

Submission to PHARMAC on the proposal to decline the funding application for bevacizumab in relapsed, recurrent glioblastoma multiforme

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Declaration of interest

Brain Tumour Support NZ works with clinicians, researchers, allied health professionals, academia, government and industry to achieve better outcomes for New Zealand brain tumour patients and their families. We are writing to provide feedback on PHARMAC's proposal to decline the funding application for bevacizumab (*Avastin*, Roche) to treat relapsed, recurrent glioblastoma multiforme. In doing so, we wish to highlight the lack of treatment options for patients with recurrent or refractory glioblastoma multiforme (GBM) and the benefits of bevacizumab as it is currently being used in this patient population.

Brain Cancer in New Zealand

- Each year, around 340 people will be diagnosed with brain cancer in New Zealand, and more than 250 will die from the disease. Brain tumours kill more New Zealand children than any other disease and more young people under 40 than any other cancer. Survival rates for brain cancer have barely improved in more than 30 years.
- Glioblastoma multiforme (GBM), the most common and aggressive form of brain cancer, has a median overall survival of 15 months and a 5-year survival rate of around 6 percent (with standard treatments). Tumour recurrence is almost universal, at which point there are limited treatment options. The last medicine to be funded by PHARMAC to treat newly diagnosed GBM was the alkylating agent temozolomide in 2006. More and better treatments are desperately needed.
- Brain cancer is a high impact cancer which has a sudden and devastating effect on the patient and their loved ones. The symptom burden is high, and can include: severe headaches; nausea and vomiting; decline in cognitive function; physical weakness, fatigue and loss of mobility; changes in behaviour and personality; problems with speech, vision and hearing; and seizures.
- Adding to the clinical symptoms are major psychosocial effects. On top of the stress of the diagnosis, there is the immediate loss of independence (eg. losing the ability to drive), changes in the wider family dynamic (changing roles and relationships), changes in employment status, financial hardship, increased stress, anxiety and depression.
- Caregiver burden is a significant and often under-recognised factor for caregivers of brain tumour patients. Compared with other cancer groups (eg. lung, breast, and prostate), caregivers of patients

with brain tumours, particularly GBM, report more severe caregiver burden and poorer health-related quality of life (HRQoL)¹.

Bevacizumab (Avastin)

- Bevacizumab received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of recurrent GBM in May 2009. This approval was based on a phase 2 clinical trial (AVG3708g) which resulted in significantly higher progression free survival (PFS) and objective response rates (ORR) over historical controls. The approval was subject to confirmatory trials.
- Two subsequent confirmatory, phase 3, randomised, controlled trials - AVAglio and RTOG 0825 - investigated bevacizumab as a first line treatment in newly diagnosed GBM. Both trials reported improvements in PFS however neither showed a statistically significant improvement in overall survival (OS). The studies also confirmed a steroid sparing effect in patients treated with bevacizumab. These results, and the overall lack of treatment options for patients with recurrent GBM, were sufficient for the FDA to grant full approval for bevacizumab in 2017, and it is now extensively used to treat recurrent GBM patients in the United States and many other countries.
- In Australia, bevacizumab is available on the PBS as an unrestricted benefit, meaning that all patients needing this medicine have unrestricted access to it. Based on conversations Brain Tumour Support NZ has had with Australian oncologists, we understand that bevacizumab is now widely used in the treatment of recurrent or refractory GBM in Australia, with a significant percentage of patients experiencing long term benefit from its use.
- In New Zealand, bevacizumab was approved in 2011 by Medsafe for the treatment of patients with high grade, relapsed malignant glioma. As it is not funded by PHARMAC, New Zealand brain tumour patients have been funding their bevacizumab treatment out of their own pockets, often resulting in financial hardship. For many New Zealand brain tumour patients, including some of the most vulnerable groups in our society, bevacizumab is completely out of reach.

