42	exp Controlled Clinical Trials as Topic/
43	"Controlled Clinical Trial (topic)"/
44	Randomization/
45	Random Allocation/
46	Double-Blind Method/
47	Double Blind Procedure/
48	Double-Blind Studies/
49	Single-Blind Method/
50	Single Blind Procedure/
51	Single-Blind Studies/
52	Placebos/
53	Placebo/
54	Control Groups/
55	Control Group/
56	(random* or sham or placebo*).ti,ab,hw,kf.
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
59	(control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
60	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
61	allocated.ti,ab,hw.
62	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
63	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.
64	(pragmatic study or pragmatic studies).ti,ab,hw,kf.
65	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
66	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
67	(phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
68	or/37-67
69	36 and 68
70	remove duplicates from 69

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.
[Search terms: bevacizumab AND glioblastoma]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials.
[Search terms: bevacizumab AND glioblastoma]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms: bevacizumab AND glioblastoma]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.
[Search terms: bevacizumab AND glioblastoma]

Grey Literature

Search dates: March 8 -13, 2023
Keywords: bevacizumab AND glioblastoma
Limits: No limits
Updated: Search updated prior to the completion of stakeholder feedback period
Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: A Practical Tool for Searching Health-Related Grey Literature* were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Health Statistics
- Internet Search
- Open Access Journals

Appendix 2: Excluded Studies

Table 11: Excluded Studies

Reference	Reason for Exclusion
Brandes AA, et al. *Oncologist.* 2019 24(4):521-528	Other design (review article, clinical practice guideline or expert opinion)
Galldiks N, et al. *Eur J Nucl Med Mol Imaging.* 2018 45(13)(2377-2386)	Ineligible outcome(s)
Gahrmann R, et al. *Neuro-Oncology.* 2017 19(6):853-861	Ineligible outcome(s)
Weathers SP, et al. *J Neuro-Oncol*. 2016 129(3):487-494	Ineligible intervention
Beije N, et al. B*r J Cancer*. 2015 113(2):226-31	Ineligible outcome(s)
Ellingson BM, et al. *Int J Oncol.* 2015 46(5):1883-92	Ineligible outcome(s)
Komotar RJ, et al. *Neurosurgery.* 2014 74(6):N14-N17	Other design (review article, clinical practice guideline or expert opinion)
Van den Vent MJ, et al. *Lancet Oncol.* 2014 15(11):e473-e474	Other design (review article, clinical practice guideline or expert opinion)
Hofer S, et al. *Memo - Magazine Eur Med Oncol*. 2013 6(4):247-250	Other design (review article, clinical practice guideline or expert opinion)
Osterweil N. *Oncol Rep.* 2013 AUG:7	Unable to retrieve publication