Record of the Cancer Treatments Specialist Advisory Committee
Meeting held on 28 April 2023

Cancer Treatments Specialist 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 Specialist 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 Specialist 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
Chair Stephen Munn
Alice Loft
Anne O'Donnell
Chris Frampton
Chris Hemmings
Lochie Teague
Matthew Strother
Michelle Wilson
Oliver Brake
Vidya Mathavan

Apologies
Alannah Kilfoyle
Peter Ganley
Richard Isaacs (attended via Zoom until 9.55am)
Scott Babington

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Nab-paclitaxel for the treatment of any person with a grade 3 or higher hypersensitivity reaction after treatment with paclitaxel within the context of treatment of malignancy	High Priority
• Plerixafor in the treatment of donors for allogenic stem cell transplants	High Priority
• Trastuzumab deruxtecan for the treatment of human epidermal growth factor receptor (HER-2) positive metastatic breast cancer	High Priority
• Ibrutinib and venetoclax Special Authority for relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL)	High Priority
• Aprepitant – nausea and vomiting associated with any moderately emetogenic chemotherapy	No change
• Bevacizumab for the treatment of relapsed or recurrent high-grade gliomas	Low Priority

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

3.1. This meeting record of the Cancer Treatments Specialist 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. The 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 Specialist Advisory Committee is a Specialist Advisory Committee of Pharmac. The Cancer Treatments Specialist Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Specialist Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for cancer 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 that differ from the Cancer Treatments Specialist 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 Specialist Advisory Committee and PTAC and any other relevant Specialist Advisory Committees when assessing applications for treatments for cancer.

4. Record of PTAC meeting held on 17 November 2022

4.1. The Advisory Committee noted the record of the Pharmacology and Therapeutics Advisory Committee (PTAC) meeting held on 17 November 2022

4.2. The Committee noted that PTAC had considered an application from Roche Products NZ Ltd for the use of pertuzumab and trastuzumab, a combined product containing two treatments that is administered subcutaneously (SC) as an additional option for people eligible for funded intravenous (IV) pertuzumab and trastuzumab.

4.2.1. The Committee noted PTAC's considerations and recommendations and requested to review the application at a future Cancer Treatments Advisory Committee (CTAC) meeting, noting the limited infusion capacity across New Zealand and the potential utility of this presentation of trastuzumab and pertuzumab.

4.3. The Committee noted that PTAC had considered a consumer application for eribulin for the treatment of locally advanced or metastatic breast cancer that has progressed following at least two lines of prior chemotherapy.

4.3.1. The Committee noted PTAC's considerations and recommendations and requested to review the application at a future Cancer Treatments Advisory Committee (CTAC) meeting.

5. Records of CTAC meetings held on 14, 28 October 2022 and 27 January 2023

5.1. The Advisory Committee reviewed the records of the CTAC meeting held on 14 October 2022 and the two ad-hoc CTAC meetings held on 28 October 2022 and 27 January 2023 and agreed that the records be accepted.

6. Record of Anti-infective Advisory Committee meeting 22 September 2022

6.1. The Advisory Committee noted the record of the Anti-infective Advisory Committee in relation to its consideration of posaconazole for the prophylactic treatment of invasive fungal infection (IFI) at its meeting of 22 September 2022.

6.2. The Committee noted the recommendations and the proposed Special Authority criteria from the Anti-infective Advisory Committee. The Committee considered there to be a significant unmet need for access to posaconazole and voriconazole as prophylaxis of invasive fungal infection.

6.3. The Committee considered there to be redundancy in the wording within the proposed criteria, such that people with aplastic anaemia, planned stem cell transplant, the listed haematological malignancies or individuals following lung or liver transplant would inherently have a greater than 10% risk of invasive fungal infection and would therefore meet that criterion already. The Committee considered therefore that the criteria could be simplified as follows (deletions in ~~strikethrough~~, additions in **bold**):

Initial – (Invasive fungal infection prophylaxis) - Applications from any relevant practitioner. Approvals valid for 3 months

~~Any of the following:~~

~~1.~~ **To be** prescribed by, or recommended by a haematologist, transplant physician or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI.~~; or~~

~~2. Both:~~

~~2.1. Patient is to be treated with high dose (re)induction therapy or chemotherapy that is expected to result in prolonged neutropenia; and~~

~~2.2. Any of the following:~~

~~2.2.1. Patient has aplastic anaemia; or~~

~~2.2.2. Patient is planned to receive a stem cell transplant; or~~

~~2.2.3. Patient has a haematological malignancy eg ALL, AML, APML, HLH; or~~

~~3. Patient has received a lung or liver transplant and is at high risk of aspergillus infection~~

Renewal – **(Invasive fungal infection prophylaxis)** - Applications from any relevant practitioner. Approvals valid for 3 months

~~Any of the following:~~

1. **To be** prescribed by, or recommended by a haematologist, transplant physician or infectious disease specialist, or in accordance with a protocol or guideline that has been endorsed by the Te Whatu Ora Hospital in the specific settings where there is a greater than 10% risk of IFI.~~; or~~
2. ~~Patient is receiving a high-risk stem cell transplant; or~~
3. ~~Patient has received a stem cell transplant and is receiving immunosuppression for GVHD*; or~~
4. ~~Patient is still receiving therapy expected to result in prolonged neutropenia; or~~
5. ~~Patient has received a lung or liver transplant and is still considered high risk for aspergillus infection; or~~
6. ~~Both:~~

~~6.1. Patient has previously received triazole prophylaxis during remission induction therapy; and~~

~~Patient is to be treated with high dose re-induction therapy or consolidation therapy;~~

7. Correspondence and Matters Arising

Nanoparticle albumin bound paclitaxel (nab-paclitaxel) for metastatic breast cancer

Application

7.1. At its request, the Advisory Committee reviewed the technology assessment reports for nab-paclitaxel for metastatic breast cancer.

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

Recommendations

7.3. The Advisory Committee recommended that nab-paclitaxel be listed with a high priority for the treatment of any person with a grade 3 or higher hypersensitivity reaction after treatment with paclitaxel within the context of treatment of malignancy subject to the following Special Authority criteria:

> Initial application – Applications only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months where patient is contraindicated to or has experienced a grade ≥3 adverse event from, prior treatment with paclitaxel chemotherapy.
>
> Renewal - Applications only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Treatment remains clinically appropriate, and the patient is benefitting from and tolerating treatment.

7.4. The Advisory Committee considered that the restriction of the proposal to fund people with at least a grade 3 hypersensitivity adverse event to only to those people who have mBC was inequitable compared to people with other tumour types, and the Committee considered that this group should be extended to any person who has at least a grade 3 hypersensitivity while receiving paclitaxel therapy for any cancer type.

Discussion

Māori impact

7.5. The Committee discussed the impact of funding nab-paclitaxel for the treatment of metastatic breast cancer on Māori health areas of focus and Māori health outcomes. The Committee noted PTAC advice (August 2013) that Māori are treated at a later stage, at a younger age and have a higher mortality from breast cancer compared with non-Māori.

Background

7.6. The Committee had requested it review the technology assessment reports for nab-paclitaxel for metastatic breast cancer undertaken by Pharmac staff. The Committee noted that these reports related to proposals (for metastatic breast cancer (mBC), mBC contraindicated or intolerant to taxanes or following a grade 3+ hypersensitivity reaction to paclitaxel) which are currently ranked on the Pharmac Options For Investment list.

7.7. The Committee noted that prior to its review in 2021, PTAC had recommended in 2019 that nab-paclitaxel for the treatment of mBC be listed only if cost-neutral to weekly paclitaxel, taking into account pharmaceutical and administration costs.

7.8. The Committee noted the 2021 recommendation from CaTSoP (recommended with a medium priority) for nab-paclitaxel for the treatment of mBC. In making this recommendation, CaTSoP had considered the reduction in burden on clinical resources from a shorter infusion duration, the likely benefit that could be achieved from nab-paclitaxel therapy compared with paclitaxel therapy, the improved toxicity profile and suitability of nab-paclitaxel compared with comparator therapies.

7.9. The Committee noted the 2021 recommendation from CaTSoP (recommended with a high priority) for nab-paclitaxel for the treatment of mBC in individuals with

history of hypersensitivity reactions, or contraindication to paclitaxel. In making this recommendation, CaTSoP had considered the health need of people with mBC contraindicated or intolerant to paclitaxel therapy, the likely benefit that could be achieved from nab-paclitaxel therapy in those contraindicated or intolerant to taxane therapy and the improved toxicity profile and suitability of nab-paclitaxel compared with comparator therapies.

Summary of feedback on cost-effectiveness modelling

7.10. The Advisory Committee provided the following feedback for consideration by Pharmac staff, in relation to the cost-effectiveness modelling:

- Incidence of severe hypersensitivity reactions to paclitaxel be increased to 2-4%, based on evidence from UpToDate
- Consider including the costs of morbidity associated with reactions (adverse events) less than a grade 3, nor clinical resource responding to these less severe events and consequent lesser delays in treatment
- The comparator in those people unable to have paclitaxel due to severe adverse events or hypersensitivity in those with mBC be amended to vinorelbine or capecitabine.
- The chair time associated with infusions should be amended to 45 minutes for nab-paclitaxel and 2 hours for paclitaxel.
- The modelling should reflect an increased opportunity cost of using clinical administration resource (ie the benefit of nab-paclitaxel requiring less time for administration of prophylactic anti-allergy medicines and re-challenges post-reaction relative to paclitaxel treatment, and requiring less chair time than comparator treatments, allowing for other treatments to be administered and reducing public waiting list times) to reflect current pressures on public hospital cancer treatment infusion services. The Committee acknowledged the difficulties associated with modelling this, and that if a change was implemented, it would need to be applied across all applications. The Committee acknowledged that the current proposal with paclitaxel as a comparator was particularly pertinent, given paclitaxel's significant usage across New Zealand and the impacts on resource utilisation in Te Whatu Ora hospitals and subsequent impacts on individual care for other conditions.

Health need

7.11. The Committee noted the three groups specified for funding: anyone with mBC, people with mBC with adverse events who discontinue paclitaxel, and people with mBC with grade 3 or 4 hypersensitivity reactions to paclitaxel.

7.12. The Committee considered the incidence of hypersensitivity reactions to paclitaxel were 45% overall (any reaction) and 1 to 2% with severe reactions (ie grade 3+) despite prophylaxis with corticosteroids and H1 and H2 blockers 30 minutes prior to administration. The Committee considered that prophylaxis only reduces the incidence but does not eliminate severe reactions. The Committee noted its previous advice from the CaTSoP July 2021 meeting that:

7.12.1. hypersensitivity reactions of any severity can occur in up to 45% of people treated with paclitaxel,

7.12.2. 10-15% of individuals experience an immediate or delayed cutaneous reaction of any severity, and 7% experience a grade 3 or 4 neuropathy reaction, likely due to the cremaphor solvent in paclitaxel,

7.12.3. severe life-threatening hypersensitivity reactions occur in approximately 2-4% of people, and 1 to 2% of individuals may still develop hypersensitivity reactions despite prophylactic anti-allergy medication.

7.13. The Committee noted that in one scenario in which usage was restricted to people with severe hypersensitivity reactions, Pharmac staff had assumed that 10% of all individuals with mBC may receive nab-paclitaxel. This represents the lower bound of the 10 to 15% estimate, since it was assumed that even if 15% experienced a reaction, not all people with mild reactions would receive nab-paclitaxel.

7.14. The Committee noted that Pharmac staff had estimated the proportion with a hypersensitivity reaction in spite of prophylactic anti-allergy medication at 1.5%; a midpoint of the range provided in July 2021.

7.15. The Committee considered, again, that hypersensitivity reactions were caused primarily by the solvent that paclitaxel is delivered in and that these reactions are less likely to occur with the nab-paclitaxel formulation. The Committee noted its advice in July 2021 that it was a concern that 7% of people experienced neuropathy associated with paclitaxel, though considered that based on current evidence, there was a similar or slightly higher risk of neuropathy with nab-paclitaxel. However, the Committee considered that treatment-related neuropathy was highly reversible, and that rates were lower with the recommended 100 mg/m ^{2} dose of nab-paclitaxel. The Committee considered that the other potential adverse effects occurred at similar frequencies and severity between formulations eg myalgia/arthralgia, alopecia, myelosuppression, and nausea and vomiting.

7.16. The Committee considered that the proposed restriction of funding for people with at least a grade 3 adverse event to apply only to those who have mBC was inequitable to people with other tumour types, and that the proposed population should be extended to any person who has a grade 3+ hypersensitivity reaction on paclitaxel therapy for any cancer type.

7.17. The Committee considered that the proposed restriction to mBC with grade 3+ hypersensitivity limited the use in anyone with grade 3+ hypersensitivity (in the curative or palliative settings and other tumour types). The Committee noted that paclitaxel is used in treating many cancers including non-small cell lung cancer, across gynaecological cancers, head and neck cancer, pancreatic cancer, and cancers whose primary sources are unknown, and that funding nab-paclitaxel as an option for these further cancer types would increase the total overall time gains to paclitaxel cancer infusion service chair times and thus further reduce the overall burden on cancer infusion services.

7.18. The Committee considered that people with pancreatic cancer and ovarian cancer would also benefit from nab-paclitaxel. The Committee noted that an application for nab-paclitaxel for first-line, metastatic pancreatic cancer had been ranked on the Pharmac Options For Investment list. The Committee noted that Pharmac has not yet received an application for nab-paclitaxel for the treatment of ovarian cancer. The Committee considered that standard treatment for ovarian cancer is paclitaxel with carboplatin, this combination having a significant (up to 10%) risk of adverse events, such that people often receive the carboplatin part of the regimen alone. The Committee considered that this carboplatin-alone option was sub-optimal, and that a future application for this group would be of interest to advise on the benefit of nab-paclitaxel for this indication.

Health benefit

7.19. The Committee considered that, compared with paclitaxel, those who received neo-adjuvant nab-paclitaxel experienced higher pathological complete response

(pCR) and invasive disease free survival (IDFS) but overall no statistically significant improvement in overall survival (OS), but considered the clinical trials were underpowered to detect statistically significant effects on OS (see previous advice from the CaTSoP July 2021 meeting). The Committee noted that nab-paclitaxel was under consideration as a treatment for metastatic disease in the present proposal, not as a neo-adjuvant treatment.

