Interim Excerpt from the Record of the Cancer Treatments Advisory Committee Meeting held on 10 and 11 October 2024 (pending publication of the full meeting record)

Cancer Treatments Advisory Committee records are published in accordance with the Terms of Reference for the Specialist Advisory Committees 2021.

Note that this document is not necessarily a complete record of the Cancer Treatments Advisory Committee meeting; only the relevant portions of the meeting record relating to Cancer Treatments Advisory Committee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Cancer Treatments Advisory Committee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

Pharmac Advisory Committees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Advisory Committee meeting will be reviewed by PTAC at an upcoming meeting.

Specialist Advisory Committees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or Specialist Advisory Committees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present
Stephen Munn – Chair
Alice Loft
Chris Frampton
Lochie Teague
Matthew Strother
Oliver Brake
Richard Isaacs
Scott Babington
Vidya Mathavan

Apologies
Alannah Kilfoyle
Alice Minhinnick
Michelle Wilson

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Bevacizumab monotherapy for the treatment of relapsed or recurrent high-grade glioma. This recommendation is in the context of ongoing lomustine supply.	Decline
• Bevacizumab in combination with lomustine for the treatment of relapsed or recurrent high-grade glioma	Decline

3. The role of Specialist Advisory Committees and records of meetings

3.1. This meeting record of the Cancer Treatments Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) 2021 and Specialist Advisory Committees 2021.Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 6.4 of the SAC Terms of Reference.

3.3. The Cancer Treatments Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cancer Treatments Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Cancer Treatments that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments for Cancer Treatments that differ from the Cancer Treatments Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac considers the recommendations provided by both the Cancer Treatments Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for Cancer Treatments.

4. Welcome and introduction

4.1. The Chair welcomed the Committee with a karakia followed by whakawhanaungatanga.

5. Bevacizumab with lomustine for high-grade glioma, relapsed or recurrent

Application

5.1. The Committee reviewed a request from Pharmac to provide further advice regarding bevacizumab in combination with lomustine for the treatment of relapsed or recurrent high-grade glioma.

5.2. The Committee took into account, where applicable, Pharmac's relevant decision-making framework when considering this agenda item.

Recommendation

5.3. The Committee **recommended** that bevacizumab monotherapy for the treatment of relapsed or recurrent high-grade glioma be **declined**. This recommendation is in the context of ongoing lomustine supply.

5.4. The Committee **recommended** that bevacizumab in combination with lomustine for the treatment of relapsed or recurrent high-grade glioma be **declined**.

5.5. In making these recommendations, the Committee:

- Recognised the high health needs of people with relapsed or recurrent high-grade glioma and the need for more effective treatments for this rapidly progressive disease.
- Noted the lack of evidence of meaningful, clinical benefit from bevacizumab in this setting in terms of overall survival, quality of life or corticosteroid sparing effects (acknowledging that a small number of individual patients may receive a meaningful benefit from a short-term increase in progression-free survival).

- Noted the international clinical guidelines that suggest the use of bevacizumab for some relapsed or recurrent high-grade gliomas (depending on mutational status) appears to be unsupported by evidence.
- Noted that previous threats to the supply of lomustine in New Zealand, due to its discontinued production globally, had since resolved, and that any need to fund bevacizumab because of absence or shortages of lomustine no longer applied.

5.6. The Committee considered that the New Zealand Aotearoa Neuro-Oncology Society should receive a copy of the record of its discussion on this topic.

Discussion

Māori impact

5.7. The Committee noted that the impact of funding bevacizumab for relapsed or recurrent high-grade glioma on Māori and Māori health outcomes has been described in the record of this Committee's meeting in April 2023.

Populations with high health needs

5.8. The Committee acknowledged the health needs of Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 as having high health needs. The Committee did not have any new advice to provide regarding the needs of these groups in relation to bevacizumab for the treatment of relapsed or recurrent high-grade glioma.

Background

5.9. The Committee noted that Pharmac had previously considered bevacizumab monotherapy or in combination with another medicine as a treatment for nine cancer types (see Pharmac Application Tracker). The Committee noted that Pharmac staff had also previously sought its advice on bevacizumab for relapsed or recurrent high-grade glioma in the context of lomustine (another treatment used for relapsed or recurrent high-grade glioma) not being available, after Pharmac was advised of its discontinuation by the supplier:

5.9.1. The application for bevacizumab monotherapy was recommended for decline by PTAC in February 2016 due to poor strength and quality of evidence (the studies did not compare bevacizumab's use with a control arm and there was a relatively small number of individuals involved). At the same time, the application for bevacizumab in combination with lomustine was deferred by PTAC pending publication of the phase III EORTC trial.

5.9.2. Subsequently, in April 2023, CTAC recommended bevacizumab monotherapy be funded with a low priority, within the context of treatments for malignancies and subject to Special Authority criteria, due to high unmet need and a lack of treatment options in the context of lomustine being discontinued globally; poor quality clinical trial data; and that bevacizumab was not life-extending but rather a corticosteroid-sparing agent that can provide clinical improvement via management of cerebral oedema. The Committee noted that this recommendation was based on a small progression-free survival (PFS) benefit and an assumed reduction in corticosteroids, with no overall survival (OS) benefit from bevacizumab in this setting.

5.10. The Committee noted that Pharmac had secured further supply of lomustine from an alternative supplier, and that lomustine capsules are currently available in New

Zealand, enabling continued use of the PCV (procarbazine, lomustine and vincristine) treatment protocol in relapsed or recurrent high-grade glioma.

