# Record of the Cancer Treatments Advisory Committee Meeting held on 10 and 11 October 2024

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

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

The Cancer Treatments Advisory Committee may:

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

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

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

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

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

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

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

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## 1. Attendance

**Present**
Stephen Munn (Chair)
Alice Loft
Chris Frampton
Lochie Teague
Matthew Strother

Oliver Brake
Richard Isaacs
Scott Babington
Vidya Mathavan

**Apologies**
Alannah Kilfoyle
Alice Minhinnick
Michelle Wilson

## 2. Summary of recommendations

| Pharmaceutical and Indication | Recommendation |
|---|---|
| • Nivolumab and ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma, within the context of treatments of malignancy, subject to Special Authority criteria | Low Priority |
| • Bevacizumab for the neoadjuvant treatment of metastatic colorectal cancer (mCRC) in people whose metastatic disease is confined to the liver | Deferred |
| • Dabrafenib and trametinib for the treatment of stage III resected melanoma, within the context of treatment of malignancy, subject to Special Authority criteria | Medium Priority |
| • Pegylated liposomal doxorubicin (PLD) for the third line treatment of advanced epithelial ovarian cancer | Decline |
| • Asciminib within the context of treatments of malignancy, subject to Special Authority criteria | High Priority |
| • Blinatumomab for the treatment of measurable residual disease in B cell lineage acute lymphoblastic leukaemia, within the context of treatment of malignancy, subject to Special Authority criteria | High Priority |
| • Ruxolitinib for the treatment of acute corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant, within the context of treatment of malignancy, subject to Special Authority criteria | High Priority |

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

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

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

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

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

## 4. Welcome and introduction

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

## 5. Te Pātaka Whaioranga | Pharmac update

5.1. The Committee noted the Pharmac update provided by staff.

5.2. The Committee noted the recent budget uplift to Pharmac and the range of funding proposals being progressed. Members noted the impact of funding new treatments requiring infusion services and the need to share information with Health New Zealand about what is needed to support these decisions. Pharmac staff reassured members that Pharmac is working closely with Health New Zealand to have these discussions.

## 6. Options to enhance capacity of the Cancer Treatments Advisory Committee

6.1. The Committee noted the discussion paper from Pharmac staff about options to seek clinical advice on funding applications for cancer treatments in a different way, to enhance timeliness and efficacy of the expert advice process and help manage workload impact on advisors.

6.2. The Committee noted the following:

6.2.1. general support to group the review of cancer applications by tumour stream, noting efficiency, better understanding of treatment paradigm and horizon scanning

6.2.2. support to establish opportunities and consistent approach to seeking advice from other groups to inform CTAC agenda setting and priorities, including input from medical oncology and haematology oncology working groups, Special Interest Groups (SIGs)

6.2.3. ideas to increase interest from new advisors wanting to join CTAC, reducing workload impact, growing membership to share the load

6.2.4. support to consider alternative meeting schedule approaches – change time of year, shorter meetings more often could help however depends on frequency and pre-work required, retain face to face opportunities but doesn't need to be every meeting

6.2.5. establish an annual CTAC workplan and link in with other agencies

6.2.6. feedback on preferred meeting formats and how to best manage urgent email advice

6.3. The Committee noted the next step is for Pharmac staff to develop a plan for 2025/26 meetings to try some different approaches. This will be dependent on capacity of members and Pharmac staff.

## 7. Record of Cancer Treatments Advisory Committee meetings held on 12 April 2024 and 12 July 2024

7.1. The Committee reviewed the record of the Cancer Treatments Advisory Committee meetings held on 12 April 2024 and 12 July 2024 and agreed that the records be accepted.

## 8. Matters Arising

### 8.1. Nivolumab with ipilimumab combination for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma

### Application

8.1.1. The Committee reviewed the consultation feedback and additional information received from the supplier for the application for nivolumab and ipilimumab in the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma.

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

### Recommendation

8.1.3. The Committee **recommended** that nivolumab and ipilimumab for the treatment of metastatic or unresectable Stage IIIc or Stage IV melanoma be funded with a **low priority**, within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **Initial application (nivolumab)** only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
>
> All of the following:
>
> 1. Patient has metastatic or unresectable melanoma (excluding uveal) stage III or IV; and
> 2. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
> 3. The patient has ECOG performance status 0-2; and
> 4. Either:
>    4.1. Patient has not received funded pembrolizumab; or
>    4.2. Both:
>       4.2.1. Patient has received an initial Special Authority approval for pembrolizumab and has discontinued pembrolizumab within 12 weeks of starting treatment due to intolerance; and
>       4.2.2. The cancer did not progress while the patient was on pembrolizumab.
>
> **Renewal (nivolumab)** only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
>
> Either:
>
> 1. All of the following:
>    1.1. Any of the following:
>       1.1.1. Patient's disease has had a complete response to treatment; or
>       1.1.2. Patient's disease has had a partial response to treatment; or
>       1.1.3. Patient has stable disease; and
>    1.2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
>    1.3. The treatment remains clinically appropriate and the patient is benefitting from treatment; or
> 2. All of the following:
>    2.1. Patient has previously discontinued treatment with nivolumab for reasons other than severe toxicity or disease progression; and
>    2.2. Patient has signs of disease progression; and

2.3. Disease has not progressed during previous treatment with nivolumab.

**Initial application (ipilimumab)** only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1. Patient has metastatic or unresectable melanoma (excluding uveal) stage III or IV; and
2. The patient has ECOG performance status 0-2; and
3. Patient has not received funded pembrolizumab or nivolumab monotherapy; and
4. Ipilimumab to be used in combination with nivolumab for up to four cycles at a maximum dose of 3 mg/kg.

8.1.4. The Committee considered the following when making its recommendation:

- The health benefit of the combination therapy that extended to 10 years of follow up data
- The high-quality phase three randomised controlled trial data

8.1.5. The Committee considered it would like to review evidence of combination use with 1mg/kg ipilimumab compared with 3mg/kg when or if it becomes available.

8.1.6. The Committee considered it would need further evidence to consider the use of the combination therapy as a second line treatment.

## Discussion

*Māori impact*

8.1.7. The Committee discussed the impact of funding nivolumab and ipilimumab for the treatment of metastatic or unresectable melanoma on Māori health areas of focus and Māori health outcomes. The Committee noted melanoma is not one of Pharmac's five Hauora Arotahi -Māori health areas of focus. The Committee noted Māori are several times less likely to be diagnosed with melanoma than non-Māori even after adjusting for age (The State of Cancer in New Zealand 2020. Te Aho o Te Kahu the Cancer Control Agency, 2021). However, the Committee noted that Māori are more than twice as likely to die of their melanoma (adjusted for age; Te Aho o Te Kahu, 2021) and more likely to present with more advanced or metastatic disease compared with non-Māori (Robson et al. Ministry of Health, 2006).

*Populations with high health needs*

8.1.8. The Committee discussed the health needs of people with metastatic or unresectable melanoma among Pacific peoples, disabled people, tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee noted that Pacific people are less likely to be diagnosed with melanoma than non-Pacific people, however there is strong evidence of poorer cancer survival for Pacific peoples in Aotearoa (The State of Cancer in New Zealand 2020. Te Aho o Te Kahu the Cancer Control Agency, 2021).

8.1.9. The Committee were not aware of any population groups experiencing health inequities who are disproportionately affected by metastatic or unresectable melanoma.

*Background*

8.1.10. The Committee noted it had previously considered the application for nivolumab and ipilimumab in April 2016 and PTAC later considered it in May 2016. The Committee noted that the application was deferred and recommended to decline by the respective Committees. The Committee noted it had deferred the application due to the immaturity of evidence at the time, significant adverse effect profile and high price.

8.1.11. The Committee noted that since the previous consideration, Pharmac had decided to fund single agent pembrolizumab and nivolumab for unresectable or metastatic melanoma from September 2016. In December 2023, Pharmac consulted to decline this application for nivolumab and ipilimumab and received feedback that there was more evidence supporting a health benefit. As a result of this feedback, Pharmac sought additional information from the supplier and sought the Committee's advice on this funding application.

*Health need*

8.1.12. The Committee noted it had previously considered the health need of individuals with metastatic or unresectable melanoma in April 2024.

*Health benefit*

8.1.13. The Committee noted it had previously considered Checkmate-067, a phase three randomised controlled trial comparing nivolumab in combination with ipilimumab (NIVO+IPI), nivolumab monotherapy (NIVO) and ipilimumab monotherapy (IPI) in people with unresectable or metastatic melanoma.

8.1.14. The Committee noted that since previous considerations, data from Checkmate-067 with a minimum of 6.5 years follow up had been published (Wolchok et al. JCO. 2021;40:127-37). Additionally, data with a minimum of 10 years follow up had been presented at the European Society of Medical Oncology 2024 annual meeting (Larkin et al. Ann Oncol. 2024; 35(suppl_2):1-72 [abstract only]).

8.1.14.1. The Committee noted that the primary endpoints in Checkmate-067 were progression-free survival (PFS) and overall survival (OS) in:

- NIVO+IPI compared to IPI
- NIVO compared to IPI

8.1.14.2. The Committee noted that the trial was not designed or powered for comparison between NIVO+IPI and NIVO monotherapy, however this was included in descriptive analysis.

8.1.14.3. The Committee noted at 10 years minimum follow up, Checkmate-067 reported a median OS of 71.9 months (95%CI 38.2 to 114.4 months) for NIVO+IPI and 36.9 months (95%CI 28.2 to 58.7 months) for NIVO and 19.9 months (HR 0.85, 95%CI 0.69 to 1.05) for IPI. The Committee noted this was consistent with previous data read-outs at earlier minimum follow up timepoints.

8.1.14.4. The Committee noted that there was a post hoc analysis of melanoma-specific survival, and this confirmed objective responses.

8.1.14.5. The Committee noted that OS at 10 years was 43% for the combination therapy compared with 37% for NIVO monotherapy, and 19% for IPI monotherapy. The hazard ratio for death compared with IPI monotherapy was 0.53 (0.44-0.65) for the combination therapy, and 0.63 (0.52-0.76) for NIVO monotherapy. A descriptive analysis for the hazard ratio for death for NIVO+ IPI compared with NIVO monotherapy was 0.85 (0.69-1.05).

8.1.14.6. The Committee noted the median PFS (95% CI) was 11.5 months (8.9-20.0) for the combination treatment, and 6.9 months (5.1-10.2) and 2.9 months (2.8-3.1) for NIV and IPI monotherapy, respectively.

8.1.14.7. The Committee noted descriptive (not comparative) data reported by Wolchok et al. (2021) suggesting a reduced time on treatment with NIVO+IPI versus NIVO monotherapy, although the number of NIVO maintenance treatment cycles and the reasons for early discontinuation

were unclear from the publications. The Committee also noted the descriptive report of a longer treatment-free interval following discontinuation occurring with NIVO+IPI compared with either monotherapy. However, members considered that the impact of these data is somewhat unclear, given that some large cohort studies reported similar OS between groups regardless of whether single-agent immune checkpoint inhibitors continued or stopped after one year of treatment.

8.1.14.8. The Committee noted 18% of individuals treated with NIVO+IPI received subsequent treatment, whilst this increased to 25% for NIVO and 57% for IPI. The Committee noted that 77% of individuals at a median follow up of 80.8 months (74.0-86.3 months) were treatment free, defined as off study treatment and did not receive a subsequent therapy. This was reduced to 69% for NIVO at 80.8 months (76.4-85.3 months) and 43% for IPI monotherapy at 81.0 months (77.0-85.6 months).