7.20. The Committee considered its previous advice at the CaTSoP July 2021 meeting, which stated that:

7.20.1. compared with paclitaxel or docetaxel, nab-paclitaxel at a dose of 125 mg/m^2 or 150 mg/m^2 in metastatic breast cancer was reported to have a higher objective response rate (ORR) and disease-free survival (DFS)

7.20.2. the main benefit of nab-paclitaxel (at the currently considered 100 mg/m^2 dose) was evidenced by a clinical review, which showed nab-paclitaxel's more manageable toxicity profile, with response rates maintained relative to solvent-based taxanes including paclitaxel (Martin M. Breast Cancer Res. 2015; 17(1):81)

7.20.3. the PICO table of the record of the July 2021 meeting reflected the findings of that clinical review and therefore stated that, for those who do not have severe hypersensitivity reactions on paclitaxel, nab-paclitaxel would offer no significant difference in overall survival, progression free survival, or quality of life.

7.21. The Committee considered that for those people that have a reaction to paclitaxel, treatment with nab-paclitaxel would result in a quality of life and at least progression-free survival (PFS) would improve resulting from them being able to continue treatment.

7.22. However, the Committee considered that a health-related quality of life (HRQOL) benefit associated with nab-paclitaxel at the 100 mg/m^2 dose may be plausible, and that a small benefit associated with improved ORR or DFS should be incorporated into cost effectiveness modelling, if material.

7.23. The Committee considered that nab-paclitaxel would only be a substitute for paclitaxel, not docetaxel, as summarised in the PICO table in July 2021.

Suitability

7.24. The Committee considered that both formulations are now given weekly as standard practice. The Committee noted its previous advice (July 2021) regarding the 30-minute time duration required to administer nab-paclitaxel but considered that 45 minutes would be allowed in practice. The Committee also noted the important difference in the chair time required for nab-paclitaxel (45 minutes allowed) and paclitaxel (2 hours total chair time allowed). The Committee considered the significant difference in the chair time was related to the administration time (30 minutes v 60 minutes) and time needed for prophylactic anti-allergy medicines prior to paclitaxel, and for those with a previous allergic reaction additional time allowed for a re-challenge.

7.25. The Committee considered the impact that the longer infusion time and other factors associated with paclitaxel has on the oncology units and use of resource (chair time) in the context of the current health system pressures., Particularly the public wait times for oncology treatment overall (all cancers, additional to metastatic breast cancer and other cancers treated with paclitaxel) and the detrimental effect of this on outcomes for these other people.

Cost and savings

7.26. The Committee noted that for those people who had either a severe adverse event or grade 3/4 hypersensitivity, the comparator used in modelling was gemcitabine. The Committee considered the use of gemcitabine was not standard therapy for mBC. The Committee considered that it would be more appropriate for modelling to use capecitabine or vinorelbine as the comparator in this population (O'Shaughnessy et al. Oncologist. 2012;17:476-84). The Committee considered that vinorelbine and capecitabine (estimated 20% response rate after anthracycline treatment) typically have lower response rates than taxanes (estimated 40% response rate) after treatment with anthracycline. The Committee considered there were no direct head-to-head comparison studies comparing either of these agents with nab-paclitaxel.

7.27. The Committee noted the modelling for all mBC (regardless of adverse events) did not include morbidity associated with reactions (adverse events) less than a grade 3, nor clinical resource responding to these less severe events and consequent lesser delays in treatment, affecting both the individual and others awaiting treatment. The Committee suggested that Pharmac staff should consider including these costs in their cost-effectiveness modelling.

Nab-paclitaxel across all considered indications

7.28. The Committee noted that in general at Pharmac, health benefit from reducing costs to the health sector are included implicitly in the cost-effectiveness analysis. Namely, if Pharmac funded a treatment like nab-paclitaxel which reduced the usage of health sector resources, like infusion services, the Vote Health budget otherwise spent on those resources would be made available to spend on other health-producing services, or the scarce resources themselves would be available for use by other individuals who would benefit from them.

7.29. The Committee considered that the benefit which can be obtained by releasing more oncology infusion capacity may be more than the average benefit from other health services, due to the limited resource available to administer oncology treatments. Hence, while the Committee considered that funding any specific treatment would not resolve the issues currently faced by the system, it considered that the potential health gain from making infusion capacity available should be appropriately reflected in the cost effectiveness modelling.

7.30. The Committee considered that making health resources available for other uses could be incorporated into economic modelling by either including a higher cost associated with services which are scarce or produce a higher level of benefit than other services, or as an additional benefit, in QALYs. The Committee noted that in either case, the additional health gain associated with specific health resources would need to be sufficiently long term to be applied consistently across economic assessments over time. The Committee considered that most oncology clinics were at, or over, capacity, and there is unlikely to be a rapid increase in capacity to administer even more infusions within the public system, which means that the opportunity cost of using infusion services was likely to be a long-standing concern.

7.31. To estimate the additional cost, the Committee considered that clinicians may be able to provide Pharmac with more accurate information about the cost in practice of providing certain services currently eg a higher cost of infusion services if, with such low capacity, clinical staff are being contracted at a higher wage to provide these. However, the Committee noted the sensitivity analysis presented by Pharmac staff in the technology assessment report where the cost of treatment administration was tripled for all agents, which resulted in a far greater increase

for comparator treatments, which have the greatest baseline administration cost. The Committee noted the minor increase in cost utility in this scenario, in both the models for people with any severe adverse event and for people with a severe hypersensitivity reaction only. The Committee noted that this was because the administration costs displaced by nab-paclitaxel are vastly exceeded by the additional treatment cost of nab-paclitaxel relative to paclitaxel.

7.32. Alternatively, the Committee considered that the additional people able to be treated in the public system through chair time saved by using nab-paclitaxel could be captured in the model as a numerating health benefit rather than a denominating nominal health sector cost offset saving (where Pharmac's technology assessments express summary metrics as incremental quality-adjusted life years saved (QALYs) per $1 million net health sector incremental costs (QALYs/$1million), with net health benefits as numerator and net costs as denominator). The Committee considered that the bed/chair and clinician time made available by funding nab-paclitaxel would allow more people overall to be treated by cancer infusion services and would increase the timeliness of treatment with infused medicines.

7.33. The Committee considered that some people may not receive treatment due to the strain on infusion services currently, and that delaying the start of chemotherapy for people who do eventually receive treatment affects the outcome of that treatment eg in colorectal cancer and triple negative breast cancer treatment, it makes a substantial difference to potentially curative outcomes whether treatment starts in the first 4 weeks. The Committee estimated that the average wait for treatment administration was 6 to 8 weeks, with a 3-to-4-week initial treatment period. The Committee considered that delays in starting treatment result in loss of benefit of the treatments, in particular a 2% loss per week for breast cancer and 4% loss per week for colorectal cancer. The Committee considered that mitigating such delays (by removing the need for lengthier and potentially more problematic paclitaxel infusions and freeing chair time for other groups) was the 'real-world' in-practice benefit from nab-paclitaxel treatment, in addition to what the Committee considered to be the incremental benefits to the individual of nab-paclitaxel itself over paclitaxel.

7.34. The Committee noted that these factors are considered qualitatively, but QALY gains of this sort are not included in the cost effectiveness model, because:

7.34.1. infusion administration time is included in the cost effectiveness model as a denominating cost, so including time savings as a numerating benefit would double-count the impact of shorter infusions,

7.34.2. capacity constraints in health services vary over time and locality, making forecasting highly uncertain, and

7.34.3. extensive information would be needed to estimate them, including:

- the number of additional people who would now be able to receive treatment,
- the magnitude of clinical benefit each individual would be expected to receive, across the gamut of cancers treated with their counterfactual health losses and converse health gains by having infused treatments more available, and
- the magnitude of clinical benefit each currently treated individual could receive, on average, by receiving more timely treatment.

7.35. The Committee considered it may be feasible to acquire available data relating to the people awaiting treatment administration (including indication and therapy required) from Te Aho o Te Kahu. Members considered this would be representative of the infusion waiting lists and priority throughout the country, but that this would not be useful without a reliable estimate of the health benefit which could be obtained with use of infusion services in each cancer indication on the waiting lists.

7.36. The Committee discussed that while funding nab-paclitaxel may free up more resource in the health sector, many investments result in increased usage of health sector resources. The Committee agreed that it would be necessary to include either the inflated cost associated with infusion services or the QALY loss associated with their use in these instances also, for consistency.

7.37. The Committee noted cost-effectiveness analyses from overseas assessing nab-paclitaxel against paclitaxel in cancers, being Lazzaro et al. 2013 (metastatic pancreatic cancer, Italy); Cui et al. 2020 (mBC, China); and Gharaibeh et al. 2015 (metastatic pancreatic cancer, UK). The Committee noted that these analyses were conducted in different contexts, with different relative prices associated with the treatment strategies.

7.38. The Committee noted that a generic nab-paclitaxel had been approved by the European Medicines Authority (EMA) and had been considered (by regulators there) to have equivalent clinical benefits. The Committee noted that this was not currently Medsafe approved or under consideration by Medsafe at this time. The Committee noted that Pharmac staff expected that generic nab-paclitaxel will be approved for use in New Zealand in 3 to 4 years.

Dasatinib Competitive Process

Discussion

7.39. The Committee noted that dasatinib has been funded for the treatment of chronic myeloid leukaemia (CML) since August 2009 and Philadelphia chromosome positive acute lymphoblastic leukaemia since May 2019.

7.40. The Committee noted that Pharmac sought advice regarding a competitive process for dasatinib that could result in a brand change for people receiving this treatment.

7.41. The Committee noted that dasatinib, like imatinib, is a small molecule medicine, and considered there would be no effects on health benefit if a brand change were to occur, as brands would be bioequivalent and thus essentially interchangeable clinically (as is the case with other brand changes for TKIs).

7.42. The Committee noted that after a period of sustained deep molecular remission, individuals with CML are offered a trial of ceasing therapy (with close molecular monitoring as around half will be able to stay off therapy but the rest will need to resume life-long tyrosine kinase inhibitor (TKI) treatment). The Committee noted that people with Philadelphia chromosome positive acute lymphoblastic leukaemia are on treatment for a shorter period. The Committee considered that loss of disease control is a concern for people with CML, if on long term treatment. However, the Committee considered that there would be no clinical concerns with people transitioning to a generic dasatinib if bioequivalence had been demonstrated.

7.43. The Committee considered that there is no evidence to indicate any clinical risk associated with a transition to a TKI. The Committee noted that the previous transition to a generic TKI (imatinib) for a similar population group had been

successful.

7.44. The Committee noted that it had previously considered that generic brand changes for TKIs would preferably not occur more frequently than every three years. The Committee considered that this preference was primarily in the interests (and for acceptability) of those being treated, but that there were no identifiable clinical risks associated with brand changes occurring more frequently than this.

7.45. The Committee noted that brand changes would likely only occur greater than every three years if there were a supply issue that necessitated a change, but that this would be clinically acceptable if this were to occur.

7.46. The Committee noted nocebo effects could be experienced, however evidence indicates no change in rates of adverse reactions compared to the innovator brand of TKI (Gemelli et al. Blood Res. 2020;55:139-45). The Committee considered that the only potential clinical risk may arise from adherence due to suitability of the generic dasatinib (eg. tablet size), but that this is something that would be considered by the relevant Committee prior to any brand change for this market.

7.47. The Committee considered that the annual invitation to tender would be an appropriate avenue for competing this market, due to the limited clinical risk and appropriateness of the usual transition period (5 months). The Committee considered that resource implications would be similar to the imatinib brand change with no additional impact expected.

7.48. The Committee noted that TKIs are effective in less common MPN/rare myeloid neoplasms. However, the Committee noted that imatinib is open listed and the evidence supporting its use in such indications is more mature. The Committee considered that dasatinib would be unlikely to be used in such niche indications due to limited evidence of benefit. The Committee noted that removal of the maximum dose of 140 mg/day from the Special Authority criteria wouldn't increase usage due to toxicity concerns above that dose.

8. Plerixafor – stem cell mobilisation

Application

8.1. The Advisory Committee reviewed the application for plerixafor in the treatment of donors for allogenic stem cell transplants.

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

Recommendation

8.3. The Advisory Committee **recommended** that plerixafor be **listed with a high priority** within the context of malignancy subject to the following Special Authority criteria:

> **Initial application – (Allogeneic stem cell transplant donor)** Applications from any relevant practitioner. Approvals valid for three treatments for applications meeting the following criteria:
>
> All of the following:
> 1. Donor stem cells are being mobilised to provide allogeneic stem cells for haematopoietic stem cell transplant; and
> 2. Donor has not experienced a previous unsuccessful mobilisation attempt with plerixafor; and
> 3. Donor is undergoing GCSF mobilisation; and
> 4. Either:

4.1. Donor has experienced a suboptimal peripheral blood CD34 count of ≤20 x 10^6/L on day 5 after 4 days of GCSF treatment; or
4.2. Efforts to collect >2×10^6 CD34 cells/kg have failed after one apheresis procedure.

8.4. In making this recommendation the Advisory Committee considered:

- That Māori may have inequitable outcomes from failed donor mobilisation due to having a decreased chance of finding a replacement stem cell donor. The Committee noted however that mobilisation failure rates were no worse for Māori donors.

- The benefit to the health system with less time for repeat donor searches, and a decrease in operating theatre time.

- Greater health benefit to the donor through more efficient stem cell collection with fewer apheresis procedures and related side effects, and reduced likelihood of a bone marrow harvest from them being required.

Discussion

Māori impact

8.5. The Committee discussed the impact of funding plerixafor for the treatment of donors of haematopoietic stem cells (HSC), when cells fail to mobilise following stimulation with granulocyte stimulating factor (GCSF), on Hauora Arotahi - Māori health areas of focus and Māori health outcomes. The Committee noted that treatment of donors of HSC does not fall within the Māori health areas of focus. The Committee noted that Māori had been shown to have a reduced chance of finding a human leukocyte antigen (HLA) matched donor, that matches 6 out of 6 loci reviewed, from transplant donor registries and therefore had a reduced likelihood of receiving a transplant. This reduced access to transplantation was particularly evident in people greater than 50 years of age (Tracey & Carter, Am J Hematol. 2005; 79:114-8).