Patient input

- Brain Tumour Support NZ regularly engages with the New Zealand brain tumour patient community, in forums such as our Support Friends (peer support), monthly online support groups, social media channels and in-person events.
- The use of bevacizumab is a frequent topic among our brain tumour patient community. Many patients do their own research and are well aware that bevacizumab is used extensively overseas to treat malignant brain tumours, especially high-grade gliomas such as GBM. These patients will ask their oncologist about the use of bevacizumab at some point in their treatment pathway, while others may be informed of bevacizumab directly by their oncologist. Despite not having shown to

¹ Boele FW, Heimans JJ, Aaronson NK, et al. Health-related quality of life of significant others of patients with malignant CNS versus non-CNS tumours: a comparative study. *J Neurooncol.* 2013;115(1):87–94.

improve survival in clinical trials, there are numerous real world studies of GBM patients receiving long term benefit from bevacizumab.^{2 3 4 5}

- Our consultations with the brain tumour community show that patients care about the quality of their life, not just the length of time they will survive. The increase in PFS associated with the use of bevacizumab is extended time living without the symptoms of their brain tumour. The resulting improvement in HRQoL brings immediate benefits to patients in their daily life and relationships.
- The steroid-sparing effect of bevacizumab is also valued highly by patients. Prolonged use of dexamethasone, commonly prescribed to alleviate symptoms, is associated with significant toxicity, including weight gain, muscle weakness and mood changes. Dexamethasone, like other corticosteroids, is also immunosuppressive. GBM patients are immunocompromised, especially whilst undergoing treatment, and are at increased risk of infections. Patients undergoing immunotherapy treatments, such as checkpoint inhibition, are not able to take dexamethasone, leaving bevacizumab as their only option for symptom control.
- The stress and worry of facing a poor prognosis is compounded by the threat of financial hardship for GBM patients considering bevacizumab. It is not uncommon for patients to experience strong feelings of guilt when self-funding expensive treatments. While they wish to live longer, they do not want to place their families into financial difficulty.

Patient comments

The following is a selection of comments from the New Zealand brain tumour patient community (names have been removed for confidentiality).

- **Carer of a GBM patient, Auckland:** *“Our family has been devastated by my husband's diagnosis of GBM one year ago. We are very aware of the realities of this disease, including the terrifying statistics predicting significant neurological symptoms and dysfunction impacting on all areas of life, followed by an untimely death. This disease kills 98% of those diagnosed, primarily because of its very high recurrence rates. All patients and caregivers hold desperately to hope for treatment options which might make a difference. Avastin is one of these possible options. It is funded in Australia and many other countries for use in recurrent GBM, but not in New Zealand. This is incredibly unfair and completely incomprehensible for those of us directly affected by this cruel and devastating disease.”*
- **Carer of a GBM patient (location undisclosed):** *“Hi, my wife has glioblastoma. She has been taking Avastin for 7 months now and she has had amazing results. The tumours have stopped growing and the swelling around those tumours has dried up. This enables her to take a lot less steroids. She*

² Poon, M.T.C., Sudlow, C.L.M., Figueroa, J.D. et al. Longer-term (≥ 2 years) survival in patients with glioblastoma in population-based studies pre- and post-2005: a systematic review and meta-analysis. *Sci Rep* **10**, 11622 (2020). <https://doi.org/10.1038/s41598-020-68011-4>

³ Schweneker et al. Effective long-term treatment with bevacizumab for relapsed glioblastoma: case report and review of the literature. *Experimental Hematology & Oncology* 2014, 3:29 <http://www.ehonline.org/content/3/1/29>

⁴ Liu, Ji, Nguyen et al. Patterns of long-term survivorship following bevacizumab treatment for recurrent glioma: a case series. *CNS Oncol.* (2019) 8(2), CNS35

⁵ Balana et al. Survival to bevacizumab rechallenge in GBM. *Neuro-Oncology Practice* 4(1), 15–23, 2017 | doi:10.1093/nop/npw004

tolerates it well and does not have the nasty side effects that chemo gives. I have emailed Pharmac with our story and we so hope that they will fund this drug. It is giving my wife a longer more quality life with her family and friends.”