8.1.14.9. The Committee noted for sites of progression, the combination treatment had less lymph node (18% compared with 25% and 35% for NIVO and IPI monotherapy respectively), as well as central nervous system (5% compared with 6% and 9% for NIVO and IPI monotherapy respectively). The Committee also noted an unplanned subgroup analysis reported that, of 38 events that occurred beyond three years of follow up (with 21 occurring beyond five years of follow up), 19 were new melanoma progression, two were deaths from melanoma, and 17 were deaths from non-melanoma causes.

8.1.14.10. The Committee noted in an unplanned analysis of individuals who were alive and progression free at 3 years of follow up that 86% of those treated with NIVO + IPI were alive at 10 years, with 85% treated with NIVO monotherapy, and 79% with IPI monotherapy respectively.

8.1.14.11. The Committee noted in a pre-planned subgroup analysis, the median OS survival at 10 years (95% CI) of individuals with a BRAF mutation treated with the combination treatment was not reached (50.7-not reached), whilst this was reduced in individuals without a *BRAF* mutation (39.1 months (27.7-84.6). Similar trends were observed for the NIVO and IPI monotherapy groups. The Committee considered that individuals with *BRAF* mutation had better OS than those without. The Committee considered there was no difference in OS between those with a PD-L1 expression of less than or greater than 5% in the intention to treat population.

8.1.14.12. The Committee considered the trial data and design was of high quality.

8.1.14.13. The Committee previously considered the baseline characteristics of the trial groups were well balanced.

8.1.14.14. The Committee considered that whilst there was no formal comparison of the combination treatment with NIVO monotherapy as a primary endpoint, there was descriptive analysis with consistent data showing median OS and PFS gains with the combination compared with the monotherapy although the proportion of each group alive at ten years was similar. The Committee considered this suggests survival beyond three years is predictive of likely survival at ten years in such individuals, given the low event numbers after three years.

8.1.14.15. The Committee considered that in respect to best tumour burden reduction, the combination therapy reported better reduction in tumour burden and quicker response in those with a high burden of disease. The Committee

considered those that had a ≥50% depth of response had a better overall survival.

8.1.14.16. The Committee considered there were good protocols for the management of treatment related toxicities. The Committee noted that grade 3-4 treatment related adverse events were higher in the combination therapy compared with the monotherapies (42% compared with 8% NIVO and 14% IPI).

8.1.15. The Committee noted there are no randomised controlled trials comparing NIVO+IPI to pembrolizumab, which would be a New Zealand comparator treatment. The Committee noted retrospective data from the Alberta Immunotherapy Database study evaluated the combination therapy with pembrolizumab monotherapy and NIVO monotherapy in 316 individuals (Gupta et al. JAMA Netw Open. 2023;6:e2319607). The Committee noted the combination arm contained more younger individuals with better performance status, with a slightly higher number of people with brain metastases and those with a *BRAF* mutation, and considered this might affect the results of the study. The Committee noted that those treated with the combination therapy had a longer time before subsequent treatment compared with pembrolizumab or NIVO monotherapy.

8.1.16. The Committee considered the available evidence was applicable to the New Zealand population and included a good quality randomised controlled trial with 10 years follow up data reporting consistent PFS and OS benefits in descriptive analysis.

8.1.17. The Committee noted there was a lack of data regarding quality of life, but considered it was plausible that there may be a difference between groups, given that individuals treated with NIVO would have had a longer (more) systemic treatment exposure compared with those treated with the combination therapy.

*Cost and savings*

8.1.18. The Committee considered there would be additional laboratory testing and hospital admissions associated with management of adverse effects from the addition of ipilimumab to currently funded nivolumab treatment. The Committee also considered there would be increased imaging within the first three years of treatment, with imaging occurring every three months. The Committee considered this might be reduced following this time period, but there are no national guidelines to guide the frequency of imaging.

8.1.19. The Committee considered there would also be additional infusion time required to administer ipilimumab.

8.1.20. The Committee considered individuals with a higher risk or aggressive/extensive disease, as indicated by the number of lesions, or with brain metastases would be more likely to benefit from combination therapy. The Committee considered this group of people require a more rapid response, which could be achieved by combination therapy. The Committee considered the combination treatment may improve outcomes in those with brain metastases, however this was not supported by high quality data.

8.1.21. The Committee considered it would be difficult to estimate uptake as it would be based on clinician and individual preference. The Committee considered this would be guided in part by disease volume and individuals' performance status. The Committee noted there was no established definition of "high-risk" in the clinical research literature that could be used to guide selection.

8.1.22. The Committee considered the number of people included in the Checkmate-067 trial with an ECOG score of 0 was higher than the New Zealand population. The

Committee considered overall the Checkmate-067 toxicity and overall survival results would likely overestimate outcomes anticipated in clinical settings in practice.

*Funding criteria*

8.1.23. The Committee noted emerging evidence of the use of ipilimumab at a dose of 1 mg/kg. The Committee considered that eligibility criteria should specify a maximum of 3 mg/kg to allow clinician discretion on appropriate dosing. The Committee considered most New Zealand clinicians would prescribe 1 mg/kg.

## 8.2. Eligibility advice – osimertinib for EGFR mutated, advanced non-small cell lung cancer (NSCLC) and trastuzumab deruxtecan for HER2-positive metastatic breast cancer

8.2.1. The Committee noted the Government had provided additional funding to Pharmac in June 2024 to fund new medicines and widen access to medicines that are already funded. The Committee noted that the funding boost covers medicines for both cancer and non-cancer related health conditions.

8.2.2. The Committee noted Pharmac had subsequently released consultation on a proposal to fund osimertinib for EGFR mutated, advanced non-small cell lung cancer (NSCLC) and trastuzumab deruxtecan for HER2-positive metastatic breast cancer. The Committee noted Pharmac sought advice on both applications.

### Discussion

*Osimertinib for EGFR mutated, advanced non-small cell lung cancer (NSCLC)*

8.2.3. The Committee noted Pharmac had received consultation feedback that included a letter from the Lung Oncology Special Interest Group that requested:

8.2.4. osimertinib be able to be used in combination with chemotherapy, citing the FLAURA 2 trial (Planchard et al. N Engl J Med. 2023;389:1935-48) and that some people may better benefit from combination treatment with osimertinib and chemotherapy (for example those with brain metastases)

8.2.4.1. amendments to the initiation criteria to remove staging information and to clarify that those with locally advanced disease that is not curable be eligible

8.2.4.2. amendments to the ECOG score for eligibility (from 0-2, to 0-3)

8.2.4.3. amendments to the initiation criteria for access to osimertinib in the first line setting, to account for people who need to start chemotherapy while awaiting EGFR results or had received chemotherapy in the adjuvant setting before presenting with locally advanced or metastatic disease.

8.2.4.4. amendments to renewal criteria to clarify in which circumstances treatment would be able to be continued.

8.2.4. The Committee considered these changes would be appropriate and would not alter the intent of its funding recommendation. The Committee recommended the following changes to the eligibility criteria (additions in **bold**, deletions in ~~strikethrough~~):

> **Initial application (NSCLC – first line)** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced ~~(Stage IIIb)~~ or metastatic ~~(Stage IV)~~, **incurable,** non-squamous non-small cell lung cancer (NSCLC); and
> ~~2. Either:~~
> **2. Any of the following:**
> 2.1. Patient is treatment naïve; or

2.2. **Patient has received prior treatment in the adjuvant setting and/or while awaiting EGFR results, or**
2.3. Both:
2.3.1. The patient has discontinued gefitinib or erlotinib due to intolerance; and
2.3.2. The cancer did not progress while on gefitinib or erlotinib; and
3. There is documentation confirming that the disease expresses activating mutations of *EGFR* ~~tyrosine kinase~~; and
~~4. Treatment must be used as monotherapy; and~~
5. Patient has ECOG performance status 0-~~2~~**3**; and
6. Baseline measurement of overall tumour burden is documented clinically and radiologically.

**Renewal (NSCLC – first line)** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications that meet the following ~~criteria~~ **criterion**:
~~Both:~~
1. Response to **or stable disease with** treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period**.**~~; and~~
~~2. No evidence of disease progression~~

**Initial application (NSCLC – second line)** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1. Patient has locally advanced ~~(Stage IIIb)~~ or metastatic ~~(Stage IV)~~, **incurable,** non-squamous non-small cell lung cancer (NSCLC); and
2. Patient has ECOG performance status 0-~~2~~**3**; and
3. The patient must have received previous treatment with erlotinib or gefitinib; and
4. There is documentation confirming that the disease expresses T790M mutation of ~~the~~ *EGFR* ~~gene~~ following progression on or after erlotinib; and
5. The treatment must be given as monotherapy; and
6. Baseline measurement of overall tumour burden is documented clinically and radiologically.

**Renewal (NSCLC – second line)** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications that meet the following ~~criteria~~ **criterion:**
~~Both~~:
1. Response to **or stable disease with** treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period**.**~~; and~~
~~2. No evidence of disease progression~~

8.2.5. The Committee considered there may be a small but insubstantial increase in uptake, as a result of these amendments, over previous assumptions.

*Trastuzumab deruxtecan for HER2-positive metastatic breast cancer*

8.2.6. The Committee noted Pharmac had received feedback requesting the use of trastuzumab deruxtecan (T-DXd) following prior treatment of metastatic breast cancer with trastuzumab emtansine (T-DM1), citing evidence from the DestinyBreast02 trial (André et al. The Lancet. 2023;401:1773-85).

8.2.7. The Committee considered the available data strongly supported a health benefit from T-DXd in people with prior exposure to T-DM1. As such, the Committee recommended the following amendments to the eligibility criteria (additions in **bold**, deletions in ~~strikethrough~~):

**Initial application** only from a relevant specialist or any relevant 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
3. Either:

3.1. The patient has received prior therapy for metastatic disease; or
3.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy; and
4. Patient has ~~a~~ good performance status (ECOG 0-1); and
**5. Patient has not received prior funded trastuzumab deruxtecan treatment; and**
~~6. Both:~~
~~6.1. Patient has not received prior funded trastuzumab deruxtecan treatment; and~~
~~6.2. Any of the following:~~
~~6.2.1. Patient has not previously received trastuzumab emtansine; or~~
~~6.2.2. Patient was receiving trastuzumab emtansine for treatment of their metastatic breast cancer prior to 1 January 2025; or~~
~~6.2.3. Patient previously received treatment with trastuzumab emtansine in the early breast cancer setting only; and~~
7. Treatment to be discontinued at disease progression.

**Renewal** only from a relevant specialist or any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for people meeting the following criteria:
Both:
1. The cancer has not progressed at any time point during the previous approval period whilst on trastuzumab deruxtecan; and
2. Treatment to be discontinued at disease progression.

8.2.8. The Committee considered that most people would be initiated on treatment with T-DXd and therefore the incident population requiring T-DXd after disease progression on T-DM1 would be small. The Committee considered there would, however, be a prevalent group of people who are currently, or previously, receiving T-DM1 and may require further treatment with T-DXd if their disease progressed.

8.2.9. The Committee considered uptake of T-DXd in these groups would be high, provided the individual was deemed medically fit and did not have specific contraindications.