8.6. The Committee considered there to be fewer donor matches available for Māori, and that this can impact on uptake of allogeneic SCT.

8.7. The Committee noted that failure to collect donor cells due to non-mobilisation would also affect these potential recipients, as a haematopoietic stem cell transplant may no longer remain a treatment option, with consequent effects on their disease, and hence longevity, and intervening quality of life.

Background

8.8. The Committee noted that plerixafor has been previously considered by the Cancer Advisory Committee, as well as the Pharmacology and Therapeutics Advisory Committee for the mobilisation of HSC for those undergoing autologous stem cell transplants. The Committee noted that plerixafor was funded in 2016 for this indication.

Health need

8.9. The Committee noted that HSC mobilisation involves the use of therapeutics to induce the movement of HSC to the peripheral blood from the bone marrow for collection, and subsequent stem cell transplantation (SCT), which is undertaken for autologous or allogenic SCT.

8.10. The Committee noted that HSCs are commonly identified by the cell surface marker CD34. The number of CD34 positive (CD34+) cells in the peripheral blood are typically low (<0.05% of the total leukocyte count), however, can be increased

up to 5–15 fold through mobilisation with treatments such as GCSF or plerixafor. This results in CD34+ cells accounting for up to 6% of the total leukocyte count (Bilgin YM, J Blood Med. 2021;12:403-12).

8.11. The Committee noted that mobilisation failure, or non-mobilisation, is commonly defined as the inability to collect greater than 2×10^6/kg CD34+ cells by apheresis. The Italian Group for Stem Cell Transplantation Gruppo Italiano Trapianto di Midollo Osseo (GITMO) has further developed definitions for poor mobilisation as peripheral blood CD34+ cells $<20\times10^9$/L after adequate mobilisation with GCSF, and where it is not possible to collect 2×10^6/kg CD34+ cells after ≤3 apheresis procedures (Bilgin, 2021).

8.12. The Committee noted that to donate HSC, donors commonly are treated with GCSF up to 5 days prior to apheresis, with over 80% of donors experiencing side effects including bone pain, headache, fatigue, and nausea/vomiting (Bilgin, 2021).). In addition, transient splenomegaly and spleen rupture have been observed (Becker et al, Biol Blood Marrow Transplant. 1997;3:45-9). The Committee noted that when mobilisation fails, donors can undergo either restimulation with GCSF with the addition of plerixafor or proceed to bone marrow harvest under general anaesthetic.

8.13. Committee noted that scientific literature estimates a 0.5-10% mobilisation failure rate in allogeneic stem cell donors (Hölig, Transfus Med Hemother. 2013;40:225-35; Bilgin, 2021). The Committee noted that there were approximately 150 allogeneic SCT in Auckland within a three-year period from 2019, of which GCSF failed to mobilise HSCs in eight donors or approximately 5%, which aligns with the literature estimates.

8.14. The Committee noted that if it is not possible to collect HSC by GCSF stimulation from the allogeneic donor, the recipient may not be able to receive a transplant. The Committee considered that mortality and morbidity in those people intended to receive HSC for their blood cancer is high if a transplant is not possible.

8.15. The Committee noted that serious adverse events can rarely occur from GCSF stimulation and mild to moderate adverse events may also occur from GCSF stimulation and apheresis collection.

8.16. The Committee noted that donors are generally well pre-mobilisation, and when GCSF stimulated collection fails, they may need to undergo bone marrow harvest (in order for them to provide the stem cells necessary for the recipient's treatment), which involves a surgical procedure with all of the clinical risk associated with a general anaesthetic and blood loss. The Committee noted the Halter et al. Haematologica. 2009; 94: 94–101 study, which reported these risks include approximately 1 in 10,000 donors dying from a fatal complication, approximately 1 in 5,000 having a severe complication leading to hospitalisation and at least 1 in 3,000 developing a hematologic malignancy. The Committee also noted the Kim et al. Int J Environ Res Public Health. 2020;17:2316 study of peripheral blood stem cell donors, which reported high incidence rates of symptoms in bone marrow harvesting donors post-operatively, with the most commonly reported physical discomfort being myalgia (72.5%), followed by bone pain (62.6%), fatigue (60.3%), and headache (55.0%).

8.17. The Committee noted that there are psychologic impacts associated with donation, and bone marrow harvesting. The Committee noted the Winterling et al. Transplant Proc. 2022 16;S0041-1345;00779-5 study that reported that 39% of donors reported great worry about the recipient, and 12% also experienced great worry about themselves, as potential donors. In addition the Committee noted the Kim et al. Int J Environ Res Public Health. 2020;17:2316 study of HSC donors

that reported that 88.5% experienced psychological discomfort, including fear (44.3%), anxiety (44.3%), stress (39.7%), depression (31.3%), loneliness (31.3%), regret (29.8%), and ambivalence (23.7%).

8.18. The Committee noted that bone marrow donors had side effects of longer duration, experienced more fatigue, and were more likely to need sick leave from paid work longer than one week compared to peripheral blood donors (Pahnke et al. J Clin Apher. 2018;33:226-35).

8.19. The Committee noted that there are several risk factors associated with mobilisation failure in healthy donors, including a pre-apheresis CD34+ count $<5\times10^9$/L, being of a female gender, older age, having poor venous access, and low weight (Wang et al. Biol Blood Marrow Transplant. 2008;14:1305-11).

8.20. The Committee noted that whilst there was no data available on the need of Māori for allogeneic SCT, the Committee considered there to be fewer donor matches available for Māori, and that this can impact on uptake of allogeneic SCT. The Committee also noted that Māori had been shown to have a reduced chance of finding a human leukocyte antigen (HLA) matched donor, that matches 6 out of 6 loci reviewed, from transplant donor registries and therefore had a reduced likelihood of receiving a transplant. This reduced access to transplantation was particularly evident in people greater than 50 years of age (Tracey & Carter, Am J Hematol. 2005;79:114-8).

8.21. The Committee noted that whilst Pacific peoples had an increased risk of chronic myeloid leukaemia, SCT was not usually used to treat this condition. However, the Committee considered there to be fewer donors available for Pacific peoples.

Health benefit

8.22. The Committee noted that plerixafor is a CXCR4 chemokine receptor antagonist that blocks the binding of stromal cell-derived factor 1α. It inhibits the retention of HSC in bone marrow and increases their number in peripheral blood. It is indicated, in combination with GCSF, to mobilise HSCs to the peripheral blood for collection and subsequent autologous transplantation in those with lymphoma or multiple myeloma.

8.23. The Committee noted that plerixafor could be used in combination with GCSF either pre-emptively, in the event of inadequate peripheral blood CD34+ cell count after five days of GCSF, or after failure to obtain an adequate stem cell collection after one apheresis procedure (with plerixafor administered on the evening of the failed apheresis procedure).

8.24. The Committee noted the Holig et al. Bone Marrow Transplantation, 2021;56:635-45 study, a multi-centre open label, uncontrolled, phase 2 prospective single arm study with 37 people.

8.24.1. Those in the study were treated with 240 µg/kg plerixafor once on the first day of apheresis (mobilisation was two doses of 7–10 µg/kg BW per day GCSF for 5 days, with apheresis on day 5). The study reported that 21/ 37 donors (57% (95%-CI, 40–73%) collected ≥4.5 × 10^6 CD34+ cells/kg during first and second apheresis. 36/37 donors donated > 2 x10^6/kg C34+ stem cells. The majority of adverse events were grade 1 or 2, with two donors experiencing grade 3 thrombocytopenia after second apheresis procedure, which was considered likely unrelated to the plerixafor.

8.24.2. The Committee considered it was a high-quality study that reported a high magnitude of effect. The Committee considered the study population was generalisable to the New Zealand population, and similar to donors outside

of the trial setting. The Committee noted that 30 days post procedure, 86% of respondents would agree to receive plerixafor again, and no significant problems with graft vs host disease were observed in the HSC recipient.

8.25. The Committee noted the Zhang et al. J Clin Apher. 2022;37:388-94 retrospective study of 1008 allogeneic donors, of which 41 (4.1%) received plerixafor (0.24 mg/kg) after the first or second collection day. After starting plerixafor there was a 0.75- to 7.74-fold (median 2.94) increase in CD34+ yield from the previous day. No donors with GCSF-only mobilisation who collected <2.0 × 106 CD34+ cells/kg on day one achieved the goal of ≥4.0 × 10^6 CD34+ cells/kg over 2 days, but 59.2% of donors who used rescue plerixafor did. Most donors (35) collected for 2 days and received plerixafor before the second day of collection. Plerixafor was well tolerated in all donors.

8.26. The Committee noted the Hauge et al, Transfusion. 2014;54:1055-8 and Gatillo et al, Transfusion. 2015;55:1993-2000 retrospective studies. Both had a small number of participants, six and eight respectively, but noted the increases in number of CD34+ cells collected was reported in both studies, with numbers increased by up to 3-fold per kilogram.

8.27. The Committee also considered the following studies:

- Cid et al, Transfusion. 2015; 55:1993-2000
- Eyre et al, Transfusion. 2014;54:1231-4
- Chen et al. Blood Adv 2019 26;3:875-83

Suitability

8.28. The Committee considered that HSC collection is time sensitive, as the recipients of HSC are also treated (conditioned) in order for them to receive the donation. The Committee noted that administration of plerixafor was a single subcutaneous injection alongside GCSF administration, with HSCs collected the following day.

8.29. The Committee noted that if there was failure to harvest an appropriate number of CD34 cells, the donor may require a bone marrow harvest to be performed under a general anaesthetic, with its attendant risks. The Committee considered that avoiding general anaesthesia is preferable.

Cost and savings

8.30. The Committee noted that it is likely, plerixafor is currently used in this setting, funded through a hospital rapid approval process. The Committee considered that if funded for allogeneic stem cell transplant donors, there would be fewer repeat donor searches, and additional blood testing for donor matching testing.

8.31. The Committee considered that plerixafor administration is less invasive than bone marrow harvesting, and would reduce the need for theatre equipment, staff, and time.

8.32. The Committee considered that bone marrow harvest should be included in the comparator, as the mobilisation of HSC is time sensitive so there is likely

insufficient time to find another donor.

8.33. The Committee noted the urgency and time sensitivity of SCT requiring bone marrow harvest if prior cell harvest was too low.

Summary for assessment

8.34. Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for plerixafor if it were to be funded in New Zealand for allogeneic stem cell transplants. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Allogeneic stem cell transplant donors who; • Experience a suboptimal peripheral blood CD34 count of ≤20 x 10^6/L on day 5 after 4 days of GCSF treatment; or • Efforts to collect >2×10^6 CD34 cells/kg have failed after one apheresis procedure.
Intervention	Plerixafor, 0.24 mg/kg body weight by SC injection, once daily, up to 3 days AND GCSF
Comparator(s) (NZ context)	Restimulation with GCSF plus bone marrow harvest
Outcome(s)	For donors, increased collection of CD34+ and lower risk of need for bone marrow harvest under anaesthesia (affecting the donor). For potential recipients of allogenic SCT, consequent health gains from improved availability of SCT, hence increased chance of benefitting from SCT for their condition. Improved longevity and quality of life with their eg, blood cancers.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Trastuzumab deruxtecan for breast cancer

Application

9.1. The Advisory Committee reviewed the application for trastuzumab deruxtecan for the treatment of human epidermal growth factor receptor (HER-2) positive metastatic breast cancer.

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

Recommendation

9.3. The Advisory Committee **recommended** that trastuzumab deruxtecan be listed **with a high priority** within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **Initial application**- (metastatic breast cancer) - Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
>
> All of the following:
> 1. Patient has metastatic breast cancer expressing HER-2 IHC3+ or ISH+ (including FISH or other current technology) and

2. Patient has previously received trastuzumab and chemotherapy, separately or in combination and
   2.1. The patient has received prior therapy for metastatic disease including prior to adjuvant therapy including anthracycline, other chemotherapy, biological drugs, or endocrine therapy or
   2.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy and
3. Patient has a good performance status (ECOG 0-1) and
4. Patient has not received prior funded trastuzumab deruxtecan treatment and
5. Treatment to be discontinued at disease progression.

Renewal – (metastatic breast cancer) Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist
The cancer has not progressed.

9.4. The Advisory Committee considered:

- The magnitude of benefit for progression free survival (PFS) and overall survival (OS) reported in comparison to currently funded alternatives.
- The health benefit to those with HER2 metastatic breast cancer with brain metastases.
- The adverse event profile associated with trastuzumab deruxtecan in comparison to currently funded alternatives.

Discussion

Māori impact

9.5. The Committee noted the impact of funding trastuzumab deruxtecan for the treatment of HER-2 positive metastatic breast cancer on Māori health areas of focus and Māori health outcomes. The Committee noted data from New Zealand Cancer Registry, 2019 that reported in 2019, the incidence of breast cancer in wāhine Māori was 122.5/100,000 compared with 95.7/100,000 in non-Māori women.

9.6. The Committee noted data from 30,000 Voices: Te Rēhita Mate Ūtaetae - Breast Cancer Foundation National Register 2003-2020 that reported fewer than half of wāhine Māori had their breast cancer detected by screening mammogram. BreastScreen Aotearoa (BSA) data (two-year screening programme participation data to September 2019) has indicated that receipt of breast screening services has been lower for Māori than for other ethnicities in New Zealand except Asian, with two-year participation to September 2019 (pre-Covid-19 pandemic) being 61.9% against the target of 70%.

9.7. The Committee also noted data from 30,000 Voices: Te Rēhita Mate Ūtaetae - Breast Cancer Foundation National Register 2003-2020, that reported wāhine Māori were more likely to have high risk tumours as defined by larger size, higher grade, and higher risk subtype, compared to European women. In addition, it reported Māori had a higher proportion of HER-2 positive breast cancer at 17.9% compared with 14.5% in European people.