- **Carer of a GBM patient, Northland:** *“Trying really hard to keep standing up to be smashed down at every turn. Currently Avastin is keeping a really nasty recurrent tumour at bay. Every day is precious but Pharmac and the current political party are happy to take our tax and support. If we lived in Australia, the UK or the USA it would be a possibly funded option.”*
- **Carer of a GBM patient, Auckland:** *“My wife has just had her second treatment with a mix of Avastin and Irinotecan and so far her improvement has been considerable. Specialist said last night that given the improvement in her balance and cognitive function he was certain that the treatment was working. She has done brilliantly (on Avastin) to beat a large tumour in the rear lobes, got back to driving and is nearly herself.”*
- **Carer of a GBM patient, Auckland:** *“Avastin changed the quality of life for my wife. She was diagnosed in January 2018, received standard of care, but suffered a recurrence after 10 months. She was in a wheelchair at this stage. We started Avastin and Irinotecan on 1 December 2018 with fortnightly infusions. At 6 weeks we knew we were one of the 40% that had a positive result and finished 10 treatments mid-March 2019. By then my wife was walking 30 minutes round our suburb. I firmly believe that Avastin gave her a vastly improved almost 12 month period - from a wheelchair to a holiday in Rarotonga in September 2019 before recurrence.”*

Clinician input

- The Brain Tumour Support NZ Medical Advisory Board (MAB) consists of nine New Zealand clinicians representing a range of disciplines, all of whom have a special interest in brain tumours. See: <https://www.braintumoursupport.org.nz/medical-advisory-board>. Following consultation with the oncologists on our MAB panel, we found that most utilised bevacizumab in their clinics to treat GBM patients to varying degrees.
- Clinicians were often placed in a difficult position when discussing bevacizumab with their patients, knowing that it is not funded by PHARMAC and therefore that the patient would need to incur significant treatment costs. These difficult discussions would not need to occur if bevacizumab was publicly funded.
- Prescribing clinicians have seen remarkable long term benefits in a number of patients with both improved quality of life and improvement in PFS (in keeping with the available published literature and the current worldwide usage).
- Clinicians were well aware that bevacizumab does not represent a cure for GBM, however they felt that it was a “useful tool in their toolbox” and a beneficial addition to their treatment armoury for what is a very difficult disease with very few effective treatment options.

The following is a selection of comments from New Zealand oncologists:

- *“I use it in the relapsed setting as steroid sparing agent. I use as single agent therapy. If it was funded by PHARMAC then we would be able to offer it for symptom control for all patients and not just those who can afford to self-fund.”*

- *“I used it regularly in the past and am convinced of a very meaningful benefit in a number of patients.”*
- *“Used in the second line it probably has PFS survival benefits, and due to lower dex usage, an improvement in QoL.”*
- *“In the setting of relapsed GBM, there is a response rate as defined by serial imaging, and possibly improved quality of life.”*
- *“I typically use it in the first relapse/recurrent setting or subsequently if it was not used [previously]. I typically combine it with another agent. If it was funded by PHARMAC more patients will be able to have it. And most insurance companies will cover the full amount. Currently, even with medical insurance, most patients will have to pay part of the cost as there is a limit to which the medical insurance will cover.”*

Brain Tumour Support NZ Recommendation

PHARMAC to review the initial funding application for bevacizumab in relapsed, recurrent GBM. Since the original application was lodged there has been substantial real-world use of bevacizumab in the clinic, both in New Zealand and abroad, establishing it as a useful treatment option for GBM patients. However, not being funded by PHARMAC, bevacizumab is unaffordable for many New Zealand patients and places many families into financial hardship. This has created a situation of “haves and have-nots” and contributes to inequities in our health system.

We recommend the review include:

1. Updated clinical trial evidence from all international trials involving the use of bevacizumab, either as monotherapy or in combination with other agents, in the treatment of brain tumours.
2. An extensive literature search, covering all meta-analyses, case studies and anecdotal reports. There is now over twelve years of real-world use of bevacizumab, both in New Zealand and overseas, for the treatment of malignant brain tumours outside of a clinical trial setting.
3. An understanding of how bevacizumab is being used in Australia since its inclusion on the PBS and the resulting benefits to Australian GBM patients.
4. Consultation with New Zealand oncologists who have prescribed bevacizumab to treat GBM patients.
5. Consultation with New Zealand brain tumour patients and caregivers who have undergone, or are undergoing, treatment with bevacizumab.

Brain Tumour Support NZ appreciates the opportunity to provide feedback on your proposal and we hope you will consider the points and recommendations made in this submission.



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Trustee, Brain Tumour Support NZ