8.2.10. The Committee noted Pharmac had also received feedback requesting that people who experience treatment intolerance to T-DXd can change to T-DM1. The Committee noted its previous considerations regarding the evidence supporting subsequent use of T-DM1 after treatment with T-DXd. However, the Committee considered that while there is insufficient evidence to support the use of T-DM1 after disease progression on T-DXd, it would be appropriate to allow people to switch if treatment could not be tolerated, provided that disease progression had not occurred during treatment with T-DXd. As such, the Committee recommended amendments to the eligibility criteria for T-DM1 as follows (additions in **bold**, deletions in ~~strikethrough~~, initial criteria shown only):

Initial application – (metastatic breast cancer) only from a relevant specialist or ~~a medical practitioner~~ **any relevant 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
3. Either:
3.1. The patient has received prior therapy for metastatic disease*; or
3.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy*; and
4. Patient has good performance status (ECOG 0-1); and
5. Either
5.1. Patient does not have symptomatic brain metastases; or
5.2. Patient has brain metastases and has received prior local CNS therapy; and
~~6. Patient has not received prior funded trastuzumab emtansine; and~~
**6. Either:**
**6.1. Patient has not received prior funded trastuzumab emtansine or trastuzumab deruxtecan treatment; or**
**6.2. Both:**
**6.2.1. Patient has discontinued trastuzumab deruxtecan due to intolerance; and**

**6.2.2. The cancer did not progress while on trastuzumab deruxtecan; and**

7. Treatment to be discontinued at disease progression.

## 9. Bevacizumab for metastatic colorectal cancer, neoadjuvant treatment for metastatic disease confined to the liver

### Application

9.1. The Committee reviewed a request from Pharmac staff for updated advice regarding bevacizumab for the neoadjuvant treatment of metastatic colorectal cancer in people whose metastatic disease is confined to the liver, which is currently ranked on Pharmac's Options for Investment list.

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

### Recommendation

9.3. The Committee **recommended** the application for bevacizumab for the neoadjuvant treatment of metastatic colorectal cancer (mCRC) in people whose metastatic disease is confined to the liver be **deferred**.

9.4. In making this recommendation, the Committee considered that:

9.4.1. It is unclear whether the subgroup with liver-only metastases who are the target of this application are the most appropriate group with mCRC to consider for bevacizumab, given that this is no longer a clinically relevant population definition in practice (due to the evidence base informing treatment selection, which is based on a range of disease characteristics, changing substantially since 2014).

9.4.2. Those with mCRC have unmet health needs, and while the proposed targeted funding of cetuximab may help to address the needs of some of this population, further consideration is needed to help define those with mCRC who will still have an unmet need and for whom bevacizumab should be considered.

9.4.3. Since 2014, the chemotherapy regimen used alongside bevacizumab for mCRC in the literature has evolved and there can be substantial variation in the treatment pathway to surgical resection, making it challenging to delineate the potential benefits of bevacizumab in mCRC.

9.4.4. Overall, there is poor quality evidence of a small, incremental survival benefit and a small but clinically significant risk of gastrointestinal perforation with bevacizumab for mCRC (in mCRC in general and in those with mCRC with liver-only metastases).

9.5. The Committee considered it unclear where bevacizumab might provide the greatest benefit in mCRC and **recommended** Pharmac engage with the Gastrointestinal Cancer Special Interest Group (GISIG) and hepatobiliary surgeons to seek their advice and views on:

9.5.1. Which group(s) with mCRC would benefit from bevacizumab and what the intended clinical outcomes of treatment are

9.5.2. How people in the group(s) are currently managed clinically

9.5.3. Where bevacizumab would be used in the mCRC treatment paradigm and for how long

9.5.4. Which treatments (pharmaceutical or otherwise) bevacizumab would displace or reduce the use of (ie comparator/s)

9.5.5. Key evidence to support the use of bevacizumab in the desired setting.

## Discussion

*Māori impact*

9.6. The Committee discussed the impact of funding bevacizumab for the treatment of mCRC on Māori health areas of focus and Māori health outcomes. The Committee noted that Māori are more likely to present with more advanced disease and would experience a greater impact from the disease, as discussed by CaTSoP (now CTAC) in 2019.

*Populations with high health needs*

9.7. The Committee discussed the health need of people with mCRC among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of bevacizumab for the treatment of mCRC and considered that:

9.7.1. People who live in rural areas are more likely to present with more advanced disease and would experience a greater impact from the disease in this context.

9.7.2. People who live in areas of greater socioeconomic deprivation are more likely to present with more advanced disease and would experience a greater impact from the disease in this context.

*Background*

9.8. The Committee noted that Pharmac proposed bevacizumab for neoadjuvant treatment of mCRC for metastatic disease confined to the liver be funded as part of a multiproduct deal in 2012, but it was declined following consultation feedback that indicated that costs were significantly underestimated. The proposal was re-ranked in 2014 to Pharmac's Options For Investment list after updated information received from the supplier was considered by PTAC and CaTSoP (now CTAC).

9.9. The Committee noted that a proposal for bevacizumab for first and second-line treatment of mCRC was formally declined in March 2022, based on clinical advice recommendations that it be declined (most recently by CaTSoP in July 2019). The Committee noted that Pharmac received minimal feedback on the consultation to decline this proposal, however, one clinician respondent indicated there were three specific subgroups with mCRC where bevacizumab should be considered (described later in this record).

9.10. The Committee noted that in August 2024, Pharmac released:

- a proposal to fund cetuximab for first- and second-line treatment of left sided, RAS and BRAF mutated colorectal cancer
- a future procurement opportunity (FPO) for bevacizumab for a range of indications.

9.11. The Committee noted that Pharmac staff sought updated advice on the proposal for bevacizumab for mCRC with metastases confined to the liver only ("liver-only metastases"), including: the current clinical relevancy of this proposal, the mCRC treatment paradigm, and the evidence for bevacizumab in this setting.

*Health need*

9.12. The Committee considered that people with mCRC have unmet health needs and the proposed funding of cetuximab will provide an additional targeted treatment for some but not all of this population, defined based on primary tumour location (sidedness) and tumour mutational status.

9.13. Additionally, the Committee considered the impact on whānau and caregivers for those living with the disease, particularly the financial, emotional, social burden(s) on carers to support their loved one through surgery, chemotherapy and other treatments for mCRC.

9.14. The Committee noted that the treatment of mCRC with liver-only metastases is complex and impacted by many uncontrolled variables. The Committee noted that surgery for resectable mCRC significantly contributes to improvements in survival for this disease, and that chemotherapy may be given prior to surgery (neoadjuvant) and/or post-surgery (adjuvant).

9.15. The Committee considered that the survival benefit of surgery received is dependent both on the rate of resection (determined by the operating surgeon and/or multidisciplinary team [MDT]) and on achieving successful surgical outcomes (i.e. a complete R0/R1 resection) which are influenced by multiple risk factors. The Committee noted some of the understandings around optimal surgery in mCRC with liver-only metastases was still evolving in clinical trials, such as the timing of primary and metastatic resection in regard to neoadjuvant chemotherapy.

9.16. The Committee noted that the pathway to surgical resection can be highly variable; may involve other procedures; treatments may be sequenced in different ways; and that this added complexity to defining a particular patient population. The Committee considered there to be regional variation in both surgeon and MDT views on resectability and the extent of attempts to “convert” disease considered initially unresectable to being resectable (versus deeming such cases not amenable to surgical intervention). The Committee considered that these variables would substantially confound the assessment of benefits from a particular treatment approach (for example the addition of bevacizumab to chemotherapy) in this context.

9.17. The Committee considered that for those receiving chemotherapy for mCRC:

- First-line treatment would usually consist of either the FOLFOX or FOLFIRI regimens (folinic acid and 5-FU plus oxaliplatin or irinotecan)
- Second-line chemotherapy might use a first-line regimen again, or consist of FOLFIRINOX/FOLFOXIRI (folinic acid, 5-FU, oxaliplatin and irinotecan).
- Chemotherapy use is likely subject to regional variation, but some centres use neoadjuvant chemotherapy to both increase resectability and allow disease biology to fully reveal itself (as the tumour changes in response to chemotherapy agents). However, adjuvant chemotherapy is not routinely used in many centres but may be offered for cases of incomplete resection (ie R2 and possibly R1).

*Health benefit*

9.18. The Committee noted that Pharmac staff sought to understand the current evidence for the role of bevacizumab when added to (neo)adjuvant chemotherapy in the treatment of mCRC with liver-only metastases. The Committee noted that individuals with mCRC targeted by this proposal could be deemed to have upfront resectable, unresectable, or borderline resectable metastases.

9.19. The Committee noted that CaTSoP (now CTAC) in 2010 had indicated that it was not feasible to prospectively define and limit funding of bevacizumab to patients with ‘potentially resectable’ mCRC and thus the population had not been split according to resectability in 2010. Members considered that this distinction might now be possible

based upon the current (2023) European Society for Medical Oncology (ESMO) clinical practice guideline for mCRC, which suggest that those who are clinically sufficiently fit to undertake targeted therapy (for example with bevacizumab or cetuximab) for conversion of unresectable/borderline resectable disease would have clinical circumstances suitable for neoadjuvant chemotherapy with or without bevacizumab (Cervantes et al. Ann Oncol. 2023;34:10-32). Members noted that the ESMO guidelines do not recommend targeted therapy as part of peri-operative therapy in those with resectable disease.

Resectable liver-only metastases

9.20. The Committee noted that Pharmac staff sought to understand the current evidence for the survival benefits from bevacizumab when added to (neo)adjuvant chemotherapy in the treatment of mCRC with resectable, liver-only metastases.

9.21. The Committee was made aware that the definitive phase III EORTC 40983 clinical trial had reported no difference in overall survival (OS) with the addition of neoadjuvant chemotherapy using FOLFOX for a total of six cycles pre and post operatively in 364 participants with colorectal cancer and up to four liver metastases (Nordlinger et al. Lancet Oncol. 2013;14:1208-15). The Committee noted that participants predominantly had T3, N0/N1 disease and that the treatment regimen excluded bevacizumab simply due to the timing of the study, which was before bevacizumab was routinely added to chemotherapy regimens internationally. The Committee considered that this negative trial indicated that there was no additional benefit from the use of neoadjuvant chemotherapy for people with resectable mCRC with liver-only metastases.

9.22. The Committee was made aware that a systematic review and meta-analysis of predominantly retrospective comparative studies reported no difference in survival with neoadjuvant chemotherapy for resectable liver-only metastases (Nigri et al. Surgeon. 2015;13:83-90).

9.23. The Committee was made aware that subsequent evidence from smaller studies and retrospective cohorts suggested some benefit from neoadjuvant chemotherapy in this context, but overall appeared inconclusive.

9.24. The Committee noted that the ESMO guidelines suggest chemotherapy be offered for people with “unfavourable oncologic criteria” and “favourable surgical criteria” based on clinician/MDT decision, but no evidence was cited to support the criteria described (Cervantes et al. 2023). Members considered there would likely be an absence of evidence to support the group as described and that use of bevacizumab for these individuals is probably based on a theoretical benefit.

Unresectable liver-only metastases

9.25. The Committee noted that Pharmac staff sought to understand the role of bevacizumab in converting colorectal cancer liver metastases that are initially considered to be unresectable into becoming resectable. The Committee considered that bevacizumab might also be considered as a neoadjuvant treatment in cases of borderline resectability. However, the Committee was made aware that, anecdotally, bevacizumab is not used in some private clinics in New Zealand due to a preference to focus on surgery and chemotherapy.