9.8. The Committee noted the Seneviratne et al, Cancer Causes Control. 2015; 26:1813-24 study that reported Māori women with breast cancer are more likely to experience a delay in the time from diagnosis to treatment. The study also reported wāhine Māori are more likely to experience barriers to treatment that prevent them from being able to receive radiation therapy and long-term adjuvant endocrine therapy, and more likely to have a mastectomy.

9.9. The Committee noted the Tin et al. BMC Cancer. 2018;18:58 retrospective study in New Zealand of 13,657 people reported that Māori women were more likely to

have comorbidities and less likely to be treated in a private facility, have a significantly longer time to first treatment after diagnosis, and less likely to have breast conserving surgery even after adjusting for stage at diagnosis. Māori women were twice as likely to die from breast cancer compared to non-Māori women in this study.

9.10. The Committee noted that the Pharmacology and Therapeutics Advisory Committee (PTAC. November 2022), had noted that breast-cancer specific survival was 84% at 10 years for wāhine Māori, compared to 87% for those of European ethnicity.

Background

9.11. The Committee noted that it had previously reviewed an application for trastuzumab emtansine in September 2018 for the same indication. Trastuzumab emtansine is funded for those with HER-2 positive metastatic breast cancer after prior trastuzumab treatment and a taxane subject to Special Authority criteria. It is also funded in the early breast cancer setting subject to eligibility critieria.

9.12. Committee noted that the National Breast Cancer Specialist Interest Group in September 2022 considered trastuzumab deruxtecan to be one of the top three priorities for unfunded drugs in New Zealand when considering potential benefit and need.

Health need

9.13. The Committee has previously noted that breast cancer is the most commonly diagnosed cancer in New Zealand women, affecting 1 in 9 women over their lifetime and is the leading cause of cancer related death (Ministry of Health NZ. 2018). The Committee previously noted that approximately 650 deaths a year can be attributed to the disease (CTAC. September 2018). Risk factors for the disease include increasing age, dense breast tissue, alcohol intake, family history, not having given birth to children, the use of combination hormone therapy and having a high BMI (Te Aho O Te Kahu Cancer Control Agency). The Committee noted that breast cancer can also affect males, with approximately 25 males diagnosed with breast cancer in New Zealand each year (Breast Cancer Foundation NZ).

9.14. The Committee noted that the 5-year survival for people diagnosed with metastatic breast cancer is 29% and 10-year survival is 16%, compared with 99% and 97%, respectively for people diagnosed with Stage 1 disease (Breast Cancer New Zealand. 2022).

9.15. The Committee noted that there are currently three molecular biomarkers which are routinely tested for at diagnosis: oestrogen receptor (ER), progesterone receptor (PR) and HER-2. The Committee noted that approximately 20% of diagnoses will have tumours with amplification of the HER-2 gene (Morey et al Pathology. 2016;48:535-42) and that this was associated with poor prognosis and resistance to cytotoxic drugs (Jiang et al, Int J Mol Sci. 2012;13:5519-27).

9.16. The Committee noted that the primary goal of treatment for metastatic breast cancer is prolongation of survival, palliation of symptoms, and maintenance or improvement in quality of life (QoL) (CTAC. September 2018).

9.17. The Committee noted the Mosher et al. Breast J. 2013;19: 285-92 study that reported that individuals with metastatic breast cancer are at risk of emotional distress, including symptoms of depression and anxiety, as well as existential distress and loneliness. The study also reported physical symptoms, including pain, fatigue, insomnia, and gastro-intestinal symptoms are also correlated with emotional and physical distress. In addition, those with metastatic breast cancer

face a wide range of challenges, including frequent medical procedures, chronic side effects (eg pain, fatigue, cognitive impairment, sexual dysfunction), and practical concerns (eg work and family role disruption, financial strain).

9.18. The Committee noted the Mosher et al. Eur J Cancer Care (Engl). 2018;27: 0.1111/ecc.12540 study that reported those with metastatic breast cancer report symptoms which contribute to activity restriction, concentration difficulties, exacerbation of physical symptoms, long term health concerns and which have a negative impact on their relationships with others, and consequently impact on their QoL.

9.19. The Committee noted a study by Verrill et al. Health Qual Life Outcomes. 2020;18:353 that reported significantly more people with metastatic disease reported an inability to work, and there was a significantly higher proportion of people in the metastatic group who were unable to be employed because of their disease, with 25% of people in the metastatic group unable to work compared with 10% in early breast cancer groups.

9.20. The Committee noted the report by the Breast Cancer Foundation National Register 2003-2020 which highlighted that metastatic breast cancer also disproportionately affects Pacific peoples. Compared with other ethnicities, Pacific women have the lowest proportion of breast cancer diagnoses made through the screening process, the lowest proportion of disease diagnosed at stage 1, and the highest proportion of disease diagnosed at Stage 3 and 4. In addition, Pacific women were more likely to decline treatment for breast cancer than any other ethnicity, had longer delays to surgery than other ethnic groups and the highest rate of mastectomy. Furthermore, following mastectomy, Pacific women were less likely to receive radiation therapy than those of European ethnicity.

9.21. The Committee noted the Breast Cancer Foundation National Register 2003-2020 reported that the requirement to travel, access to transport, taking time off work for both the person undergoing treatment and the caregiver, and other costs are likely barriers preventing equitable access to care.

Health benefit

9.22. The Committee noted that trastuzumab deruxtecan is a humanised HER-2-targeted antibody and topoisomerase I inhibitor conjugate. The anti-HER-2 component (monoclonal antibody) has the same amino acid sequence as trastuzumab and is specifically targeted to HER-2-expressing cells.

9.23. The Committee noted that there were no HER2 targeted treatment options in New Zealand available, beyond a second-line option of trastuzumab emtansine, for people with HER-2 positive metastatic breast cancer. Other treatment options would include chemotherapy.

9.24. The Committee noted the following phase 1 and 2 trials:

- Modi et al. J Clin Oncol. 2020; 38:1887-96:
- Tamura et al. Lancet Oncol. 2019;20:816-26:
- Modi et al. N Engl J Med. 2020;382:610-21

The Committee noted that in these trials trastuzumab deruxtecan was administered at a dose of 6.4mg/kg. The Committee noted that interstitial lung disease (ILD) was observed as a side effect of trastuzumab deruxtecan in these trials, and that later trials administered a reduced dose of 5.4mg/kg.

9.25. The Committee noted the DESTINY-03 trial (Cortes et al. Annals of Oncology 2021;32:S1287-8, Cortes et al. N Engl J Med .2022;386:1143-54, Hurvitz et al.

Lancet. 2023;401:105-17). An international, open label, phase 3 study of 524 people, randomised 1:1 between that trastuzumab deruxtecan or trastuzumab emtansine. The median follow up was 28.4 months.

9.25.1. The Committee noted that the comparator treatment, trastuzumab emtansine, is commonly used in New Zealand in this setting and therefore this trial was applicable to the New Zealand setting.

9.25.2. The Committee noted the median number of prior therapies were two, however some had received up to four lines. Approximately 16% had baseline brain metastases at baseline, of which 70% had visceral disease.

9.25.3. The Committee noted that in the previous trial publication (Cortes et al. 2022) the percentage of people who were alive without disease progression at 12 months was 75.8% (95% CI, 69.8 to 80.7) trastuzumab deruxtecan vs 34.1% (95% CI, 27.7 to 40.5) trastuzumab emtansine (HR for progression or death from any cause, 0.28; 95% CI, 0.22 to 0.37; P<0.001). OS rate at 12 months was 94·1% (95% CI 90·4–96·4) in the trastuzumab deruxtecan group and 86·0% (81·1–89·8) in the trastuzumab emtansine group. OS rate at 24 months was 77·4% (95% CI 71·7–82·1) in the trastuzumab deruxtecan group and 69·9% (63·7–75·2) in the trastuzumab emtansine group.

9.25.4. The Committee noted that in the latest analysis published in 2023 (Hurvitz et al. 2023), PFS was 28.8 months (22.4-37.9, 95% confidence interval [CI]) for those receiving trastuzumab deruxtecan versus 6.8 months (5.6 -8.2, 95% CI) trastuzumab emtansine, with a hazard ratio (HR) of 0.33 (0.26-0.43, 95% CI) and p value of <0.0001. Median overall survival was not reached (95% CI 40·5 months–not estimable), with 72 (28%) overall survival events, in the trastuzumab deruxtecan group and was not reached (34·0 months–not estimable), with 97 (37%) overall survival events, in the trastuzumab emtansine group (HR 0·64 [95% CI 0·47–0·87]; p=0·0037). The median treatment duration was 18·2 months (IQR 9·0–29·4) with trastuzumab deruxtecan and 6·9 months (2·8–12·3) with trastuzumab emtansine.

9.25.5. The Committee noted that 17% of people crossed over from trastuzumab emtansine to trastuzumab deruxtecan. The Committee also noted that 35% of people crossed over from trastuzumab deruxtecan to trastuzumab emtansine. The Committee considered that given the rate of crossover from trastuzumab emtansine to trastuzumab deruxtecan, the finding of a significant survival benefit was impressive.

9.25.6. The Committee noted in the latest analysis published in 2023 (Hurvitz et al. 2023) that any-grade treatment-emergent adverse events occurred in 256 (>99%) people in the trastuzumab deruxtecan group and 249 (95%) people in the trastuzumab emtansine group. Drug-related treatment-emergent adverse events led to discontinuation in 51 (20%) in the trastuzumab deruxtecan group and 17 (7%) in the trastuzumab emtansine group. The most common drug-related treatment-emergent adverse events that led to discontinuations with trastuzumab deruxtecan were pneumonitis (15 [6%] people), ILD (13 [5%]), and pneumonia (five [2%]), and with trastuzumab emtansine were platelet count decreased (four [2%]), pneumonitis (three [1%]), and thrombocytopenia (three [1%]).

9.25.7. The Committee noted that median time to first onset of ILD or pneumonitis was variable.

9.26. The Committee considered the DESTINY-03 study to be a high-quality randomised control trial, with clinically relevant endpoints. The Committee considered that overall, the DESTINY-3 study showed statistically significant and

clinically meaningful improvements in PFS in those treated with trastuzumab deruxtecan, that could provide additional health benefit for those with HER-2 positive metastatic breast cancer, and their whānau. The Committee also noted that the increase in OS was statistically and clinically significant, particularly given the crossover observed.

9.27. The Committee noted the Fu et al. EClinicalMedicine. 2022;55:101795 meta-analysis that reported that side effects were observed at a higher rate with trastuzumab deruxtecan compared to trastuzumab emtansine. The study reported the highest odds ratio was observed in the comparison group of trastuzumab emtansine (3.6 mg/kg]) and trastuzumab deruxtecan (5.4 mg/kg) for the mean incidence of serious adverse event (2.04; 95% CrI, 1.79–2.31). The odds ratio in the same comparison group of the mean incidences of high-grade adverse event and drug discontinuation due to adverse event were 1.78 (95% CrI, 1.65–1.90) and 1.56 (95% CrI, 1.25–1.91), respectively. In addition, the overall mean incidences of adverse events of trastuzumab deruxtecan was also higher than trastuzumab emtansine, the odds ratio of high-grade adverse event and serious adverse event were 1.49 (95% CrI, 1.42–1.58) and 1.45 (95% CrI, 1.32–1.58), respectively. The Committee considered that the evidence available suggests that trastuzumab deruxtecan is associated with an increase in the rate of high-grade adverse events and drug discontinuation compared to trastuzumab emtansine, and that the most prominent adverse event requiring monitoring and treatment was ILD.

9.28. The Committee also noted the following meta-analyses:

- Guo et al. J Clin Pharm Ther. 2022;47:1837-44
- Ma et al. Expert Rev Clin Pharmacol. 2022;15:1351-61

9.29. The Committee considered that if funded, given the significant improvement in efficacy of trastuzumab deruxtecan compared to trastuzumab emtansine most people with HER-2 positive metastatic breast cancer would be treated with trastuzumab deruxtecan (approximately 90%). However, the Committee considered that physically frailer individuals may be treated with trastuzumab emtansine due to the increased toxicity of trastuzumab deruxtecan. The Committee considered that this was unlikely to change over time.

9.30. The Committee considered the Curigliano et al. Ann. Oncol. 2022 33 Supplement 3 (S196-7) study. The study assessed patient-reported outcomes (PROs) from the DESTINY-Breast03 trial. PRO endpoints included European Organization for Research and Treatment of Cancer QoL questionnaires (EORTC QLQ-C30; primary variable: global health status [GHS]/QoL scale score) and the EuroQol 5-dimension 5-level (EQ-5D-5L) visual analogue scale (VAS). QLQ-C30 baseline GHS scores recorded for trastuzumab deruxtecan (n = 253) and trastuzumab emtansine (n = 260) were similar. Median time to definitive deterioration (TDD) of QLQ-C30 GHS was 9.7 months for trastuzumab deruxtecan vs 8.3 months for trastuzumab emtansine (HR, 0.88 [95% CI, 0.70-1.11]), Median TDD of EQ-5D-5L VAS was 13.2 months for trastuzumab deruxtecan vs 8.5 months for trastuzumab emtansine (HR, 0.77 [95% CI, 0.61-0.98]). With trastuzumab deruxtecan vs trastuzumab emtansine, 18 (6.9%) vs 19 (7.2%) were hospitalised; median time to first hospitalisation was 219.5 vs 60.0 days, respectively. The Committee considered that additional data on QoL endpoints would be beneficial, but that the current data did not indicate that QoL was decreased when treated with trastuzumab deruxtecan.

Trials in those with brain metastases

9.31. The Committee considered that overall, the DESTINY-3 study showed statistically significant and clinically meaningful improvements in PFS in those treated with trastuzumab deruxtecan, that could provide additional health benefit for those with HER-2 positive metastatic breast cancer, and their whānau.

9.32. The Committee noted the Hurvitz et al, DESTINY-Breast 03 presentation that was presented at the San Antonio Breast Cancer Symposium in December 2021, that evaluated the efficacy of trastuzumab deruxtecan and trastuzumab emtansine in a subset of the study population with stable brain metastases (36 people in each group). The study reported that in the trastuzumab deruxtecan group, 10 (27.8%) had complete response, compared to 1 person (2.8%) in the trastuzumab emtansine group. When reviewing partial response, the study reported 13 (36.1%) in the trastuzumab deruxtecan group compared to 11 (30.6%) in the trastuzumab emtansine group had a partial response.