5.11. The Committee noted that after the June 2024 medicine budget uplift, Pharmac released a Future Procurement Opportunity (FPO) for bevacizumab for several cancer types.

General

5.12. The Committee noted that Pharmac staff now sought further advice on the use of bevacizumab in combination with lomustine for relapsed or recurrent high-grade glioma, given that the previous advice for this indication was sought in the context of lomustine being unavailable. The Committee noted that the term 'high-grade glioma' used here refers to both rare grade III gliomas referred to as anaplastic astrocytoma (AA) and the more common grade IV astrocytoma subtype known as glioblastoma (GBM).

5.13. The Committee noted that it had previously considered evidence from the phase II BELOB trial (Taal et al. Lancet Oncol. 2014;15:943-53) and phase II/III EORTC 26101 trial (Wick et al. N Engl J Med 2017;377:1954-63). The Committee noted that the latter was statistically powered to assess superiority of overall survival (OS) with bevacizumab plus lomustine vs lomustine alone but eventually reported no difference in OS, and that BELOB investigated lomustine alone vs bevacizumab alone vs bevacizumab plus lomustine. The Committee considered that the phase III EORTC 26101 trial was the most relevant evidence to the New Zealand population with high-grade gliomas. The Committee noted that isocitrate dehydrogenase (IDH) mutated disease was rare in both the EORTC and BELOB trials. Members considered that testing for IDH in glioma was likely routine in major centres but could be less accessible for those in regional centres.

5.14. The Committee noted that Pharmac staff had conducted a literature search and identified the following evidence, most of which report additional analyses from the phase III EORTC-26101 trial:

- Brandes et al. Oncologist. 2019; 24: 521–8
- Kessler et al. Clin Cancer Res. 2023;29:3892-900
- Le Rhun et al. Eur J Cancer. 2023:178:13-22
- Kickingereder et al. Radiology. 2020;297:164-75.

5.15. The Committee considered that the benefits of bevacizumab in combination with lomustine for high-grade gliomas remained unsupported by robust evidence. The Committee noted that the moderate quality clinical trial evidence reported:

5.15.1. No difference in overall survival (OS).

5.15.2. A small difference of about three-months in progression free survival with bevacizumab. Members acknowledged that this could be associated with a meaningful if short-term impact for a small subset of patients with relapsed or recurrent high-grade glioma and their families. However, members noted that at a population level, the evidence indicates that treating with the aim of achieving a three-month increase in PFS would increase exposure to potential side effects without adding an overall survival benefit or quality of life benefit, and without reducing the use of corticosteroids. Members further considered that PFS is a radiologic measure that does not necessarily convey clinical or patient-level meaning in terms of disease symptoms or survival.

5.15.3. No difference in quality of life (QoL). The Committee considered it unclear whether a reported reduction in social functioning (one element of a QoL assessment in one study) with bevacizumab and lomustine was a true signal. Members acknowledged that people with relapsed/recurrent high-grade glioma generally have poor QoL.

5.15.4. No difference in the use of corticosteroids. The Committee was made aware of anecdotal reports that corticosteroid-sparing occurs with use of bevacizumab for relapsed or recurrent high-grade glioma in clinical practice, although no evidence was identified that supported this. The Committee considered that a reduction in the use of corticosteroids could have been a surrogate for QOL in this context, however, there is evidence of no QOL benefit.

5.16. The Committee was made aware that international clinical guidelines suggest bevacizumab as an option in the treatment of relapsed or recurrent high-grade glioma, but considered that the use of bevacizumab in these guidelines was not supported by clinical evidence. Members were informed that some guidelines acknowledge the suboptimal benefits from available treatment options and recommended people with relapsed or recurrent high-grade glioma be considered for clinical trials where possible. The Committee considered that the guidelines likely suggested bevacizumab as an option in the context of limited effective treatments for rapidly progressive disease, with bevacizumab being available in many other jurisdictions despite poor evidence of a limited benefit.

5.17. The Committee was made aware of the European Association of Neuro-Oncology (EANO) guidelines on the diagnosis and treatment of diffuse gliomas of adulthood (Weller et al. Nat Rev Clin Oncol. 2021;18:170-86). The Committee noted that bevacizumab is not indicated for the treatment of IDH-mutant GBM, however it is indicated for IDH wild type AA or GBM. Members considered that this distinction was likely due to an absence of evidence rather than evidence of harm from this treatment. Members noted that updated recommendations for relapsed or recurrent high-grade glioma were not identified by key groups who produce cancer treatment guidelines (ie the European Society for Medical Oncology [ESMO], American Society for Clinical Oncology [ASCO] and National Comprehensive Cancer Network [NCCN]).

5.18. The Committee noted the body of clinical evidence, clinical guidelines, previous advice, and testimonials from patients, carers and clinicians provided to Pharmac (that were reviewed by CTAC in April 2023) regarding the benefits of bevacizumab in this context. The Committee acknowledged there is a desire to have effective treatments available to offer for relapsed or recurrent high-grade glioma and the strong belief that bevacizumab spares corticosteroid use in relapsed or recurrent high-grade glioma in practice. However, the Committee considered, based on the available evidence, that there was not sufficient benefit demonstrated to recommend funding bevacizumab in this setting.

5.19. The Committee maintained its previous low priority recommendation for bevacizumab monotherapy for the treatment of relapsed or recurrent high-grade glioma as being only in the context of lomustine being unavailable. This is given the significant health need that would be created by any discontinuation of lomustine. The Committee however considered that its earlier April 2023 assumption of a reduction in corticosteroid use with bevacizumab was not supported by the evidence.