9.26. The Committee was made aware that chemotherapy regimens for conversion therapy for unresectable disease had evolved over the years since this proposal was last reviewed, with more recent evidence using the FOLFIRINOX/FOLFOXIRI triplet chemotherapy regimens instead of the FOLFOX doublet used previously. The Committee was made aware that there was sparse randomised controlled trial evidence investigating the addition of bevacizumab to triplet chemotherapy, as

bevacizumab has been used alongside chemotherapy regimens in the literature since its addition to standard of care doublet chemotherapy internationally.

9.27. The Committee noted that the ESMO guidelines describe a role of bevacizumab in neoadjuvant conversion therapy (Cervantes et al. 2023). However, the Committee considered that the two studies cited by the guidelines did not provide evidence to support this (the post hoc publication did not report the rate of resection; the preliminary abstract of a randomised controlled trial did not report values for key outcomes; neither study reviewed colorectal cancer 'sidedness' although both investigated standard chemotherapy plus cetuximab vs standard chemotherapy plus bevacizumab).

9.28. The Committee was made aware of a propensity score-adjusted analysis of two randomised controlled trials investigating the FOLFOXIRI triplet chemotherapy +/- bevacizumab for mCRC (Cremolini et al. Ann Oncol. 2016;27:843-9; based on the TRIBE trial reported by Loupakis et al. (N Engl J Med. 2014;371:1609-18) and the trial by Masi et al. [J Natl Cancer Inst. 2011;103:21-30]). The Committee noted that significant differences between the two groups meant that the FOLFOXIRI alone group was generally less well, had received more prior treatment and had a worse prognosis than the FOLFOXIRI + bevacizumab group, which had a smaller proportion of people with liver-only disease. Members considered that the Köhner score for fitness for liver surgery was not used routinely in New Zealand.

9.28.1. The Committee noted that 12% of those receiving FOLFOXIRI and 18% of those receiving FOLFOXIRI + bevacizumab proceeded to radical resection of liver metastases. Members considered that these figures could represent a difference in resectability of the groups rather than a treatment effect and noted that differences in surgical conversion or resection rate were not reported.

9.28.2. The Committee noted that an OS benefit of 29.8 (95% CI: 26.0, 34.3) months with FOLFOXIRI + bevacizumab was reported vs 23.6 (95% CI: 19.5, 26.7) months with FOLFOXIRI, acknowledging the between-group differences.

9.28.3. The Committee noted that 55.7% received a RECIST response with FOLFOXIRI vs 65.1% with FOLFOXIRI + bevacizumab, although neither the unadjusted or adjusted odds ratio (OR) were statistically significant (adjusted OR, 1.29, 95% CI 0.81, 2.05; *P*=0.280).

9.29. The Committee was made aware of a pooled analysis of 205 people from three phase II/III clinical trials predominantly conducted by an Italian research collaboration (Cremolini et al. Eur J Cancer. 2017:73:74-84). The Committee noted that participants had mostly bilobar liver-only mCRC and a high proportion had four or more metastases. The Committee noted that R0 resections were performed in about 30% of cases and that this was consistent with the TRIBE study where the proportion resected after receiving a triplet chemotherapy regimen + bevacizumab was 36% (compared with 12% who were resected after receiving a chemotherapy doublet + bevacizumab) (Loupakis et al. 2014). The Committee considered that this suggested an additional 20% increase in resection rate from the use of triplet chemotherapy compared with doublet chemotherapy (not from the addition of bevacizumab).

9.29.1. The Committee noted that the authors reported survival according to resection outcomes as a sub-analysis, with 74 receiving a complete R0/R1 resection and having median OS of 44.3 months, while 131 who had chemotherapy plus bevacizumab but either no resection or an incomplete resection (ie R2) had an overall survival of 24.4 months (hazard ratio: 0.32, 95% CI: 0.22, 0.48; *P*<0.001). Members noted the OS of incomplete or non-

resected individuals was similar to the OS reported with FOLFOXIRI in the propensity score-adjusted analysis.

9.30. The Committee was made aware that the underlying evidence cited by the ESMO guidelines for conversion of potentially resectable metastatic disease indicates that FOLFOXIRI triplet provides better outcomes than the FOLFIRI doublet (Falcone et al. J Clin Oncol. 2007;25:1670-6), and that two of the cited trials included bevacizumab in both treatment arms as opposed to investigating its addition to chemotherapy in one treatment arm (Gruenberger et al. Ann Oncol. 2015;26:702-8; Loupakis et al. 2014).

9.31. The Committee noted the indicative selection of additional evidence for bevacizumab in the treatment of mCRC with liver-only metastases identified by a Pharmac staff literature search, which defined and split trial populations based on a range of disease characteristics. Of these trials, members specifically noted:

9.31.1. That the trials reporting outcomes from FOLFOX treatment reported survival benefits that were ~10% lower than those with the FOLFOXIRI triplet.

9.31.2. The randomised BECOME trial of 241 individuals with RAS-mutated mCRC with unresectable liver-only metastases who received median four cycles of pre-operative modified FOLFOX (mFOLFOX6) with or without bevacizumab (Tang et al. J Clin Oncol. 2020;38:3175-84). The authors reported a higher rate of R0 resections in the bevacizumab group vs the mFOLFOX6 alone group (27/121 [22.3%] vs 7/120, [5.8%]) and an OS benefit with bevacizumab in the overall cohort irrespective of resectability (25.7 months vs 20.5 months, respectively; HR 0.71; *P*=0.031). Acknowledging the regional variation in selection of patients for resection, the applicability of the results to the New Zealand context, obtained from the trial's stringent resectability criteria, is unclear.

9.31.3. The multicentre prospective ASSO-LM1 trial of 43 individuals with potentially curable mCRC who received (neo)adjuvant XELOX (oxaliplatin and capecitabine) with bevacizumab (Dong et al. Cancers (Basel). 2024;16:857). Members noted that this uncontrolled, hypothesis-generating study suggests (but cannot confirm) that there could be some benefit from adjuvant treatment post-resection.

9.32. The Committee considered that the evidence for bevacizumab in mCRC with liver-only metastases indicates that:

9.32.1. Triplet chemotherapy increases the rate of conversion to resectable disease compared with doublet chemotherapy, but the evidence is unable to inform whether adding bevacizumab increases the curative resection rate. Members noted that R0 resection rates for triplet chemotherapy plus bevacizumab ranged from 15-50%.

9.32.2. Progression-free survival (PFS) and OS benefits with bevacizumab are plausible based on indirect evidence (extrapolation from data reporting outcomes with triplet chemotherapy plus bevacizumab). Members noted that OS ranged from 22-33 months in whole cohorts with mCRC, including both resected and non-resected individuals, and was about 44 months in those with complete (R0/R1) resection.

9.33. The Committee noted that the ESMO guidelines (Cervantes et al. 2023) suggest:

9.33.1. Neoadjuvant bevacizumab treatment be given for eight weeks. Members noted that in clinical practice this is given for approximately two to three months and is limited by the need to preserve liver function, which can be reduced by irinotecan. Members were made aware of anecdotal reports of

an increased risk of peri-operative mortality with neoadjuvant bevacizumab, although considered this was based on rare patient cases that were not reflected in the small case series reported in the literature.

9.33.2. Adjuvant bevacizumab treatment be considered for those whose resection was incomplete or was intended but unable to occur. Members noted that there was no strong evidence to support this specific context which is, in effect, the treatment of metastatic disease.

Other subgroups

9.34. The Committee noted clinician correspondence that suggested that bevacizumab could be considered for three potential subgroups (detailed below), but no funding application had been received for these groups at this time. The Committee noted that the ESMO guidelines (Cervantes et al. 2023) depicted the three groups and cited supporting evidence for some of them, as follows:

9.34.1. First-line treatment of right-sided mCRC (regardless of mutational status). The Committee considered that this group would have an unmet need if cetuximab is funded as proposed for first- and second-line treatment of left sided, RAS and BRAF mutated colorectal cancer, given that those with right-sided mCRC would not be eligible for cetuximab. Members considered that bevacizumab in this setting appeared to be supported by moderate strength evidence from retrospective cohorts (not prospectively developed studies).

9.34.2. First-line treatment of RAS or BRAF mutated mCRC (regardless of primary tumour location). The Committee considered this subgroup would include those whose disease would be ineligible for cetuximab, and that some of this group (ie those with RAS-mutated disease) were targeted by the BECOME clinical trial (Tang et al. 2020). Members considered that bevacizumab in this setting appeared to be supported by moderate strength evidence from retrospective cohorts (not prospectively developed studies). The Committee considered it was unclear whether bevacizumab would actually be used in this population and suggested Pharmac seek advice from the New Zealand Gastrointestinal Special Interest Group (GISIG) on this patient group.

9.34.3. Second-line treatment of left-sided, RAS and BRAF wild-type mCRC, following treatment with cetuximab. The Committee noted that the ESMO guidelines (Cervantes et al. 2023) suggested second-line FOLFIRI-bevacizumab for left-sided disease after oxaliplatin-based first-line chemotherapy that is assumed to be given with cetuximab (although not explicit in the guideline) and noted that evidence for bevacizumab in this setting was not identified at the time.

9.35. The Committee noted that clinical guidelines are not always well supported by good quality evidence. The Committee was made aware that anecdotally, there is a clinical desire to offer a monoclonal antibody to people with mCRC and that bevacizumab is often suggested for those who are not eligible for cetuximab, although this is not necessarily evidence based. The Committee considered that more information would be needed to inform an assessment of these groups, including the intervention, clinically relevant outcomes and supportive evidence.

Evidence summary

9.36. The Committee noted that both the underlying chemotherapy regimen and literature informing treatment selection (based on a range of disease characteristics) had changed substantially since 2014. Further, the Committee considered it challenging to delineate potential benefits from bevacizumab given the potentially substantial variation in the treatment pathway.

9.37. Overall, the Committee noted that there is poor quality evidence of a small, incremental survival benefit and a small but clinically significant risk of gastrointestinal (GI) perforation with bevacizumab for mCRC, as noted by PTAC in 2010.

9.38. The Committee considered that colorectal cancer subgroupings are good example of an ongoing evidence challenge in oncology where patient cohorts are created retrospectively (unplanned subset analyses), resulting in an abundance of relatively poor-quality evidence. The Committee noted that such subgroups are commonly referred to in clinical guidelines and practice and that while these defined groups are based upon clinical trial data, they are not prospectively validated cohorts.

*General*

9.39. The Committee considered that, if bevacizumab were funded for mCRC, there could be substantial resource implications for infusion services in areas where it would be used.

9.40. Members considered that the impact of GI perforation would be substantial as this is a very significant adverse event.

9.41. The Committee considered that the uptake of bevacizumab would be highly uncertain and likely driven by clinician preference. The Committee considered that current use in private practice may indicate that surgery would be the preferred treatment. Members considered that use of neoadjuvant chemotherapy plus bevacizumab would be primarily based on individual clinician preference with substantial regional variation and more likely considered for those with borderline resectability or unresectable disease. The Committee considered that the duration of standard of care chemotherapy may be longer for the group of people who were not considered eligible for resection, noting the benefit from treatment with bevacizumab was unclear for this group.