9.33. The Committee noted the Bartsch et al. Nat Med. 2022;28:1840-7 study (TUXEDO-1) which was a prospective, open-label, single-arm, phase 2 trial, (n=15). Of these 40% were untreated, whilst 60% were previously treated. Two people (13.3%) had a complete intracranial response, nine (60%) had a partial intracranial response and three (20%) had stable disease as the best intracranial response, with a best overall intracranial response rate of 73.3% (95% confidential interval 48.1–89.1%) meeting the predefined primary outcome (intracranial response rate) measured according to the response assessment in neuro-oncology brain metastases criteria.

9.34. The Committee noted the Perez- Garcia et al. Neuro Oncol. 2023;25:157-66 five-cohort, phase 2 study (DEBBRAH) in those with pre-treated HER-2-positive or HER-2-low advanced breast cancer with stable, untreated, or progressing brain metastisis, and/or leptomeningeal carcinomatosis. Results from three cohorts were reported; non-progressing brain metastasis after local therapy (n = 8; cohort 1), asymptomatic untreated brain metastisis (n = 4; cohort 2) or progressing brain metastisis after local therapy (n = 9; cohort 3). The Committee noted that in cohort 1 16-week PFS rate was 87.5% (95%CI, 47.3-99.7; P < .001). In cohort 2, overall response rate intra-cranial (ORR-IC) was 50.0% (95%CI, 6.7-93.2), and in cohort 3 ORR-IC 44.4% (95%CI, 13.7-78.8; P < .001). Those with intracranial or extracranial lesions at baseline: ORR was 66.7% (12 out of 18 individuals; 95%CI, 41.0-86.7), 80.0% (95%CI, 28.4-99.5) in cohort 1, 50.0% (95%CI, 6.7-93.2) in cohort 2, and 66.7% (95%CI, 29.9-92.5) in cohort 3. All responders had partial responses.

9.35. The Committee noted the studies of individuals with brain metastases involved a small number of participants, however considered that larger studies were unlikely to be undertaken in this population group.

9.36. The Committee noted the Fu et al. 2022 metanalysis had reported that side effects were observed at a higher rate with trastuzumab deruxtecan compared to trastuzumab emtansine. The study reported the highest odds ratio was observed in the comparison group of trastuzumab emtansine (3.6 mg/kg) and trastuzumab deruxtecan (5.4 mg/kg) for the mean incidence of serious adverse event (2.04; 95% CrI, 1.79–2.31). The odds ratio in the same comparison group of the mean incidences of high-grade adverse event and drug discontinuation due to adverse event were 1.78 (95% CrI, 1.65–1.90) and 1.56 (95% CrI, 1.25–1.91), respectively. In addition, the overall mean incidences of adverse events of trastuzumab deruxtecan was also higher than trastuzumab emtansine, the odds ratio of high-grade adverse event and serious adverse event were 1.49 (95% CrI, 1.42–1.58) and 1.45 (95% CrI, 1.32–1.58), respectively. The Committee considered these results indicated benefit in those with brain metastases, and this

was clinically meaningful.

9.37. The Committee also considered the following meta-analyses:

- Guo et al. J Clin Pharm Ther. 2022;47:1837-44
- Ma et al. Expert Rev Clin Pharmacol. 2022;15:1351-61

Suitability

9.38. The Committee noted that trastuzumab deruxtecan is administered as an intravenous infusion, over the same time and frequency as trastuzumab emtansine. The Committee considered that it was likely that people treated with trastuzumab deruxtecan would stay on treatment significantly longer when compared with trastuzumab emtansine.

9.39. The Committee noted that an increase in monitoring due to ILD risk would be required including regular computerised tomography (CT) monitoring. The Committee noted any increased length of treatment would be associated with an increased requirement for individuals to travel for treatment and monitoring.

Cost and savings

9.40. The Committee considered that additional screening for ILD would be necessary. The Committee noted that ILD was monitored in the key trial through CT monitoring and pulmonary function tests, although considered that pulmonary function tests do not occur routinely in practice. The Committee considered that while CT scans occurred every 6 weeks in the trial population to check for ILD, this may occur approximately every 3 months in New Zealand clinical practice for those with metastatic breast cancer.

9.41. The Committee considered that if ILD was not detected early, and prior to symptoms, it could lead to rapid deterioration and potentially death. The Committee noted that ILD was treated with corticosteroids.

9.42. The Committee considered that it was possible that there may be a greater need for central line access with the funding of trastuzumab deruxtecan, given the duration of treatment with trastuzumab deruxtecan. However, the Committee considered that the vast majority of those eligible for trastuzumab deruxtecan would already have central line access, given the infusion requirements for currently funded treatments.

9.43. The Committee considered that if funded, given the improvement in efficacy of trastuzumab deruxtecan compared to trastuzumab emtansine, most people with HER-2 positive metastatic breast cancer would be treated with trastuzumab deruxtecan (approximately 90%). However, the Committee considered that individuals who were more physically frail may instead be treated with trastuzumab emtansine due to the increased toxicity of trastuzumab deruxtecan. The Committee considered that this was unlikely to change over time.

Funding criteria

9.44. The Committee considered that there was insufficient evidence to support subsequent treatment of this population group with trastuzumab emtansine following treatment with trastuzumab deruxtecan. However, those who received trastuzumab emtansine in the early breast cancer setting, or are receiving trastuzumab emtansine in the metastatic setting at the time a positive funding decision is made, should be eligible to receive trastuzumab deruxtecan in the metastatic setting upon progression.

9.45. The Committee noted that additional amendments to the Special Authority criteria for both trastuzumab emtansine and trastuzumab deruxtecan would be needed to

reflect this, should a positive funding decision be made.

Summary for assessment

9.46. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for trastuzumab deruxtecan if it were to be funded in New Zealand for HER-2 positive metastatic breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with HER-2-positive metastatic breast cancer, previously treated with trastuzumab and a taxane
Intervention	Trastuzumab deruxtecan at a dose of 5.4mg/kg every 3 weeks until disease progression, death or unacceptable toxicity.
Comparator(s)	Trastuzumab emtansine at a dose of 3.6mg/kg every 3 weeks All individuals are assumed to otherwise receive trastuzumab emtansine (ie no individual would otherwise receive other treatments)
Outcome(s)	Increased progression-free survival vs trastuzumab emtansine (median 28.8 months vs 6.8 months, hazard ratio 0.33) Increased overall survival vs trastuzumab emtansine (hazard ratio 0.64) Increase in rate of serious adverse events compared to trastuzumab emtansine
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

10. Ibrutinib and venetoclax Special Authority in the context of relapsed/refractory chronic lymphocytic leukaemia (CLL)

10.1. The Advisory Committee reviewed the application for Ibrutinib and venetoclax Special Authority for relapsed/refractory (R/R) chronic lymphocytic leukaemia (CLL) Application.

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

Recommendation

10.3. The Advisory Committee **recommended** that access to venetoclax and ibrutinib for relapsed/refractory CLL be widened with a high priority within the context treatment of malignancy, subject to the following Special Authority criteria (additions to the current criteria in **bold**, deletions in ~~strikethrough~~):

VENETOCLAX
Initial application — (relapsed/refractory chronic lymphocytic leukaemia) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 7 months for applications meeting the following criteria:
All of the following:
1. Patient has chronic lymphocytic leukaemia requiring treatment; and
2. Patient has received at least one prior therapy for chronic lymphocytic leukaemia; and
3. Patient has not previously received funded venetoclax; and
4. ~~The patient's disease has relapsed within 36 months of previous treatment; and~~

5. Venetoclax to be used in combination with six 28-day cycles of rituximab commencing after the 5-week dose titration schedule with venetoclax; and
6. Patient has an ECOG performance status of 0-2.

Renewal — (relapsed/refractory chronic lymphocytic leukaemia) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment; and
2. Venetoclax is to be discontinued after a maximum of 24 months of treatment following the titration schedule, unless earlier discontinuation is required due to disease progression or unacceptable toxicity.

IBRUTINIB
Initial application — (chronic lymphocytic leukaemia (CLL)) from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has chronic lymphocytic leukaemia (CLL) requiring therapy; and
2. Patient has not previously received funded ibrutinib; and
3. Ibrutinib is to be used as monotherapy; and
4. Any of the following:
   - 4.1 Both:
     - 4.1.1 There is documentation confirming that patient has 17p deletion or TP53 mutation; and
     - 4.1.2 Patient has experienced intolerable side effects with venetoclax monotherapy; or
   - 4.2 All of the following:
     - 4.2.1 Patient has received at least one prior immunochemotherapy for CLL; and
     - 4.2.2 Patient's CLL has relapsed within 36 months of previous treatment; and
     - 4.2.3 Patient has experienced intolerable side effects with venetoclax in combination with rituximab regimen; or
     - 4.2.4 Patient's CLL is refractory to, or has relapsed ~~within 36 months of~~ **after, treatment with** a venetoclax regimen.

Renewal — (chronic lymphocytic leukaemia (CLL)) from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
Both:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the patient is benefitting from treatment.

Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL) and B-cell prolymphocytic leukaemia (B-PLL)*. Indications marked with * are Unapproved indications.

10.4. In making this recommendation, the Advisory Committee considered:

10.4.1. That individuals with better prognosis CLL are being disadvantaged by the current Special Authority requirement to relapse within 36 months.

10.4.2. That approximately 45%-50% of individuals with CLL would require next line therapy within 36 months of ending first line treatment and estimated the other 50%-55% would require this therapy post the 36-month period.

10.4.3. If the 36-month restriction were removed, the treatment paradigm for individuals with 17p deletion/TP53 mutated CLL would be first line venetoclax (more likely to be fixed duration due to criteria removal), and second line ibrutinib.

10.4.4. If the 36-month restriction were removed, the treatment paradigm for individuals with non-17p deletion/TP53 mutated CLL would be first line FCR/BR/G-Chl, second line venetoclax with rituximab, and third line ibrutinib.

10.4.5. That there was no reason to assume any difference in the health-related quality of life (HRQOL) or applicability of pivotal trial outcomes for people receiving treatment for released/refractory CLL before or after 36 months.

10.4.6. If the 36-month restriction was removed from the Special Authority criteria, more individuals with 17p deletion/TP53 mutated CLL would likely be prescribed fixed term venetoclax (instead of continuous use), as they would be assured they could access funded BTKi treatment after the 36-month period, which may result in a reduction in the use of venetoclax for this patient population.

10.4.7. That there are likely pragmatic approaches taken to ensure eligibility of individuals for these targeted treatments.

10.5. The Advisory Committee **recommended** that retreatment with venetoclax for relapsed/refractory CLL **be deferred**.

10.6. In making this recommendation, the Advisory Committee considered:

10.6.1. Presently, there is insufficient evidence supporting the health benefits of retreatment with venetoclax for people with CLL.

10.6.2. Higher quality evidence with larger sample size, better defined patient group and appropriate study design would be required for consideration of widened access for this group.

Discussion

Māori impact

10.7. The Committee discussed the impact of widening access to venetoclax and ibrutinib for the treatment of CLL on Māori health areas of focus and Māori health outcomes. The Committee noted that CLL is not specifically a Pharmac Hauora Arotahi Māori health area of focus. The Committee considered that there is no direct evidence to suggest that incidence of CLL in Māori is any greater than that of other New Zealand populations.

Background

10.8. The Committee noted that in November 2019 venetoclax was funded in combination with rituximab, for the treatment of CLL that has relapsed within 36 months of previous treatment, and as monotherapy for the treatment of previously untreated CLL with a specific genetic mutation (17p deletion or TP53 mutation), both subject to Special Authority criteria. The Committee noted that enetoclax in combination with rituximab was recommended with a high priority for funding by CaTSoP (April 2019). The Committee noted that the Subcommittee had considered it reasonable at that time to limit the use of venetoclax to treat individuals who relapse within 36 months of prior treatment as these individuals were considered to be a group with a higher health need.

10.9. The Committee noted that in November 2022, ibrutinib monotherapy was funded for people with relapsed or refractory chronic lymphocytic leukaemia, following treatment with venetoclax, subject to Special Authority criteria.

10.10. The Committee noted following the funding of venetoclax, CaTSoP recommended ibrutinib as a subsequent line of therapy (relapsed/refractory or intolerance) to venetoclax-containing regimens be listed with a high priority (July 2020). The Committee noted that at the time of this recommendation, CaTSoP had considered that while venetoclax met the health need for the majority of previously untreated people with del17p/TP53 mutation and people who relapsed within 36 months, there remained an unmet health need for individuals with CLL who are intolerant of, or refractory to venetoclax, who relapse after treatment with venetoclax, or for whom treatment with venetoclax is inappropriate. The Committee considered that individuals who were intolerant of, or refractory to, venetoclax containing regimens had the highest unmet health.

10.11. The Committee noted that when Pharmac issued a public consultation prior to the funding of ibrutinib for CLL (September 2022) seeking feedback on the proposal, Pharmac received multiple submissions relating to the requirements around individuals with CLL relapsing within 36 months of prior treatment. The Committee noted that consumers and clinicians voiced their concerns around individuals with CLL who have relapsed after 36 months not being able to access effective treatment.

Health need

10.12. The Committee noted that in New Zealand, individuals with non-17p deleted/TP53 mutated CLL who relapse after greater than 36 months, after first line fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine and rituximab (BR) therapy, are unable to access funded venetoclax. This group of individuals are therefore also unable to access funded ibrutinib, which is only funded subsequent to venetoclax. The Committee also noted that individuals who are treated with FCR first line are unable to access BR second line. The Committee noted that individuals who are considered "fit" are unable to access obinutuzumab with chlorambucil (Chl) second line, so are often retreated with FCR. The Committee considered that retreatment with FCR is associated with increased toxicity including risk of developing secondary malignancies such as myelodysplastic syndrome.

