Appendix 4: Stakeholder Input – Industry

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Amgen Canada Inc.

Does the proposed project scope accurately reflect the treatment landscape?

Amgen welcomes the proposed project to evaluate whether bevacizumab and lomustine should be publicly reimbursed for recurrent glioblastoma multiforme.

Patients with previously treated glioblastoma multiforme face a dismal prognosis and have no effective chemotherapeutic options if they are unable to undergo re-resection or re-irradiation. Single chemotherapeutic agents are approved and funded in some jurisdictions but provide only modest benefits that must be balanced with potentially high toxicity.[1] Unfortunately, there have not been any substantial improvements in the second-line treatment options over the last decade. Given the aggressive nature of glioblastoma multiforme and the complexity of targeting the central nervous system, access to additional effective treatment options is a major unmet medical need.[2]

Are you aware of relevant published studies that you would like considered in the clinical review?

Data supporting the combination of bevacizumab and lomustine are available from the EORTC 26101 trial[3], the randomized controlled Phase 2 BELOB Study[4], a meta-analysis by Ren *et al*[5], and a Cochrane network meta-analysis by McBain *et al*[6].

The EORTC 26101 trial enrolled glioblastoma multiforme patients with first progression after radiotherapy with concurrent/adjuvant temozolomide, which reflects the first-line standard of care in Canada. These patients were randomized to receive bevacizumab 10 mg/kg IV every 2 weeks plus lomustine (283 patients) or lomustine alone (149 patients). Lomustine remains the standard of care for recurrent glioblastoma multiforme in Europe and in clinical trials, where the median PFS does not exceed 2 months.[7] Bevacizumab plus lomustine was associated with a clinically and statistically significant improvement in PFS (4.2 months vs. 1.5 months; $p < 0.001$). In this trial, statistical significance was not reached for the difference between the combination and lomustine monotherapy in the primary end point of median OS (9.1 vs 8.6 months). Of note, of the 138 lomustine monotherapy patients for whom follow-up information was available, 49 (35.5%) went on to receive bevacizumab post-disease progression on lomustine. Grade 3–5 adverse events (AEs) were numerically more common in the combination arm (63.6% vs. 38.1%), driven in part by the longer duration of treatment in the combination arm (median: 3 [1–16] cycles vs. 1 [1–8] cycles). The higher AE rate was not associated with a significant QoL decrease in the combination arm. No significant differences were observed in neurocognitive function. Given the devastating nature of recurrent glioblastoma multiforme and the very limited effective therapeutic options, median PFS gained of approximately 4.2 months while avoiding worsening QoL or neurocognitive function may be clinically meaningful and worth offering the patient.

In the Ph 2 BELOB study, the bevacizumab-lomustine combination provided a better 9-month OS rate (63% [49–75%]) than bevacizumab alone (38% [25–51%]) or lomustine alone (43% [29–57%]).[4]

A recent meta-analysis also evaluated bevacizumab plus lomustine for glioblastoma multiforme (516 patients) versus various control arms (579 patients). The results revealed that bevacizumab plus lomustine significantly improved OS (+1.37 months; p = 0.002 vs. bevacizumab, lomustine, or bevacizumab plus irinotecan), PFS (+1.46 months; p = 0.02 vs. the control groups), and the 6-month PFS rate (risk ratio: 2.29 [95% CI: 1.43-3.65]; p = 0.0005 vs. bevacizumab or lomustine).[5]

A Cochrane network meta-analysis also evaluated 401 patients from 3 trials that were included in the other meta-analysis. This study also confirmed that bevacizumab plus lomustine significantly improved PFS (HR: 0.57, 95% CI: 0.44–0.74).[6]

When these studies are considered together,[3-6] there is comparative evidence that bevacizumab plus lomustine is effective for treating patients with glioblastoma multiforme after relapse or disease progression following prior therapy.

Do you have additional comments that you feel are pertinent to this review?

Place in Therapy

Initial therapy for glioblastoma multiforme remains maximal tumour resection followed by chemoradiotherapy (typically using temozolomide).[1,8] However, the vast majority of patients experience progression/recurrence and face a dismal prognosis.[1,8]

Optimal management of relapsed or recurrent glioblastoma multiforme remains uncertain and must be personalized. Re-resection or re-irradiation remain options for select patients (e.g., young and fit) and systemic therapy is used for a large subset of patients.[1,8] However, there remains no standard-of-care systemic therapy in the second-line setting,[1] and patients have an urgent unmet need for effective alternative options in this setting.

If bevacizumab, in combination with lomustine, is reimbursed for previously treated glioblastoma multiforme, the available systemic therapy options would be:

- bevacizumab combined with lomustine
- lomustine monotherapy
- temozolomide rechallenge
- PCV regimen (procarbazine, lomustine or carmustine, and vincristine)
- etoposide monotherapy.

Lomustine monotherapy only provides an objective response rate of approximately 10%, median PFS of <2 months, and a 6-month PFS rate of approximately 20%.[3,7] Temozolomide rechallenge only slightly delays progression (1.8–2.0 months to treatment failure, PFS: 2.85 months), and the benefit may be limited to patients with MGMT promoter methylation.[1,9,10] The PCV regimen may provide some activity in second line, although its use is limited by much greater toxicity.[1,11] Etoposide monotherapy may be used for recurrent glioblastoma multiforme, where it only slightly delays progression (median time to progression: 7.5 weeks).[12] There is little evidence that any of these interventions prolongs OS or improves QoL.

The EORTC 26101 trial along with the Ren *et al* and McBain *et al*[5,6] meta-analyses confirmed that second-line use of bevacizumab plus lomustine provides a statistically significant improvement in PFS. This PFS benefit is clinically meaningful and approximately 2-fold longer than the PFS with lomustine monotherapy in this setting.[7]

Therefore, bevacizumab, in combination with lomustine, is expected to be used for patients with glioblastoma multiforme progression/recurrence who value an improvement in PFS.

Safety and QoL with bevacizumab

As expected for a combination therapy, bevacizumab plus lomustine had a higher rate of grade 3–5 AEs than lomustine monotherapy in the EORTC 26101 trial.[3] However, this was partially driven by the 3-fold longer median time on the combination therapy (3 cycles vs. 1 cycle with lomustine monotherapy).[3] In addition, the largest difference between the two groups was observed in arterial hypertension, which might be managed via appropriate anti-hypertensive treatment.[13]

The addition of bevacizumab to lomustine does not significantly impair overall QoL or neurocognitive functioning even with the higher rate of grade 3–5 AEs.[3] Thus, bevacizumab plus lomustine appears to be a tolerable option for patients with recurrent glioblastoma multiforme, especially considering that they lack effective treatment options in this setting.

Adoption Feasibility

Bevacizumab is administered via intravenous infusion once every 2 weeks until disease progression.[14] The first infusion is delivered over 90 min, which can be shortened to 60 min if the first infusion is well tolerated and then to 30 min for all subsequent infusions if the second infusion is well tolerated.[14]

Baseline assessments generally involve blood tests, urinalysis, blood pressure evaluation, and magnetic resonance imaging.[3,15] Guidelines from BC Cancer recommend repeating urinalysis and blood pressure evaluations before each bevacizumab dose, as well as blood tests after the first 3 doses.[15] In practice, magnetic resonance imaging is usually performed every 2 to 3 months while on therapy to identify relapse/progression.[8,15]

Thus, the administration of bevacizumab and related evaluations are not abnormally burdensome and not likely to impede adoption.

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