9.42. The Committee considered it unclear where bevacizumab might provide the greatest benefit in mCRC and recommended Pharmac engage with the Gastrointestinal Cancers Special Interest Group (GISIG) and hepatobiliary surgeons to seek their advice and views on:

9.42.1. Which group(s) with mCRC would benefit from bevacizumab and what the intended clinical outcomes of treatment are

9.42.2. How people in the group(s) are currently managed clinically

9.42.3. Where bevacizumab would be used in the mCRC treatment paradigm and for how long

9.42.4. Which treatments (pharmaceutical or otherwise) bevacizumab would displace or reduce the use of (ie comparator/s)

9.42.5. Key evidence to support the use of bevacizumab in the desired setting.

## 10. Dabrafenib and trametinib for the treatment of melanoma, stage III resected or resectable

### Application

10.1. The Committee reviewed the application for dabrafenib and trametinib for the treatment of stage III resected or resectable melanoma.

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

## Recommendation

10.3. The Committee **recommended** that dabrafenib and trametinib for the treatment of stage III resected melanoma be funded with a **medium priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application - (resected stage III malignant melanoma)** only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has resectable or resected stage IIIB, IIIC or IIID melanoma; and
> 2. Treatment must be adjuvant to complete surgical resection; and
> 3. Treatment must be initiated prior to or within 13 weeks of surgical resection, unless delay is necessary due to post-surgery recovery; and
> 4. The patient has confirmed BRAF mutation; and
> 5. Patient must not have received prior systemic treatment in the neoadjuvant setting; and
> 6. [Dabrafenib/Trametinib] must be administered in combination with [dabrafenib/trametinib]; and
> 7. The patient has ECOG performance status 0-2.
>
> **Renewal - (resected stage III malignant melanoma)** only from a medical oncologist or on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of disease recurrence; and
> 2. [Dabrafenib/Trametinib] must be administered in combination with [trametinib/dabrafenib]; and
> 3. Treatment to be discontinued at signs of disease recurrence or at completion of 12 months total treatment course; and
> 4. Maximum of three renewals per patient.

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

10.4.1. the unmet health need related to recurrence of disease

10.4.2. recurrence is less likely with treatment with dabrafenib and trametinib, and individuals who do not experience recurrence following treatment have better health outcomes

10.4.3. the evidence of a survival benefit in individuals who received dabrafenib and trametinib.

## Discussion

*Māori impact*

10.5. The Committee discussed the impact of funding to dabrafenib and trametinib for people with stage III resected melanoma as proposed on Pharmac | Te Pātaka Whaioranga's Hauroa Arotahi | Māori health areas of focus and Māori health outcomes. The Committee discussed the impact of funding treatments for resected or resectable stage III melanoma, with and without BRAF mutations, on Māori health outcomes.

10.5.1. The Committee noted its previous discussions in April 2024 and noted that melanoma is not one of Pharmac's five Hauora Arotahi | Māori health areas of focus.

10.5.2. The Committee noted Māori are several times less likely to be diagnosed with melanoma than non-Māori even after adjusting for age (The State of Cancer in New Zealand 2020. Te Aho o Te Kahu the Cancer Control Agency, 2021). However, the Committee noted that Māori are more than twice as likely to die of their melanoma (adjusted for age; Te Aho o Te Kahu, 2021) and more likely to present with more advanced or metastatic disease compared with non-Māori (Robson et al. Ministry of Health, 2006).

10.5.3. The Committee previously considered that given the much lower incidence of melanoma for Māori the funding of BRAF/MEK inhibitors would likely have a relatively limited impact on health outcomes for Māori. The Committee noted that the literature suggests higher rates of acral melanoma in Māori, and there is a lower rate of BRAF mutations in acral melanoma compared with non-acral (Sneyd et al. Cancer Epidemiol Biomarkers Prev. 2009;18:1706-13), further limiting the impact funding BRAF/MEK inhibitors may have on Māori health outcomes.

*Populations with high health needs*

10.6. The Committee discussed the health need(s) of stage III resected melanoma among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee noted its previous considerations in April 2024, where the Committee noted a New Zealand study reported in Pacific peoples showed the population were less likely to have a BRAF mutation due to tumour type, but that 37% of melanomas in Pacific peoples were >4 mm thick at diagnosis compared with 7.9% in New Zealand Europeans indicating a poorer prognosis (Sneyd et al. 2009).

*Background*

10.7. The Committee noted it considered the use of BRAF/MEK inhibitors and immune checkpoints inhibitors for the (neo)adjuvant treatment of resectable melanoma in April 2024. Dabrafenib and trametinib were considered as part of this review. No formal recommendation was received for this treatment combination in the adjuvant setting.

10.8. The Committee recommended pembrolizumab for the adjuvant treatment of resected stage III melanoma with a low priority as part of the April 2024 review of melanoma.

*Health need*

10.9. The Committee noted its previous discussions in April 2024 regarding the health need of individuals with resected melanoma.

10.10. The Committee noted that 33-47% of melanomas had a BRAF mutation, with up to 85% of these being V600E mutations, with 10-20% associated with a V600K mutation (Long et al. J Clin Oncol. 2011;29:1239-46).

10.11. The Committee considered individuals with *BRAF* mutated melanomas could receive immunotherapy, but individuals with pre-existing autoimmune disease or poor performance status due to comorbidities may receive less benefit with this treatment compared to targeted treatment.

*Health benefit*

10.12. The Committee noted COMBI-AD, a double-blind, randomised (1:1), placebo-controlled trial including 870 individuals. Trial results were published in the following publications:

- Long et al. N Engl J Med. 2017;377:1813-23
- Schadendorf et al. Lancet Oncol. 2019;20:701-10
- Hauschild et al. J Clin Oncol. 2018;36:3441-9
- Dummer et al. Lancet Oncol. 2020;21:358-72
- Dummer et al. N Engl J Med. 2020;383:1139-48

- Long et al. N Engl J Med. 2024.

10.13. The Committee noted at the following results for COMBI-AD were reported at a median of 60 months follow up in the combination therapy group:

- 5-year Relapse-free survival (RFS) analysis: 52% (95% CI, 48 to 58) combination group alive without relapse vs 36% (95% CI, 32 to 41) placebo. Median RFS not reached with combination therapy (95% CI, 47.9 to NR) vs 16.6 months placebo (95% CI, 12.7 to 22.1) (HR, 0.51; 95% CI, 0.42 to 0.61). Results consistent across subgroups and stages incl. AJCC 8th Ed (post-hoc).
- Updated Distant metastasis–free survival (DMFS) analysis: 65% (95% CI, 61 to 71) combination group alive without distant metastasis vs 54% (95% CI, 49 to 60) placebo (HR, 0.55; 95% CI, 0.44 to 0.70); similar benefit for AJCC 7th Ed stages.
- Systemic therapy post-recurrence: received by 173/435 (40%) combination group and 232/432 (54%) placebo. Median interval between recurrence and subsequent therapy: 7.9 weeks. Most common subsequent treatment was immunotherapy for the combination therapy group (114 [26%]) and small-molecule targeted therapy for the placebo group (153 [35%]).

10.13.1. The Committee considered the results reported early and clear separation of the Kaplan-Meier curves, with effects lasting to five years of follow up.

10.13.2. The Committee considered some groups had higher risks, including those with increased size of tumour, node involvement or ulcerations. The Committee considered these groups would gain the most benefit from this treatment.

10.13.3. The Committee noted adverse events including fever, pyrexia, and photosensitivity. The Committee considered that whilst these were low frequency events, many individuals (38%) did have to reduce the dose, or interrupt treatment, whilst 26% discontinued due to toxicity. The Committee noted that shorter treatment duration could still result in clinical benefit. The Committee considered that photosensitivity is particularly important in the New Zealand setting.

10.13.4. The Committee noted that more individuals in the placebo arm had systemic therapy post recurrence, with some individuals rechallenged with another small molecular targeted therapy or an immunotherapy.

10.13.5. The Committee considered that whilst there were no overall survival results provided at five years of follow up, the difference in RFS was significant between the treatment and placebo arms. The Committee considered that most relapses occur within three years post resection.

10.14. The Committee noted at the following results were reported for COMBI-AD at a median of 8.33 years follow up in the combination therapy group and 6.87 years in the placebo group:

10.14.1. Kaplan–Meier estimates for overall survival were not statistically significantly different (hazard ratio for death, 0.80; 95% confidence interval [CI], 0.62 to 1.01; P=0.06 by stratified log-rank test).

10.14.2. A survival benefit was reported for several subgroups including individuals with a *BRAF* V600E mutation (hazard ratio for death, 0.75; 95% CI, 0.58 to 0.96).

10.14.3. RFS favoured dabrafenib plus trametinib over placebo (hazard ratio for relapse or death, 0.52; 95% CI, 0.43 to 0.63), as did DMFS (hazard ratio for

distant metastasis or death, 0.56; 95% CI, 0.44 to 0.71)

10.14.4. The Committee considered there was less benefit for those people with the *BRAF* V600K mutation, and that these individuals may be more sensitive to immunotherapy options due to a higher mutational burden.

10.15. The Committee noted that there were more second malignancies in the COMBI-AD treatment arm, however no deaths were attributed to these events. The Committee considered that these events did not account for a survival difference, and all events occurred within the first three years of follow up.

10.16. The Committee considered the benefits of treatment were maintained for over 8 years of follow up in COMBI-AD. The Committee considered that the overall survival curves began to converge late in the follow up period and may have been influenced by crossover, later line therapies, or by the clinical trial design. The Committee noted the small number of individuals in later years of the data. The Committee noted considered that Kaplan–Meier estimates for overall survival favoured dabrafenib plus trametinib over placebo, and therefore it was plausible there was an overall survival benefit.

10.17. The Committee noted the following systematic reviews and meta-analyses:

- Sharma et al. J Comp Eff Res. 2019;8:1349-63
- Longo et al. J Eur Acad Dermatol Venereol. 2020;34:956-66
- Toor et al. BMC Cancer. 2021;21:3.

10.17.1. The Committee noted that the meta-analyses compared the benefits of combination inhibitors compared with immunotherapies. The Committee considered that the studies reported the combination inhibitors to be at least as effective as immunotherapies, with one analysis indicating an overall survival benefit.

10.18. The Committee considered overall the evidence was of high quality to support the use of dabrafenib and trametinib in the adjuvant setting for resected stage III melanoma. The Committee considered overall the evidence would support most individuals with *BRAF* mutations receiving targeted therapy, with data suggesting better health outcomes than with primary immunotherapy.

10.19. The Committee considered overall in those with a *BRAF* mutated melanoma, the combination treatment would prevent relapse in approximately 15% of people. The Committee also considered the combination treatment does have significant toxicity and up to 26% of people could not complete the full 12 months of treatment.

10.20. The Committee considered that the adverse events from treatment would present more rapidly than with immunotherapies, however adjustment of dose or cessation of treatment would also result in a quicker reduction in symptoms compared to immunotherapies.

10.21. The Committee considered there was limited evidence to support retreatment with a *BRAF* targeted therapy in the metastatic setting if received in the adjuvant setting. However, the Committee noted one study reported a response rate with retreatment being 25% and with median PFS and OS times of 5.7 and 8.5 months respectively. Other studies have reported a higher response rate if individuals with metastatic disease stop treatment in remission, then relapse (Lee et al, Eur J Cancer. 2023:179:87-97). Overall, the Committee considered it may be appropriate for individuals to receive a BRAF/MEK inhibitor in the metastatic setting if they had previously received it in the adjuvant setting.