10.13. The Committee considered that individuals with 17p deleted/TP53 mutated CLL may benefit from a treatment break at 24 months (as per the Murano trial) but are currently not recommended to take one because if they relapse after 36 months of first-line venetoclax therapy they cannot then access Bruton tyrosine kinase inhibitor (BTKi) therapy. The Committee noted that the cost of venetoclax treatment would be reduced without a reduction in treatment benefit, if individuals could access treatment of fixed duration (24 months), followed by a break, without the consequent risk of not being able to meet the criteria for subsequent BTKi treatment. The Committee considered that if the 36-month criterion was removed, almost all of those who are on treatment with first line venetoclax at 24 months would stop treatment at 24 months.

10.14. The Committee considered that individuals with better prognosis CLL are being disadvantaged by the Special Authority requirement to relapse within 36 months.

Health benefit

10.15. The Committee noted that the MURANO trial (Seymour et al. N Engl J Med. 2018;378:1107-20): a phase III multicentre open-label parallel-arm randomised controlled trial including individuals aged 18 years or over with relapsed or refractory CLL, and compared venetoclax plus rituximab (n=194) with bendamustine plus rituximab (n=195), reported health benefit derived from venetoclax plus rituximab, which would be generalisable to people who relapse and require treatment after 36 months following their prior line of therapy. The Committee noted CaTSoP's consideration of the trial in April 2019.

10.16. The Committee noted the results of the RESONATE trial, an open label Phase III study comparing ibrutinib to ofatumumab in individuals with CLL or SLL requiring therapy if they had at least one prior treatment (Byrd et al. N Engl J Med. 2014;371:213-23). The Committee considered that the comparator arm (ofatumumab) showed weak efficacy in comparison to ibrutinib. The Committee considered that ibruitinib showed substantial PFS benefit over ofatumumab. The Committee considered that there was no clear reason to think that the health benefits would be different in a New Zealand population to the study population, however noted that no individuals in the study had received venetoclax. However,

prior treatment with venetoclax is a requirement for accessing funded ibrutinib in New Zealand. The Committee also noted CaTSoP's prior consideration of the trial in July 2020.

10.17. The Committee reviewed evidence for venetoclax retreatment for CLL (Thompson et al. Blood Adv. 2022;6:4553-7). The Committee considered that the only study available was of poor quality due to its small sample size, heterogenous patient population and retrospective, chart-review design. The Committee considered that presently, there is insufficient quality evidence to make a positive recommendation for re-treatment with venetoclax for CLL, so venetoclax for this group was deferred until higher quality evidence with larger sample size, better defined patient group and appropriate study design became available.

10.18. The Committee considered that in New Zealand, the CLL population receiving second line re-treatment is older than that in the MURANO trial (where the median age in the trial was 65 years), so the number of individuals requiring subsequent treatment was maybe 10% lower than that number that would be estimated based on PFS data from the MURANO trial (also taking into account that, in CLL, PFS does not equal time to next treatment).

10.19. The Committee considered that in the context of treatment after venteoclax with rituximab for relapsed/refractory CLL, approximately 50% of individuals would meet current Special Authority criteria for ibrutinib based on the median time to next treatment in the MURANO study of 57.8 months. The Committee considered that the proportion of people accessing ibrutinib as third line therapy is likely to be higher in New Zealand due to using less efficacious third line treatment/s (cyclical chlorambucil or steroids) to meet current ibrutinib Special Authority criteria. The Committee estimated that in New Zealand approximately 30% would receive obinutuzumab +Chl and that 15% would receive no treatment following venetoclax and rituximab therapy. The Committee made these estimates considering the lack of published data for Obinutuzumab + Chl as third line.

10.20. The Committee considered that the treatment paradigm for individuals with non-17p deletion/TP53 mutated CLL would be first-line FCR/BR/G-Chl, second-line venetoclax with rituximab, and third-line ibrutinib.

Cost and savings

10.21. The Committee noted that to date the MURANO trial was utilised for Pharmac's economic modelling for venetoclax and the RESONATE trial was utilised for Pharmac's economic modelling for ibrutinib in the relapsed/refractory CLL setting. The Committee considered that the data utilised for economic modelling for both treatments is applicable to these treatments used in the population subgroups considered, excepting the group proposed to receive venetoclax re-treatment.

10.22. The Committee considered that if the 36-month restriction was removed from the Special Authority criteria, more individuals with17p deleted CLL/TP53 mutated CLL would likely be prescribed fixed-term venetoclax (instead of continuous use), as prescribers would be assured these individuals could access funded treatment after the 36-month period, which may result in reduced cost of venetoclax.

Funding criteria

10.23. The Committee noted that the evidence indicating appropriateness of a 36-month cut-off requirement came from Fornecker et al. Am J Haematol. 2015;90:511-4, a retrospective non-randomised study treating 132 individuals with CLL treated with various regimens post-relapse after receiving FCR upfront. The authors of the study concluded that new treatment regimens should be offered to people who relapse in less than 36 months after ceasing FCR, as those who relapsed after 36

months of FCR responded well to re-treatment with first line therapy (FCR). The Committee considered that this evidence was not of great quality due to its size, and retrospective and non-randomised design. The Committee also noted that the study is referenced in the European Society for Medical Oncology (ESMO) CLL guidelines, in the recommendations to initiate novel therapy with venetoclax plus rituximab, or a BTKis as continuous therapy in individuals whose disease is refractory to or has relapsed within 3 years of first -line therapy, or refractory to first therapy.

10.24. The Committee considered the Special Authority criteria for venetoclax with rituximab for relapsed/refractory CLL currently allows access to venetoclax through interpretation of the wording "progression free survival". The Committee considered that clinicians currently deem people to have progressed within 36 months of ceasing prior treatment, though they do not initiate their next treatment at the documented time of progression. That is, if disease has progressed before 36 months, then clinicians can still use venetoclax beyond the 36-month restriction.

10.25. The Committee also considered that in order to access these treatments, clinicians may prescribe short term treatment with other chemotherapy (eg chlorambucil) on which individuals will likely relapse, and then access and utilise funded venetoclax or ibrutinib depending on the treatment history as the Special Authority criteria for venetoclax will have been met.

10.26. The Committee considered that in light of these prescribing behaviours, the likely cost of making this change to the criteria, for ibrutinib especially, would be minimal. The Committee considered that almost all individuals who relapse more than 36 months after ceasing prior treatment before venetoclax or ibrutinib are still likely to receive treatment with these agents, but with some incurring cost and exposure to an additional ineffective line of chemotherapy before initiating treatment with venetoclax or ibrutinib, potentially compromising outcomes.

10.27. The Committee considered it reasonable to assume based on the proportion of people who are progression free for 42 months after first-line treatment that approximately 50% of individuals with relapsed/refractory CLL are eligible for treatment currently, and that this number would nearly double with the proposed removal of the 36-month criterion. However the Committee noted that this estimate was not relevant to the New Zealand context, as these individuals do ultimately end up receiving venetoclax or ibrutinib, albeit after another line of therapy.

Summary for assessment

10.28. The Committee considered that less than 20% of people would receive FCR retreatment in the third-line setting, as a comparator to ibrutinib (see PICO table below). The Committee considered more suitable assumptions to be that 10% would receive FCR retreatment, while 80% would receive obinutuzumab with chlorambucil.

10.29. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for venetoclax and ibrutinib if their access criteria were to be widened in New Zealand. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change, based on new information, additional clinical advice, or further analysis by Pharmac staff:

	VTX-R remove 36-month criterion	Ibrutinib remove 36-month criterion
Population	CLL which has relapsed and requires treatment after at least one prior disease modifying treatment, without identified 17p deletion, who have an ECOG 0-2	
	Previous treatment: at least one line, not VTX AND Relapse 36 months or more after cessation of previous treatment	Previous treatment: at least two lines, one of which was VTX-R AND Relapse was 36 months or more after cessation of prior treatment OR Intolerable side effects with VTX-R
Intervention	VTX-R (six cycles max. rituximab) Discontinued at the earlier of: disease progression or intolerable toxicity, OR at 24 months	Ibrutinib monotherapy, until disease progression.
Comparator(s) (NZ context) *	Fludarabine, cyclophosphamide and rituximab (FCR) (six cycles at most) OR Obinutuzumab with chlorambucil (Obi + ch) (six cycles at most), if not received in earlier lines. Most of the people who receive this in earlier lines have inferior co-morbidity scores	80% Obinutuzumab with chlorambucil (six cycles at most), if not received in earlier lines. Most of the people who receive this in earlier lines have poor prognostic scores 10% FCR re-treatment 10% chlorambucil monotherapy.
Outcome(s)	The therapeutic intent of treatment for CLL is to prolong PFS and OS. Health-related quality of life (HRQOL) associated with prolonged PFS has been resolved in previous modelling, and it is assumed that there will be no improvement in HRQOL independent of improved PFS.	

Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.

* Comparator based on advice received in January 2021 (email correspondence with CaTSoP members)

11. Aprepitant – nausea and vomiting associated with any moderately emetogenic chemotherapy (P-0017490)

Application

11.1. The Advisory Committee reviewed the application for aprepitant in the treatment of nausea and vomiting associated with any moderately emetogenic chemotherapy.

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

Recommendation

11.3. The Advisory Committee **recommended** that the following Special Authority restrictions for aprepitant **remain unchanged**:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months where the patient is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy for the treatment of malignancy.
>
> **Renewal** from any relevant practitioner. Approvals valid for 12 months where the patient is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy for the treatment of malignancy.

11.4. In making this recommendation, the Advisory Committee considered:

11.4.1. That chemotherapy-induced nausea and vomiting (CINV) is a high priority in oncology care.

11.4.2. That New Zealand clinical guidance has enabled the widening of access to aprepitant, whilst remaining within the intent of the current Special Authority wording.

Discussion

Māori impact

11.5. The Committee discussed the impact of widening access to aprepitant for the treatment of nausea and vomiting associated with any moderately emetogenic chemotherapy on Māori health areas of focus and Māori health outcomes. The Committee noted that lung and breast cancer (both of which are treated with carboplatin-based chemotherapy) are Hauora Arotahi - Māori health areas of focus. The Committee noted that for both cancers, Māori are diagnosed at a later stage of disease and are less likely to receive the benefit from a completed treatment course. Māori are also more likely than non-Māori to decline treatment and not access appointments (Stevens et al. J Thorac Oncol. 2008;3:237-44). The Committee considered that that there are numerous reasons as to why Māori experience access and treatment barriers and associated outcomes.

Background

11.6. The Committee noted that aprepitant was funded in New Zealand in 2009/10 for individuals receiving highly emetogenic chemotherapy or anthracycline containing chemotherapy.

11.7. The Committee noted that in August 2021, PTAC reviewed an application for the widened use of aprepitant to include treatment of nausea and vomiting associated with carboplatin-based chemotherapy. The Committee noted PTAC's recommendation that access to aprepitant be widened for this group, with a high priority. The Committee noted that in making this recommendation, PTAC considered the high health need of individuals experiencing nausea and vomiting associated with carboplatin-based chemotherapy and evidence of benefit of aprepitant in the reduction in nausea and vomiting in this treatment population with potential reductions in nausea and vomiting associated hospital admissions, possible improved adherence to carboplatin-based chemotherapy, and the suitability of aprepitant therapy as an oral treatment. The Committee noted PTAC considered that further advice from CTAC should be sought on which groups of people with cancer would benefit from access to aprepitant.

11.8. The Committee noted PTAC also recommended that advice be sought from CTAC regarding whether aprepitant would be most appropriate as a first- or second-line treatment, noting that the Canadian Agency for Drugs and Technologies in Health (CADTH) has recommended that aprepitant be added to antiemetic treatment in the second chemotherapy cycle if nausea and vomiting are significant with highly emetogenic chemotherapies.

11.9. The Committee noted that in 2023, the National Comprehensive Cancer Network (NCCN) guidelines were updated to include carboplatin-based chemotherapy as a highly emetogenic chemotherapy and to include aprepitant as a treatment option for nausea and vomiting related to moderately emetogenic chemotherapy.

Health need

11.10. The Committee noted that chemotherapy-induced nausea and vomiting (CINV) is a high priority in oncology care, and that chemotherapy agents can be classified by their CINV potential. The Committee noted that commonly agreed classification

is published in the MASCC and ESMO Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting: ESMO Clinical Practice Guidelines (MASCC/ESMO). The Committee noted that within the "moderately emetogenic" category, chemotherapy agents ranged from 30%-90% chance of causing CINV. The Committee considered it a challenge to provide one solution for all these agents due to this wide range.

11.11. The Committee considered that risk factors for higher rates of emesis at the individual level include: previous emesis in pregnancy, and the propensity for travel/motion sickness. It was considered that CINV risk could be influenced and classified by individual-related risk factors, as well as the classification of chemotherapy agents. The Committee considered that the duration and control of CINV experienced over the first cycle of chemotherapy is predictive of the control of CINV in subsequent chemotherapy cycles.

11.12. The Committee considered that control of CINV is highly valued by individuals receiving chemotherapy, their whānau, and their wider community. It was considered that poorly controlled CINV negatively impacts the quality of life of both individuals receiving treatment and those around them and leads to higher rates of treatment discontinuation. The Committee noted evidence which shows that poorly controlled CINV can affect treatment outcomes including progression-free survival and overall survival (Woopen et al. Support Care Cancer. 2020;28:73-8).

Health benefit

11.13. The Committee noted that anti-emetic agents have different mechanisms of action, which target the different areas in the central nervous system that are involved in the emetic process. The Committee noted that aprepitant is a neurokinin-1 (NK1) antagonist, which blocks signals given from NK1 receptors in the chemoreceptor trigger zone in the brain, thus decreasing the likelihood of emesis and vomiting.

11.14. The Committee noted that, whilst carboplatin had previously been considered as moderately emetogenic, it is now widely considered as highly emetogenic. This is outlined in various international guidelines, including the American Society of Clinical Oncology (ASCO), NCCN, and MASCC/ESMO. The Committee noted that the eviQ guidelines now include carboplatin in protocols where carboplatin dose AUC ≥ 4. Aprepitant is available through the Pharmaceutical Benefits Scheme (PBS) for any dose of carboplatin.

11.15. The Committee noted other examples of chemotherapy which were previously considered moderately emetogenic and which are now considered highly emetogenic in certain guidelines. The Committee noted that actinomycin-D, irinotecan, high dose methotrexate and epirubicin are now considered highly emetogenic in the NCCN guidelines. The Committee noted that eviQ states in clinical practice, oxaliplatin may be highly emetogenic, and that aprepitant is available on PBS as primary prophylaxis.