10.22. The Committee considered that if dabrafenib and trametinib were funded for adjuvant treatment of resected melanoma, the treatment paradigm would be amended to targeted BRAF/MEK treatment in first line, followed by immunotherapy if the cancer relapses and is unresectable, and then further targeted treatment if available. The Committee considered this would not change if an immune checkpoint inhibitor was available in the adjuvant setting.

10.23. The Committee noted that in the metastatic setting, BRAF/MEK therapy followed by immunotherapy resulted in reduced efficacy of immunotherapy. There was a lack of data on of how this may translate to adjuvant BRAF/MEK followed by immunotherapy at the metastatic setting.

*Suitability*

10.24. The Committee considered the oral administration of this treatment would not add additional pressure to infusion services.

10.25. The Committee noted a US study that reported the prevalence rates of pre-existing autoimmune comorbidities increased from 11.7% in 2004 to 19.8% in 2014 in individuals with non-metastatic melanoma, and from 7.9% in 2004 to 9.2% in 2014 in the general population (Ma et al. BMC Cancer. 2018;18:145).The Committee noted that not all of these would be absolute contraindications. The Committee considered that BRAF/MEK inhibitor treatment would be suitable for these individuals.

*Cost and savings*

10.26. The Committee considered many of these individuals would not currently be reviewed or treated by a medical oncologist. Therefore, there would be an increase in resource required for monitoring, and management of treatment, and any related toxicities. Initially this would require monthly visits for 2-13 months toxicity monitoring.

10.27. The Committee noted that the stage of melanoma at diagnosis is not possible to identify from registry data, and as such the estimates of numbers of eligible people are uncertain.

*Funding criteria*

10.28. The Committee considered those with higher risk disease including those with increased tumour size, node involvement or ulcerations would benefit most. In addition, the Committee considered people with melanomas that had the V600E mutation would benefit more than those with the V600K mutation however funding should not be restricted based on these criteria.

*Summary for assessment*

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

| | |
|---|---|
| **P**opulation | People with stage IIIB-D melanoma, with confirmed BRAF mutation, who have undergone surgical resection within the last 13 weeks. |
| **I**ntervention | Adjuvant treatment for melanoma in a regimen as follows:<br>• Dabrafenib capsules 150mg twice daily with trametinib capsules 2mg once daily (eviQ – melanoma adjuvant – dabrafenib and tramatenib). |

| | |
|---|---|
| | • Treatment initiated prior to or within 13 weeks of surgical resection.<br>Treatment to continue until disease progression or unacceptable toxicity, for a maximum of 12 months. |
| **C**omparator(s) (NZ context) | No adjuvant treatment (active surveillance following surgical resection) |
| **O**utcome(s) | Relapse-free survival favoured dabrafenib plus trametinib over placebo (hazard ratio for relapse or death, 0.52; 95% CI, 0.43 to 0.63)<br><br>Distant metastasis–free survival (hazard ratio for distant metastasis or death, 0.56; 95% CI, 0.44 to 0.71)<br><br>Improved OS, although the benefit was not significant (hazard ratio for death, 0.80; 95% confidence interval [CI], 0.62 to 1.01; P=0.06). CTAC noted this effect size was affected by crossover and subsequent treatments, and it is probable there is an OS benefit.<br>Long et al. N Engl J Med. 2024 |
| *Table definitions:*<br>**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)<br>**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).<br>**C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).<br>**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data. | |

## 11. Pegylated liposomal doxorubicin for the treatment of advanced epithelial ovarian cancer

### Application

11.1. The Committee reviewed the application for pegylated liposomal doxorubicin (PLD) for the third line treatment of advanced epithelial ovarian cancer, that is platinum resistant, or platinum sensitive/partially sensitive/ intolerant.

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

### Recommendation

11.3. The Committee **recommended** that pegylated liposomal doxorubicin (PLD) for the third line treatment of advanced epithelial ovarian cancer be **declined**.

11.4. In making this recommendation, the Committee considered:

- The lack of good quality trial data
- The lack of evidence to support health benefit.

### Discussion

*Māori impact*

11.5. The Committee discussed the impact of funding PLD for people with advanced epithelial ovarian cancer as proposed on Pharmac | Te Pātaka Whaioranga's Hauroa Arotahi | Māori health areas of focus and Māori health outcomes. The Committee discussed the impact of funding PLD for individuals with ovarian cancer. The Committee noted data from the Te Whatu Ora | Health NZ Cancer web tool that reported the rate of registrations of ovarian cancer between 2017 and 2021 was

higher for Māori than NZ European or Asian New Zealanders, with a rate of 4.83 per 100,000 compared with 3.34 and 2.74 per 100,000 respectively. In addition, the rate of deaths from ovarian cancer was also higher at 2.57 deaths per 100,000 compared with 1.21 and 1.95 respectively.

*Populations with high health needs*

11.6. The Committee discussed the health need(s) of people with advanced ovarian cancer among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee noted data from the Te Whatu Ora Cancer web tool between 2017 and 2021 reported that there was an increased number of registrations and deaths in Pacific peoples. The rate of cancer registrations was 5.45 diagnoses registered per 100,000 in Pacific peoples compared with 3.34 and 2.74 per 100,000 people in New Zealand European or Asian New Zealanders respectively. The rate of cancer deaths was also higher, with a rate of 2.65 per 100,000 compared with 1.21 and 1.95 per 100,000 people respectively. The Committee noted data from the Te Whatu Ora Cancer web tool that reported 30% higher age-standardised rates of ovarian cancer registrations in New Zealand between 2017 and 2021 in those living in higher socioeconomic deprivation quintiles (Relative Risk was 1.07/0.83 = 1.3 times more likely for those living the most deprived quintile 5 vs quintile 1).

*Background*

11.7. The Committee noted it had previously reviewed two applications for PLD for the treatment of advanced ovarian cancer; in individuals with platinum sensitive, or partially sensitive advanced ovarian cancer or individuals who were platinum intolerant, and in individuals who had advanced ovarian cancer that was platinum resistant.

11.8. The applications were last reviewed in 2012, and additional advice was sought on updated evidence and clinical guidelines.

*Health need*

11.9. The Committee noted PTAC discussed the health need of individuals in May 2022.

11.10. The Committee noted that ovarian cancer is often diagnosed at an advanced stage, due to early phases of the disease being largely asymptomatic. The Committee considered that the disease tends to have a relapsing remitting course, with many individuals receiving multiple rounds of palliative chemotherapy over years.

11.11. The Committee noted the European Society for Medical Oncology (ESMO) guidelines (González-Martín et al. Ann Oncol. 2023;34:833-48), which summarised the treatment paradigm for newly diagnosed epithelial ovarian cancer. The Committee considered that in New Zealand, tumour debulking surgery is undertaken if there is a high likelihood of achieving complete cytoreduction, followed by six cycles of chemotherapy with carboplatin and paclitaxel. This can be received in combination with bevacizumab, however this is not funded in New Zealand but was recommended for funding with a medium priority by PTAC in May 2022. The Committee considered those individuals where there is a low likelihood of success from debulking surgery would receive three cycles of with carboplatin and paclitaxel before being considered for interval cytoreductive surgery, before completion of the remaining three cycles of chemotherapy.

11.12. The Committee considered that following initial treatment and molecular testing, poly-ADP ribose polymerase (PARP) inhibitor maintenance treatment is an option.

Olaparib is advised for those who have germline BReast CAncer gene (BRCA) mutations, and niraparib is also funded for homologous recombination deficiency (HRD)-positive or -negative tumours, with varying degrees of benefit accordingly.

11.13. The Committee considered approximately 70% of people will relapse within two years of completing first line therapy. At recurrence the platinum status of the cancer is assessed, and treatment varies depending on if the person has had a prior response to platinum or has resistant disease or platinum cannot be tolerated.

11.14. The Committee considered those for whom platinum cannot be tolerated can be treated with hypersensitivity regimes, allowing successful treatment, however approximately 5% of people remain intolerant to platinum therapy despite hypersensitivity regimes. The Committee considered the second line treatment for individuals whose cancer is platinum sensitive would be carboplatin plus either paclitaxel or gemcitabine, and people with platinum-resistant cancer would receive monotherapy with either paclitaxel, gemcitabine or cyclophosphamide.

11.15. The Committee considered that those people for who platinum cannot be tolerated or whose disease is platinum-sensitive are considered similar in terms of disease status. The Committee considered that individuals who experience platinum intolerance would likely have different outcomes to people with platinum-resistant disease. The Committee considered that whilst neither group's diseases would respond to receiving platinum-based chemotherapy, the responsiveness to other cytotoxic agents may be different.

*Health benefit*

11.16. The Committee noted it had previously reviewed the Gordon et al Gynecol Oncol. 2004;95:1-8 study. The Committee considered the comparator of topotecan would not be used in the New Zealand setting. The Committee noted the progression free survival (PFS) and response rates were not significantly different between the treatment arms, but there was a 3 week overall survival (OS) difference favouring PLD that was statistically significant. The Committee noted a post-hoc subgroup analysis reported that the survival benefit was driven by the platinum-sensitive population. The Committee noted there was less neutropenia and thrombocytopenia in the PLD arm, but more mucositis and hand-foot syndrome.

11.17. The Committee noted it had previously considered the CALYPSO trial data (Wagner et al. Br J Cancer. 2012;107:588-91). The Committee noted that subsequently published subgroup analyses have reported that the PFS is not significantly different for individuals whose cancer is platinum sensitive, whilst another subgroup analysis of people with partially platinum sensitive cancers reported improved PFS with PLD in combination with carboplatin compared with carboplatin and paclitaxel. The Committee noted there were significantly lower rates of severe non-haematological toxicity in the experimental arm, driven mainly by a reduction in the rate of neuropathy. The Committee noted that CALYPSPO included both second- and third-line individuals and the evidence of OS and PFS includes both groups.

11.18. The Committee noted the Gibson et al. Oncologist. 2013;18:1022-31 meta-analysis, which reviewed randomised controlled trials to assess the efficacy and toxicity of PLD as a mono or doublet therapy. Three large trials that evaluated double therapy reported improvements in PFS but not in OS, and whilst there were differences in toxicity there was no overall evidence of improved tolerability. Of five monotherapy studies, there was no difference in PFS or OS reported for PLD in comparison to the gemcitabine, topotecan, canfosfamide or patupilone. The analysis reported equivalent PFS and OS overall, with only the Gordon trial reporting a positive OS. The Committee considered that overall, the study reported improved tolerability with PLD

monotherapy, with PLD associated with an increased risk of hand foot and mucositis but decreased risk of gastrointestinal toxicity and myelosuppression.

11.19. The Committee noted the Cochrane review (Newhouse et al. Cochrane Database Syst Rev. 2023;7:CD006910) that was updated in 2023. The review reported the following results:

- PLD offered no OS gain but did provide a PFS gain for individuals with platinum sensitive cancers
- PLD offered no OS gain and likely no PFS gain in individuals whose cancers are platinum resistant
- overall quality of life was slightly superior in the PLD arm three months after randomisation, however the study authors questioned if this was clinically meaningful
- no quality-of-life information was available for individuals whose cancer was platinum resistant.