11.16. The Committee noted that in New Zealand, the Anti-Cancer Therapy Nationally Organised Workstreams (ACT-NOW) programme has categorised a range of chemotherapy regiments based on their CINV risk. All regimens containing carboplatin, oxaliplatin and actinomycin are classified as having a "high emetogenicity factor", and aprepitant is the recommended first-line prophylactic and treatment therapy. The Committee considered that this supporting clinical guidance has enabled support for widening use of aprepitant, whilst remaining within the intent of the current Special Authority criteria.

11.17. The Committee considered that the global benefit of NK1 antagonist containing regimens for the entire moderately emetogenic therapy category cannot be confirmed at this time due to the lack of high-quality evidence currently available.

11.18. The Committee considered that the use of aprepitant was preferred in the first-line setting. The Committee considered that its use as first- or second-line therapy to not be pertinent for consideration of its use, given its utility in the control of CINV when a person is undergoing highly emetogenic chemotherapy and noting the interpretation of 'highly emetogenic' within the oncology community.

Cost and savings

11.19. The Committee considered that the budget impact of aprepitant will not change for this group given treatment is already being accessed within the current Special Authority criteria.

12. Bevacizumab for gliomas

Application

12.1. The Advisory Committee reviewed the application for bevacizumab for the treatment of relapsed or recurrent high-grade gliomas.

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

Recommendation

12.3. The Advisory Committee **recommended** that bevacizumab be listed with a **low priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

> **Initial application – (relapsed recurrent high-grade gliomas)** Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Either:
> 1.1. Patient has relapsed diagnosed glioblastoma multiforme, or
> 1.2. Patient has relapsed diagnosed anaplastic astrocytoma: and
> 2. The patient has been assessed for maximal safe resection or radiotherapy; and
> 3. The patient has received temozolomide previously; and
> 4. Patient has not previously received funded treatment with bevacizumab for this disease.
>
> **Renewal application – (relapsed recurrent high-grade gliomas)** Applications only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist Approvals valid for 6 months for applications meeting the following criteria:
> Either:
> 1. Clinically stable disease; or
> 2. The treatment remains appropriate, and the patient is benefiting from treatment.

12.4. The Advisory Committee has made this recommendation based on a high unmet health and lack of treatment options.

12.4.1. The Committee considered the clinical trial data to be of poor quality. The Committee considered that bevacizumab is not a life-extending treatment but rather a steroid-sparing agent that can be used to manage cerebral oedema, whose use can consequently result in clinical improvement of signs and symptoms.

Discussion

Māori impact

12.5. The Committee discussed the impact of funding bevacizumab for the treatment of high grade recurrent relapsed gliomas on Hauora Arotahi - Māori health areas of focus and Māori health outcomes. The Committee was informed of data from Te Whatu Ora that reported up to 10% of cases of malignant neoplasms of the brain in 2020 were Māori. The Committee noted despite similar incidence rates, there have been reports of Māori waiting 1.32 (95% CI 0.98–1.79) times longer to receive radiotherapy, and having poorer median survival times compared to non-Māori (hazard ratio 1.55 [95% CI 0.95–2.55]) (Alexander et al. J. Clin. Neurosci. 2010;17;1144-7).

Background

12.6. The Committee noted that PTAC had previously recommended that bevacizumab as a monotherapy for individuals with relapsed or recurrent glioblastoma multiforme (GBM) be declined, following their consideration of the clinical benefit and risk, the cost effectiveness, and the budgetary impact (PTAC February 2016). PTAC had considered that the evidence was of poor strength and quality, as the studies did not compare bevacizumab's use with a control arm, and due to the relatively small number of individuals involved. The Committee noted that PTAC had also deferred making any recommendation for bevacizumab as a combination therapy with lomustine for individuals with relapsed or recurrent gliomas, pending publication of data from the EORTC phase III trial.

12.7. The Committee noted that lomustine, a treatment used to treat the same population, is being discontinued by the supplier, and that as Pharmac has not been able to secure an alternative brand.

Health need

12.8. The Committee noted that gliomas refer to all forms of intra-axial tumours that originate from glial cells of the central nervous system (CNS).

12.8.1. The World Health Organization (WHO) Classification of Tumours of the CNS classifies gliomas into grades (I-IV) based on pathological evaluation using molecular information on the malignancy level.

12.8.2. The Committee noted the most common form of high-grade glioma is a grade IV subtype GBM, with grade III glioma, anaplastic astrocytoma (AA), a rarer form. The Committee noted that GBM refers to an astrocytoma with WHO grade 4 classification, and an AA is the same tumour type, but with a grade 3 classification. The Committee noted that the determination of grade is related to adverse histologic prognostic factors identified following biopsy.

12.9. The Committee noted that clinical presentation of glioma depends on the tumour location and size at diagnosis. The most common presenting symptoms and signs at diagnosis are headaches and/or nausea and seizures in the context of a large tumour or significant cerebral oedema. The Committee noted that differentiation of tumour type between grade III or IV usually occurs at surgery, as the clinical symptoms and radiological signs associated with the two tumour types are relatively similar and nonspecific in nature, and noted that both have a poor response to medical management and a poor prognosis (Tian et al, Front Oncol. 2019;9:876).

12.10. The Committee noted that the 5-year overall relative survival rate for those with GBM is 6.8%, which varies by age at diagnosis and sex, with median overall survival (OS) approximately 10-12 months in a New Zealand population-based studies (McManus, Neurooncol Pract. 2022;9:43-9). The Committee noted that a study that used evidence from the Surveillance, Epidemiology and End Results (SEER) database reported the overall 5-year survival of AA is reported to be 22%,

with the highest 5-year survival rate of 49.9% seen in those in the 15- to 24-year-old age group, and the lowest of 2.5% seen in the 75- to 84-year-old age group (Smoll et al, Neuro Oncol. 2014;16:1400-7).

12.11. The Committee noted that the annual incidence of gliomas is approximately six cases per 100,000 individuals worldwide. Men are 1.6-fold more likely to be diagnosed with gliomas than women, with approximately 5% of gliomas having a familial origin (Weller et al. Nat Rev Clin Oncol. 2021;18:170-86). The Committee noted the incidence of malignant gliomas is bimodal with the highest incidence observed in the young and the elderly, the age distribution varying by histological type. GBM is known to have the highest incidence in people aged in their late 60s and early 70s, with frequency then reducing in older age groups. (Ostrom et al, Neuro Oncol. 2019; 21:1357-75). The incidence of AA has been reported to also increase with age (Smoll et al. 2014).The rates were 2.6 in young adults, 4.7 in adults, and 8.4 in elderly per million person-years (Smoll et al, Neuro Oncol. 2014; 16:1400-7).

12.12. The Committee previously noted (CaTSoP March 2014) that approximately 260 people were diagnosed with primary brain cancer each year in New Zealand, with peak incidence occurring between 45-75 years old. Members had noted that approximately 70% were diagnosed with GBM, and the rest AA.

12.13. The Committee noted individuals with relapsed, recurrent gliomas including AA and GBM present with a variety of largely non-specific symptoms that vary based on the position of the tumour but which can also be accompanied by problems in motor function and speech and commonly epileptic seizures, which reduce quality of life (Jovčevska Bosn et al. J Basic Med Sci. 2019;19:116-24). In addition, treatment with radiotherapy can reduce the quality of life in some individuals from the associated adverse effects (AEs) such as hair loss, fatigue, somnolence, or cognitive problems, and some may also experience the progression of dementia.

12.14. The Committee noted that at present there is no cure for relapsed, recurrent gliomas or GBM, with a life expectancy of 12 to 18 months after diagnosis (Jovčevska Bosn et al. 2019).

12.15. The Committee noted that treatment is aimed at reducing symptoms and prolonging progression free survival (PFS) and survival times. The Committee noted first-line management includes maximum safe surgical resection, followed by radiotherapy plus six cycles of maintenance temozolomide chemotherapy (Stupp regimen). The Committee noted standards of care at recurrence are less well defined. A minority of individuals with recurrence may be offered a second surgery or irradiation treatment if possible. The majority of those affected then progress to systemic treatment, mostly with nitrosourea-based regimens or temozolomide (Schaff et al JAMA. 2023;329:574-87). The Committee noted that temozolomide is funded for people with newly diagnosed high grade gliomas and that funding allows for beyond six cycles of maintenance temozolomide treatment.

12.16. The Committee noted a recent study of caregivers of people with a GBM diagnosis that found that performance status is a critical clinical factor that significantly affects caregiver burden, caregiving tasks, and caregiver time. Additionally, caring for individuals with GBM who are confused, affects multiple facets of caregiver burden and their quality of life. *(*Au et al, Supportive Care in Cancer, 2022;30:1365-75).

12.17. The Committee noted a study that highlighted that, despite similar incidence rates, Māori waited 1.32 (95% CI 0.98–1.79) times longer to receive radiotherapy, and had poorer median survival times compared to non-Māori (hazard ratio 1.55 [95% CI 0.95–2.55]) (Alexander et al. osci. 2010;17;1144-7).

12.18. The noted that approximately 50% of individuals with newly diagnosed GBM are over the age of 65. Overall survival (OS) in this population remains low, with this group reported as surviving approximately 9 months compared to approximately 15 months for the those aged below 65 years *(*Chahal et al. Curr Oncol. 2022;29:360-6*).* The Committee noted that older individuals may be treated with less aggressive surgical care due to concerns regarding the greater relative frailty of this population.

Health benefit

12.19. The Committee noted that bevacizumab is a humanised monoclonal antibody that binds to and inhibits the biologic activity of vascular endothelial growth factor A (VEGF-A). Neutralising the biologic activity of VEGF reduces tumour angiogenesis, thereby inhibiting tumour growth.

12.20. The Committee considered the Wick et al, N Engl J Med 2017;377:1954-63 study that reported the results of the phase 3 EORTC trial. 437 people at first progression of glioblastoma, after standard chemotherapy, were randomised 2:1 to lomustine plus bevacizumab (combination group, 288 people) or lomustine alone (monotherapy group, 149 people). Health-related quality of life and neurocognitive function were evaluated at baseline and every 12 weeks. The primary end point of the trial was OS.

12.20.1. The Committee noted there was a total of 329 OS events (75.3%), the combination therapy did not provide a statistically significant survival advantage; the median OS was 9.1 months (95% confidence interval [CI], 8.1 to 10.1) in the combination group and 8.6 months (95% CI, 7.6 to 10.4) in the monotherapy group (hazard ratio for death, 0.95; 95% CI, 0.74 to 1.21; P=0.65).

12.20.2. The Committee noted that the locally assessed progression free survival (PFS) was 2.7 months longer in the combination group than in the monotherapy group: 4.2 months versus 1.5 months (hazard ratio for disease progression or death, 0.49; 95% CI, 0.39 to 0.61; P<0.001). Deterioration-free survival was also longer in the combination group than in the monotherapy group (12.4 weeks vs. 6.7 weeks; P<0.001). Grade 3 to 5 AEs occurred in 63.6% of the people in the combination group and 38.1% of the people in the monotherapy group. The addition of bevacizumab to lomustine affected neither health related quality of life nor neurocognitive function.

12.21. The Committee noted the Chinot et al N Engl J Med 2014; 370:709-22 phase 3 randomised, double-blind, placebo controlled trial in 921 people with newly diagnosed, histologically confirmed, supratentorial glioblastoma. People were treated with bevacizumab or placebo, plus radiotherapy (2 Gy 5 days a week; maximum, 60 Gy) temozolomide. Median PFS was 10.6 months bevacizumab vs 6.2 months placebo (stratified hazard ratio for progression or death with bevacizumab, 0.64; 95% confidence interval [CI], 0.55 to 0.74; P<0.001 with the use of the log-rank test) Median OS was 16.8 months bevacizumab vs 16.7 months placebo (stratified hazard ratio for death with bevacizumab, 0.88; 95% CI, 0.76 to 1.02; P=0.10). The study reported that for quality of life, deterioration-free survival significantly longer in bevacizumab than placebo group for all five prespecified scales ((global health status, social functioning, and communication deficit, (hazard ratio for deterioration in global health status with bevacizumab, 0.64; 95% CI, 0.56 to 0.74; P<0.001 for all comparisons). Glucocorticoid (ie corticosteroid) use was discontinued (for ≥5 consecutive days) in 66.3% of the bevacizumab treated individual's vs 47.1% in placebo treated receiving corticosteroids at baseline. Among those who were not receiving glucocorticoids at baseline, the time to initiation of glucocorticoids was longer with bevacizumab

than with placebo (12.3 months vs. 3.7 months; hazard ratio, 0.71; 95% CI, 0.57 to 0.88; P=0.002). Adverse events of any grade were reported at 98.5% bevacizumab vs 96.0% placebo.

12.22. The Committee noted the Gilbert et al. N Engl J Med. 2014;370:699-708 study, a phase 3 randomised, double-blind, placebo-controlled trial in 637 people with newly diagnosed glioblastoma and a Karnofsky performance status of at least 70. Median follow-up time of 20.5 months. Median OS: 15.7 months (95% confidence interval [CI], 14.2 to 16.8) in the bevacizumab group vs 16.1 months (95% CI, 14.8 to 18.7) in the placebo group (hazard ratio for death in the bevacizumab group, 1.13; 95% CI, 0.93 to 1.37; P = 0.21 by the log-rank test). Tumour progression or death occurred in 512 people (82.4%). Median duration of PFS: 10.7 months (95% CI, 10.0 to 12.2) in the bevacizumab group vs 7.3 months (95% CI, 5.9 to 7.9) in the placebo group (hazard ratio for progression or death, 0.79; 95% CI, 0.66 to 0.94; P = 0.007 by the log-rank test). Greater deterioration in bevacizumab group than in the placebo group in neurocognitive-function test battery (P = 0.05),

12.23. The Committee noted the Kreisl et al. J Clin Oncol. 2009;27:740-5 phase 2, non-randomised, open label, non-comparative longitudinal observational study of 46 people with glioblastoma, recurrent after standard external-beam fractionated radiotherapy and temozolomide chemotherapy, a Karnofsky performance status (KPS) of ≥ 60%, and an estimated survival of at least 2 months. The median PFS was 16 weeks (95% CI, 12 to 26 weeks). Progression free survival after 6 months (PFS6) was reported at 29% (95% CI, 18% to 48%), with a 6-month survival rate of 57% (95% CI, 44% to 75%). The median OS was reported to be 31 weeks (95% CI, 21 to 54 weeks), with an overall radiographic response rate being 71% based on the Levin criteria (34 partial responses [PRs]) and 35% based on Macdonald criteria (one complete response [CR,] 16 PRs).