11.20. The Committee noted the following studies:

- Motohashi et al. J Gynecol Oncol. 2021;32:e9
- Fujiwara et al. Int J Clin Oncol. 2019;24:1284-91
- Staropoli et al. Cancer Biol Ther. 2014;15:707-20
- Li et al. J Ovarian Res. 2021;14:42
- Jiang et al. Oncotarget. 2017;8:19125-36
- Qu et al. Medicine (Baltimore). 2017;96:e5797.

11.21. The Committee considered overall in platinum sensitive cancer, there was some evidence of a modest PFS advantage (approximately two months) with carboplatin in combination with PLD, in comparison to carboplatin in combination with paclitaxel. There is no evidence of any OS benefit in this population. The Committee noted that PLD has a lower rate of neuropathy, which can be long lasting and, in some cases, permanent. The Committee considered the evidence for doublet carboplatin-PLD treatment to be of reasonable quality, with a large non-inferiority RCT and multiple meta-analyses giving consistent results.

11.22. The Committee considered overall in individuals whose cancer is platinum resistant, there was no evidence of superiority of PFS nor OS. The Committee considered as a monotherapy there was evidence to suggest PLD may be more tolerable than other agents including gemcitabine and topotecan which are used in the New Zealand context. The Committee considered the strength of the evidence in the platinum resistant setting to be weaker than for the doublet platinum sensitive context.

*Suitability*

11.23. The Committee noted the infusion time of PLD was reduced compared to paclitaxel, with an infusion time of 60 minutes compared to three hours. The Committee noted the infusion time of PLD was similar to other chemotherapeutic agents including carboplatin and gemcitabine. For individuals receiving paclitaxel, PLD might represent a reduction in time spent away from whānau and paid employment.

*Cost and savings*

11.24. The Committee considered all individuals with stage III and IV ovarian cancer would be treated with chemotherapy.

11.25. The Committee considered up to 70% would receive treatment in second line. In those individuals who are platinum intolerant who have relapsed >6 months from previous platinum, the combination of trabectedin and PLD may be recommended or a single agent non platinum based chemotherapy including weekly paclitaxel, PLD, topotecan or gemcitabine. In individuals at first relapse who remain responsive to platinum therapies, surgery may be considered, followed by platinum-based doublet therapy including paclitaxel, PLD or gemcitabine.

11.26. The Committee considered PLD would be used for individuals whose cancers are platinum intolerant at the point of developing platinum intolerance (regardless of what line this is). The Committee considered the incidence of intolerance rises with repeated exposure to platinum, most commonly for carboplatin being the eighth dose (second dose of second line therapy). The Committee considered PLD would likely be used in second or third line for platinum sensitive ovarian cancer. The Committee considered PLD would be used as 'later line' therapy for platinum resistant ovarian cancer.

*Summary for assessment*

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

PICO for PLD if it were to be funded in New Zealand for ovarian cancer, advanced, epithelial, recurrent, platinum resistant

| | |
|---|---|
| **P**opulation | • Ovarian cancer, advanced, epithelial, recurrent, platinum resistant<br>• Individuals who have platinum resistant disease have less than 6 months between the completion of platinum-based treatment and the detection of relapse, ie platinum-free interval (PFI) |
| **I**ntervention | • Pegylated liposomal doxorubicin 50mg/m$^2$ every 4 weeks, capped at a maximum of 6 cycles (or progression) |
| **C**omparator(s)<br><br>(NZ context) | • Monotherapy chemotherapy:<br>  • paclitaxel<br>  • cyclophosphamide (oral)<br>  • gemcitabine 1000mg/m2 on days 1 and 8 of each 21-day cycle. |
| **O**utcome(s) | • Little to no difference in OS gain (HR 0.96, 95% CI 0.77 to 1.19; 6 studies, 1995 participants; moderate-certainty evidence).<br>• Much uncertainty in the evidence about the effect of PLD on PFS (HR 0.94, 95% CI 0.85 to 1.04; 4 studies, 1803 participants; very low-certainty evidence) (Newhouse et al. 2023) |

*Table definitions:*
**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)
**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
**C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

PICO for PLD if it were to be funded in New Zealand for ovarian cancer, advanced, epithelial, recurrent, platinum sensitive/ partially sensitive/ intolerant

| | | |
|---|---|---|
| **P**opulation | • Ovarian cancer, advanced, epithelial, recurrent platinum sensitive/ partially sensitive/ intolerant,<br>• Individuals who have platinum sensitive disease and have more than 6 months between the completion of platinum-based treatment and the detection of relapse, known as the platinum-free interval (PFI) | |
| **I**ntervention | **Platinum sensitive, platinum partially sensitive**<br>• carboplatin (auc dosing) plus<br>• pegylated liposomal doxorubicin 30mg/m$^2$ every 4 weeks, capped at a maximum of 6 cycles (or progression) | **Platinum intolerant** (cannot be salvaged through hypersensitivity regime, 5% of people with ovarian cancers)<br>• pegylated liposomal doxorubicin 50mg/m$^2$ every 4 weeks, capped at a maximum of 6 cycles (or progression) |
| **C**omparator(s)<br>(NZ context) | • carboplatin (auc dosing) plus<br>• paclitaxel 175mg/m$^2$ every 3 weeks or<br>• gemcitabine | • Monotherapy chemotherapy<br>• Paclitaxel<br>• Cyclophosphamide (oral)<br>• gemcitabine 1000mg/m2 on days 1 and 8 of each 21-day cycle. |
| **O**utcome(s) | • Increased PFS of 11.3 months vs current 9.4 months on carboplatin + paclitaxel<br>• Resultant HRQoL benefit. | • Uncertain, no literature on platinum intolerant alone.<br>• Individuals can't receive platinum based regime but their disease may respond better to other regimes than those with platinum resistant disease (where people with platinum resistant disease are often at the end of the disease course) |

*Table definitions:*
**P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)
**I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).
**C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).
**O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

## 12. Renal cell carcinoma treatment paradigm

## Application

12.1. The Committee reviewed the treatment paradigm for metastatic renal cell carcinoma (mRCC), and relative health benefits of different treatments.

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

## Discussion

*Māori impact*

12.3. The Committee discussed the impact of funding treatments of mRCC on Māori health areas of focus and Māori health outcomes. The Committee noted in July 2023 the higher incidence of cases in Māori, who also present at an earlier age (at an average of 52 years old compared to 63 years old in the general population) (Delahunt et al Urology. 1994;43:300-9). The Committee previously noted in 2017 the Effect of Comorbidity on Care and Cancer Survival Inequalities Study – known as the C3 (Quantitative) study – conducted by the University of Otago in 2014 that reported Māori with kidney cancer were 52% more likely to die of their cancer than non-Māori (HR: 1.52; 95% CI, 1.01 to 2.29) (Sarfati et al. 2014. Wellington: University of Otago).

*Populations with high health needs*

12.4. The Committee discussed the health need(s) of mRCC among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding treatments for mRCC, and noted it had previously considered in July 2023:

12.4.1. Whilst there was no evidence to suggest a difference in prevalence in Pacific peoples, these individuals may have more comorbidities that exclude them from current therapy options.

12.4.2. Within New Zealand people living in the most socioeconomically deprived areas have a reduced survival time, independent of the stage of disease compared to those from less deprived areas (Jeffreys et al. Cancer Epidemiol Biomarkers Prev. 2009;18:915-21).

*Background*

12.5. The Committee noted it had previously reviewed the first- and second-line treatment paradigms, as well as provided recommendations for different therapeutics. Since this time, nivolumab for the second-line treatment of mRCC has been funded. Advice was sought on the relative health benefit of the different treatments, and how treatment paradigms could be impacted.

12.6. The Committee noted feedback had been received from the Genitourinary Special Interest Group (GU SIG) regarding the benefit of different treatments. The Committee noted the GU SIG's top priority of having either an immunotherapy (IO-IO) combination (ie nivolumab and ipilimumab) and an IO-tyrosine kinase inhibitor (TKI) combination, noting that it would be preferential to have access to both IO-IO and IO-TKI for clinicians and the individual to choose the most suitable option.

12.7. The Committee noted that PTAC recently reviewed applications for the use of pembrolizumab in combination with either axitinib or lenvatinib in the first line treatment of advanced mRCC in May 2024. PTAC recommended the axitinib combination with a medium priority, and the lenvatinib combination with a low priority, both for individuals with intermediate and poor prognosis. The Committee noted feedback had been received from the supplier of pembrolizumab.

12.8. The Committee were made aware of a consultation to widen access to pazopanib and sunitinib to individuals with a favourable prognosis. The Committee were also made aware of a consultation to fund lenvatinib in combination with everolimus for the second line treatment of mRCC.

*Health need*

12.9. The Committee noted pazopanib or sunitinib were currently funded for the first line treatment of individuals with intermediate or poor prognosis kidney cancer with a clear cell component, with one switch allowed in the first three months for intolerance. The Committee noted nivolumab will be funded for the second line treatment from 1 November 2024. The Committee noted there are currently no treatments funded for the first line treatment of individuals with favourable prognosis kidney cancer with a clear cell component but that access to pazopanib and sunitinib for this group was being consulted on.

12.10. The Committee noted the European Society for Medical Oncology (ESMO) updated guidelines (Powles et al. Ann Oncol. 2024;35:692-706). The Committee considered that currently in New Zealand most people with favourable prognosis are monitored until their disease progresses to intermediate or poor prognosis when they are treated with sunitinib or pazopanib.

*Health benefit*

First line

12.11. The Committee noted that PTAC and the Committee had reviewed health benefit evidence for first- and second-line treatments in May 2024 and July 2023 respectively.

12.12. The Committee noted the Cochrane systematic review and network meta-analysis (Aldin et al. Cochrane Database Syst Rev. 2023;5:CD013798).

12.12.1. The Committee noted when comparing the first line therapies the trials were in comparison to sunitinib, with no inter-agent comparisons. The Committee considered all trials had a high risk of bias, and the data cut off for inclusion in the analysis was 2022.

12.12.2. The Committee noted there was some variation in the hazard ratio of overall survival (OS) benefit when comparing each of the treatments to sunitinib across all risk groups combined.

12.12.3. The Committee considered that in the combined risk groups when comparing pembrolizumab in combination with either lenvatinib or axitinib, there was more data to support the health benefit for axitinib, providing more certainty of benefit, however there was a lower overall survival (OS) benefit in comparison to lenvatinib. The Committee considered whilst the lenvatinib combination reported a better OS benefit, there was less certainty of the benefit, with less mature data available. The Committee considered that the hazard ratio (HR) for overall survival benefit, when compared to sunitinib, for nivolumab in combination with ipilimumab was 0.69 (0.69-1.00), for pembrolizumab axitinib the HR was 0.73 (0.50-1.07) and for pembrolizumab lenvatinib the HR was 0.66 (0.42-1.03).

12.12.4. The Committee considered there was sparser evidence for the use of the treatments in favourable prognosis disease. The Committee considered risk factors were a stratifying factor when randomising individuals, to balance arms in the trials. The Committee considered that subgroup analyses were generally reported, and post-hoc, without being powered for specific differences or not reported. The Committee considered the hazard ratios of

the treatments were very similar in this prognosis group. The Committee noted that subgroup analyses were not reported for pembrolizumab in combination with axitinib trial data.

12.12.5. The Committee noted that in the intermediate/poor risk group pembrolizumab in combination with lenvatinib had an overall survival OS HR of 0.55 (0.33-0.91) compared with nivolumab in combination with ipilimumab HR 0.65 (038-1.10).