12.24. The Committee noted the Gilbert et al. J. Neurooncol.2017;131:193-9 prospective phase 2 randomised trial of bevacizumab in combination with either temozolomide or irinotecan in 123 people with recurrent glioblastoma. The Committee noted those included in the irinotecan arm were younger, however the other baseline characteristics was well balanced overall. The Committee noted the 6-month PFS was 39% in the temozolomide group, whilst 38.6% in the irinotecan group. Median PFS was 4.7 months compared with 4.1 months in the temozolomide group compared to the irinotecan group respectively. The median OS was 9.4 months compared to 7.7 months in the temozolomide group compared to the irinotecan group respectively.

12.25. Committee noted the Friedman et al. J Clin Oncol. 2009;27:4733-40 phase 2, multicentre, open label, randomised trial in 167 people with recurrent glioblastoma. Participants were treated with bevacizumab alone (n=85) or in combination with irinotecan (CPT-11) (with or without concomitant enzyme-inducing antiepileptic drugs, respectively) (n=82) once every 2 weeks. Estimated 6-month PFS was 42.6% (97.5% CI, 29.6% to 55.5%) bevacizumab group vs 50.3% (97.5% CI, 36.8% to 63.9%) bevacizumab + CPT-11. The study reported 6 -month PFS rates for those in first and second relapse of 46.4% and 27.8%, respectively, in bevacizumab group and 49% and 57.1%, respectively with bevacizumab + CPT-11. Overall response was reported occurring in 24 people (28.2%; 97.5% CI, 18.5% to 40.3%) in the bevacizumab group and 31 people (37.8%; 97.5% CI, 26.5% to 50.8%) in the bevacizumab + CPT-11. The OR rates for people in first and second relapse were 31.9% and 12.5%, respectively bevacizumab and 39.4% and 31.3%, respectively bevacizumab + CPT-11 group. Most people experienced tumour shrinkage during the treatment period. Median PFS was 4.2 months (95.0% CI, 2.9 to 5.8 months) bevacizumab vs 5.6 months

(95.0% CI, 4.4 to 6.2 months) for the bevacizumab + CPT-11. Median PFS times for people in first and second relapse: 4.4 and 3.1 months, respectively, bevacizumab vs 5.5 and 5.6 months, respectively, in bevacizumab + CPT-11. The median response durations were 5.6 months (95.0% CI, 3.0 to 5.8 months) vs 4.3 months (95.0% CI 4.2 months to not reached) in the bevacizumab + CPT-11 group. Median OS times from the time of random assignment was 9.2 months (95.0% CI, 8.2 to 10.7 months) bevacizumab vs 8.7 months (95.0% CI, 7.8 to 10.9 months) for the bevacizumab + CPT-11 group. Median OS times in first or second relapse were 9.1 and 9.2 months, respectively, bevacizumab group and 8.7 and 7.0 months, respectively, bevacizumab + CPT-11 group. The study reported a trend for people who were taking corticosteroids at baseline to take stable or decreasing doses over time.

12.26. The Committee noted the Taal et al Lancet Oncol. 2014;15:943-53 open-label, three-group, multicentre phase 2 randomised trial in 153 people with recurrent glioblastoma, treated with lomustine every 6 weeks, bevacizumab every 2 weeks or combination treatment with either 90 or 110 mg/m^2 lomustine and bevacizumab. The study reported in the bevacizumab group, percentage 9-month OS [95% CI] of 38% (25–51), median PFS of 3 months and percentage 6-month PFS [95%] 18 (9,30). In the lomustine group percentage 9-month OS [95% CI] of 43% (95% CI 29–57), median PFS of 2 months and percentage 6-month PFS [95%] of 11 (4,11). In the bevacizumab and lomustine 90 mg/m^2 group percentage 9-month OS [95% CI] of 59% (43-72), median PFS of 4 months and percentage 6-month PFS [95%] of 41 (26,55). In the bevacizumab and lomustine 110 mg/m^2 group percentage 9-month OS [95% CI] 87% (39-98), median PFS of 11 months and percentage 6-month PFS [95%] of 50 (15,77).

12.27. The Committee also noted the following studies:

- Wick et al. N Engl J Med. 2017;377:1954-63
- Reardon et al. J Neurooncol. 2012; 107:155-64
- Ali et al. J Neurosurg. 2008;109:268-72.
- Duerinck et al. J Neurol. 2015;262:742-51
- Gramatzki et al. Ann Oncol. 2018; 29:1431-6
- Kaley et al. CNS Oncol. 2013;2:413-8
- Narita et al. Jpn J Clin Oncol. 2013;43:587-95
- Jeck et al. Ther Adv Neurol Disord. 2018; 11:1-10
- Hofer et al. Acta Oncol. 2011;50:630-5

12.28. The Committee noted the McBain et al. Cochrane Database Syst Rev. 2021;5:CD013579 indirect comparison network meta-analysis reviewing treatment options for progression or recurrence of glioblastoma. The study reported that evidence of treatment efficacy on second recurrence is sparse.

12.29. The Committee noted the testimonials provided of people with the disease, those caring for someone with the disease and clinicians. Brain Tumour Support NZ stated that affected individuals cared about the quality of life, not just the extended survival time. In addition, they stated bevacizumab provided an increase in PFS that extended time living without the symptoms of their brain tumour. They also stated that the resultant improvement in quality of life brings immediate benefits to people in their daily life and relationships.

12.30. The Committee noted the testimonial of one carer of an individual with GBM who had taken bevacizumab for 7 months, the carer stating that there had been a reduction in the swelling around the tumours that enabled a reduction in corticosteroid use. Several carers provided statements on the use of

bevacizumab in combination with irinotecan, with one stating it had improved balance and cognitive function in a person with GBM, whilst another carer testified that for another person it allowed progression from being wheelchair bound to walking 30 minutes around their neighbourhood.

12.31. The Committee noted the testimonials of clinicians which also stated that they were convinced of its very meaningful benefit in PFS, and enabling lower corticosteroid use, to improve quality of life in a number of those affected.

12.32. The Committee considered that whilst there were positive testimonials from clinicians, the clinical trial data was of poor quality. The Committee considered co-endpoints of PFS and OS indicated an improvement in PFS, however there was no evidence to suggest an increase in survival. The Committee considered that PFS is difficult to measure in gliomas, as there are imaging difficulties measuring cerebral oedema in recurrence. The Committee considered however that while bevacizumab is not a life-extending treatment, it is a corticosteroid sparing agent that can be used to manage and reduce oedema, which can result in clinical improvement in signs and symptoms.

12.33. The Committee considered that given its use and primary efficacy as a corticosteroid sparing agent, bevacizumab would not be a useful replacement for lomustine, which is being discontinued globally. The Committee considered that replacement therapies for lomustine would likely be other cytotoxic agents.

Suitability

12.34. The Committee noted bevacizumab is administered as an intravenous infusion, and this treatment must be administered in an infusion centre, thereby placing a potential burden on anyone who must travel from rural or remote areas to receive treatment, as well as on the capacity of infusion services.

Cost and savings

12.35. The Committee considered that there would be a reduction in the use of corticosteroids in those receiving bevacizumab. The Committee noted that anti-hypertensives are also prescribed with high dose corticosteroids, and these are likely to be reduced with bevacizumab administration.

12.36. The Committee considered that modelling cerebral oedema, the clinically relevant outcome bevacizumab affects in this context, would be difficult as it had been an exploratory/secondary endpoint (hence underpowered). The Committee considered that the evidence for effects on cerebral oedema was of poor quality and from trials that were negative in their primary endpoints (OS and PFS). The Committee however considered that treatment with bevacizumab would reduce the likelihood of cerebral oedema, and this may result in the increases observed in PFS. However, members considered this unlikely to translate to a benefit in overall survival.

12.37. The Committee noted that bevacizumab could be used in combination with carmustine, temozolomide, irinotecan and carboplatin. The Committee considered that the PICO (referred to below) should reflect that the comparator for bevacizumab as monotherapy (in comparison to the addition of bevacizumab to an active agent) would be corticosteroids such as dexamethasone and prednisone. The Committee considered that the rationale for this was based on the reduction in side effects bevacizumab may offer over high dose corticosteroids. The Committee however considered that relevant evidence would be difficult to find, but that the research literature on myeloma could inform these extrapolations.

12.38. The Committee considered that bevacizumab may not result in any significant changes in health-sector expenditure (diagnostic testing, nursing costs or treatment of side effects) except for the additional need for the infusions associated with bevacizumab administration. The Committee estimated that if funded, approximately 50% of people would receive best supportive care, instead of bevacizumab monotherapy or combination therapy.

12.39. The Committee considered that modelling of AE was unlikely to be relevant, as serious AEs are rare and responders have a short survival time to experience any complications with bevacizumab.

Summary for assessment

The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for bevacizumab if it were to be funded in New Zealand for individuals with relapsed, recurrent high-grade gliomas who have had a prior first line systemic therapy. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with relapsed, recurrent high-grade gliomas who have had a prior first line systemic therapy
Intervention	Monotherapy: Bevacizumab 10mg/kg via 30–90-minute intravenous infusion every 2 weeks until disease progression. Combination therapy: Bevacizumab (dosing as above for monotherapy) in combination with systemic therapy.
Comparator(s)	Systemic therapy plus oral corticosteroids (dexamethasone or prednisone) at higher doses as per Yan et al. 2019
Outcome(s)	Improved HRQoL from a reduction in side-effects of high dose steroids.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

13. Lomustine discontinuation and bevacizumab procurement

Application

13.1. The Advisory Committee noted lomustine (brand name CeeNU) is due to be discontinued at the end of 2023, as part of a worldwide discontinuation, Pharmac has been unable to secure an alternative brand at this stage. The Committee noted Pharmac was seeking advice on its options to procure replacement treatments for those who received lomustine as part of the procarbazine, lomustine and vincristine (PCV) treatment protocol.

13.2. The Advisory Committee noted that Pharmac was also seeking advice regarding a potential competitive procurement process for bevacizumab and the widening access for temozolomide for the treatment of gliomas.

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

Recommendation

13.4. The Advisory Committee considered it was likely there was health benefit in the use of temozolomide in the treatment of those with low-grade gliomas and recurrent/relapsed high-grade gliomas, of which it is not currently funded for. The Advisory Committee requested additional information to assess this health benefit further, before supporting the widening of access to temozolomide to alleviate any health need following the delisting of lomustine.

Discussion

Addressing unmet health need with lomustine discontinuation

13.5. The Committee noted the Yan et al. J Med Imaging Radiat Oncol. 2019;63:665-73 New Zealand-based study conducted between 2006-2015, involving 405 people, of whom 363 had high-grade gliomas. As first-line treatment, the majority were treated with surgery, radiation, and chemotherapy. At recurrence of 146 people with GBM, 106 had recurrence. These individuals were treated with the following: 50% best supportive care only, 26% chemotherapy alone, 8.5% surgery alone, and 11% surgery and chemotherapy. The chemotherapy given included procarbazine, PCV regime, temozolomide, irinotecan, carboplatin, and carboplatin plus etoposide. The Committee considered this highlighted the impact of the lomustine discontinuation on those with relapsed high-grade gliomas, as part of the PCV regime.

13.6. The Committee considered however that the primary use of lomustine was in those with newly diagnosed low-grade gliomas. The Committee therefore considered that it would be useful to consider the potential widening of access to temozolomide for this indication, to mitigate some of the impact of the lomustine discontinuation.

13.7. The Committee considered it important to review the evidence supporting the use of temozolomide in both high-grade gliomas upon recurrence and in low-grade gliomas as a replacement product, to inform any potential widening of access to address the unmet need that would result from the discontinuation of lomustine.

13.8. The Committee considered that the delisting of lomustine should be clearly communicated to the prescribing community as soon as possible, and that it was important to engage with consumer advocacy groups regarding the discontinuation of lomustine. The Committee considered that it would be reasonable, if access to a replacement product were enabled, to limit new individuals commencing treatment with lomustine, to ensure that no one was required to change from lomustine mid-course.

13.9. The Committee noted regorafenib may be an alternative treatment for those currently receiving lomustine. The Committee also noted the Lombardi et al. Lancet Oncol. 2019;20:110-9 randomised, multicentre, open-label phase 2 trial REGOMA study that compared the use of lomustine or regorafenib in those with glioblastoma at first relapse. The Committee considered the trial to be well balanced in trial participant baseline characteristics in each treatment arm. The Committee noted the overall survival was significantly improved in the regorafenib group compared with the lomustine group, with a median overall survival of 7·4 months (95% CI 5·8-12·0) in the regorafenib group and 5·6 months (4·7-7·3) in the lomustine group (hazard ratio 0·50, 95% CI 0·33-0·75; log-rank p=0·0009). The Committee noted that an application to Pharmac for this pharmaceutical has not yet been received.

Procurement considerations for bevacizumab

13.10. The Committee noted bevacizumab's utility in the treatment of recurrent glioblastomas is as a steroid sparing agent. The Committee considered that it

would therefore not directly replace lomustine in the treatment of gliomas.

13.11. The Committee noted several bevacizumab biosimilars are approved by Medsafe. The Committee noted that there were no concerns regarding the implementation of biosimilar bevacizumab, as no brand is currently funded in New Zealand.

13.12. The Committee noted other indications for the use of bevacizumab have been previously reviewed by either PTAC or CTAC including:

- advanced cervical cancer
- advanced first line ovarian cancer
- advanced second line ovarian cancer
- metastatic colorectal cancer.

13.13. The Committee noted that cancer services' infusion capacity was a concern in ensuring the equitable implementation and availability of bevacizumab treatment if it were funded.