12.12.6. The Committee noted that quality of life comparison data was not available for many of the trial studies comparing treatments including pembrolizumab in combination with axitinib, nivolumab in combination with cabozantinib, pembrolizumab in combination with lenvatinib, and nivolumab in combination with ipilimumab.

12.12.7. The Committee considered the frequency of serious adverse events of all treatments was slightly increased compared to sunitinib across all treatments compared.

12.12.8. Overall, the Committee considered that the Cochrane meta-analysis reported that pembrolizumab in combination with lenvatinib or axitinib have a similar OS, however there was less certainty in the data for axitinib. Nivolumab in combination with ipilimumab offers a similar OS benefit, with a similar toxicity profile to pembrolizumab in combination with either lenvatinib or axitinib.

12.13. The Committee noted a network meta-analysis that compared first line immunotherapy combinations (Lombardi et al. Cancer Treat Rev. 2022:106:102377).

12.13.1. The Committee noted this compared the treatments in comparison to sunitinib.

12.13.2. The Committee considered many of the treatments ranked similarly for OS including cabozantinib in combination with nivolumab, lenvatinib in combination with pembrolizumab, nivolumab in combination with ipilimumab, and pembrolizumab in combination with axitinib. The Committee noted all of these combinations reported a survival benefit in comparison to sunitinib.

12.13.3. The Committee noted that overall, the analysis ranked lenvatinib in combination with pembrolizumab as first for overall survival benefit, followed by cabozantinib in combination with nivolumab, nivolumab in combination with ipilimumab and pembrolizumab in combination with axitinib with surface under the cumulative ranking (SUCRA) ranging from 80.7% to 65.6% respectively. The Committee noted the outcome of safety of these combinations was seventh, fifth, first and sixth respectively with SUCRA of 10.9%, 38.4%, 96.0% and 36.5% respectively.

12.14. The Committee considered there was inherent bias in reporting of toxicity data in trials which might influence the analysis. The Committee considered immunotherapy related adverse events may appear later than those related to TKIs with events lasting longer, and be more challenging to manage. The Committee considered the trial design and toxicity metrics may underestimate these in the longer term, and underestimate later appearing toxicities, in immunotherapy trials.

12.15. Overall, the Committee considered any of cabozantinib in combination with nivolumab, nivolumab in combination with ipilimumab, or pembrolizumab in combination with either axinitib or lenvatinib in the first line setting would address unmet health needs for individuals with intermediate or poor prognosis.

12.16. The Committee considered that having both IO-TKI and IO-IO available in the first line setting would be useful to allow for clinicians to choose between prescribing an IO-IO or IO-TKI combination as a first line treatment option, dependent on the individual's needs. The Committee considered that it would be difficult to define which individuals would benefit from a particular combination over others through eligibility criteria, and this would be determined by the treating clinician.

12.17. The Committee considered overall there was weak clinical trial evidence to support treatment of individuals with favourable prognosis disease. The Committee considered the evidence of treatment compared to monitoring alone was sparse. The Committee considered many of the individuals would be monitored until progression and treated in the intermediate or poor risk groups, where at this stage they would be treated with an immunotherapy combination if funded.

Second line

12.18. The Committee noted clinical trial data that reported variable response rates to second line treatment depending on what treatments were received in the first line setting (Sammarco et al. Cancers (Basel). 2023;15:3172). The Committee considered these trials were mostly in phase II, with a limited number of phase III trials in progress. The Committee considered this data would not be available for a number of years. The Committee considered at present, there was limited data on the health benefit of sequential treatment options, however the guidelines recommend sequencing options based on IIIB rated evidence. The Committee considered there is currently no strong evidence to guide sequencing.

12.19. When considering the consultation to widen access to sunitinib to individuals with a good prognosis, the Committee considered there is limited data to support treatment with a combination IO-TKI second line if individuals received sunitinib (or other TKI) in the first line setting. The Committee considered it would be reasonable to restrict IO-IO or IO-TKI to those people who are treatment naïve in the metastatic setting .

12.20. The Committee considered there was weak evidence from phase I and II trials that supports the use of nivolumab second line if the person was treated with an IO first line. The Committee considered overall the data reports a significantly reduced overall response rate, but prolonged PFS duration of response when individuals are treated with a combination IO-IO, or IO – novel TKI following progression on an IO monotherapy or IO-TKI. The Committee therefore considered the health benefit of a second line IO monotherapy was unclear. The Committee considered it would be appropriate to restrict second line IO to those who have not been previously treated with IO.

12.21. The Committee considered there was limited evidence to support rechallenge with a particular TKI, and therefore did not consider it appropriate to rechallenge with the same TKI in later lines of therapy.

12.22. The Committee considered there was limited evidence to support TKI rechallenge following progression on an intermediary agent with re-acquisition of TKI sensitivity for example when a MEK inhibitor is used following the initial TKI. The Committee considered this was based on case series evidence (Grunwald et al. Onkologie. 2011;34:310-4). The Committee considered there was an assumption that the resistance mechanism for the first line TKI would be similar across all TKIs, unless treated with an intermediary agent. The Committee considered overall it was not appropriate to rechallenge with the same TKI in later lines of therapy.

12.23. The Committee considered most people would receive either an IO-IO or IO-TKI first line if it was funded. The Committee considered the choice of second-line therapy would depend on the first line treatment used. The Committee noted the evidence to support this is weak, with the evidence in the ESMO guidelines rated as III B

evidence. The Committee considered there was no strong evidence to support selection of third line or later treatments and considered it would be appropriate to restrict the use of TKI monotherapy to the second line setting only, in line with previous considerations and recommendations for lenvatinib-everolimus and axitinib. The Committee stated it would welcome a funding application for third line (or later) use of these agents should evidence to support this use becomes available. The Committee noted that international guidelines recommended the use of TKIs that had not been tried for the patient previously, however considered there was insufficient evidence to support a clinically meaningful benefit.

12.24. The Committee considered that progression onto second line is based on disease progression rather than IMDC risk score.

12.25. The Committee considered there is no strong evidence to support the use of an IO monotherapy in second line, where an IO in used in the first line setting. The Committee considered there is no strong evidence to support the use of an IO in second line if an IO-IO in used in the first line setting. The Committee considered there is weak evidence to support the use of an IO-IO in second line if an IO-TKI is used in the first line, however there is an expectation that this would result in a low response rate but would be expected to result in a PFS response in some individuals. The Committee considered it would be reasonable to use a TKI in second line following progression on an IO-IO combination therapy in the first line setting.

*Suitability*

12.26. The Committee considered that an IO-TKI would have suitability advantages compared to an IO-IO as the combination was easier to adjust dose to manage toxicity.

12.27. The Committee considered that the TKI dose received by each individual changes over time, with doses reduced to minimize toxicity. The Committee noted that TKIs are supplied in multiple strengths to allow for dose titration.

*Cost and savings*

12.28. The Committee considered it would be difficult to estimate uptake, however global data has reported that IO-TKI combinations have increased uptake (approximately 80%) compared with other therapies, with approximately 10% receiving an IO-IO combination. The Committee considered the lower IO-IO uptake was driven by concerns regarding tolerance of the drug including in those who are older or have poorer prognosis status. The Committee noted that this data does not stratify by prognosis factor(s) and this data does vary compared with international guidelines.

12.29. The Committee considered that treatment uptake would be unlikely to be 100%. The Committee considered that given the adverse event profiles of the treatment, some would not receive treatment due to their clinical status. The Committee considered the uptake would occur earlier for individuals with a favourable prognosis who would currently receive treatment post transition to an intermediate or poor prognosis. The Committee considered over time the number of individuals treated would be similar, however the timing would vary based on which groups were funded.

12.30. The Committee considered that if funded cabozantinib, axitinib and/or lenvantinib in combination with everolimus would be the likely preferred second line treatment option due to improvements in survival outcomes compared to sunitinib and pazopanib.

12.31. The Committee considered the funding of consider cabozantinib in combination with nivolumab, nivolumab in combination with ipilimumab and pembrolizumab in combination with either axinitib or lenvatinib would provide similar health benefits in the first line setting in individuals with an intermediate or poor prognosis.

12.32. The Committee considered there would be a good proportion of people who would progress to third line treatment.

*Summary for assessment*

12.33. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for first line mRCC treatments if they were to be funded 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 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 previously untreated advanced clear-cell renal cell carcinoma (mRCC), with an intermediate risk or poor prognosis. |
| Intervention | *Pembrolizumab with axitinib or lenvatinib*<br><br>Pembrolizumab 200mg administered via thirty to sixty minute intravenous infusion every three weeks (some may receive six weekly 400mg doses) until disease progression, unacceptable toxicity, for a maximum of two years, plus one of:<br><br>- Oral axitinib 5mg twice per day<br><br>- Oral lenvatinib 20mg once per day<br><br>*Nivolumab with ipilimumab*<br>Induction - Nivolumab 3mg/kg combined with ipilimumab 1mg/kg administered via intravenous infusion every three weeks for four doses.<br><br>Maintenance - Nivolumab 3mg/kg administered via intravenous infusion every two weeks until disease progression or unacceptable toxicity.<br><br>*Nivolumab with cabozantinib*<br>Nivolumab 3mg/kg administered via intravenous infusion every two weeks until disease progression or unacceptable toxicity, in combination with oral cabozantinib 40mg once daily. |
| Comparator(s) | • Oral sunitinib 50mg once daily for four weeks, followed by two weeks 'rest period' continued until disease progression or unacceptable toxicity, for a maximum of two cycles.<br>• Oral pazopanib 800mg taken once per day until disease progression or unacceptable toxicity, for a maximum of three months. |
| Outcome(s) | • Longer overall survival, possibly confounded by subsequent treatments.<br>• Longer progression-free survival, which is likely to be associated with improved health-related quality of life (HRQoL)<br><br>Comparable survival outcomes and adverse event profiles between the different combination regimes compared to sunitinib. |
| 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. Asciminib for Ph+ CML in chronic phase, previously treated with two or more tyrosine kinase inhibitors

## Application

13.1. The Committee reviewed the application for asciminib in the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase (Ph+ CML), previously treated with two or more tyrosine kinase inhibitors.

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

## Recommendation

13.3. The Committee **recommended** that asciminib be listed for the treatment of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase with a **high priority,** within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **Initial application – (Philadelphia chromosome-positive chronic myeloid leukaemia).** Applications only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has a diagnosis of Philadelphia chromosome-positive chronic myeloid leukaemia in chronic phase; and
> 2. Any of the following:
>  2.1. Patient has documented CML treatment failure with at least two tyrosine kinase inhibitors (TKIs); or
>  2.2. Patient has documented CML treatment failure with at least one TKI and developed an intolerance to another TKI; or
>  2.3. Patient has experienced treatment limiting toxicity with a TKI precluding further treatment with other TKIs; and
> 3. Subsidised for use as monotherapy only.
>
> **Renewal – (Philadelphia chromosome-positive chronic myeloid leukaemia).** Applications only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. Lack of treatment failure while on asciminib as defined by Leukaemia Net Guidelines; and
> 2. Subsidised for use as monotherapy only.
>
> Note: *treatment failure as defined by Leukaemia Net Guidelines

13.4. When making this recommendation the Committee considered the following:

13.4.1. The small number of people who have an unmet health need following treatment with other currently funding TKIs.

13.4.2. The efficacy of asciminib in the third or fourth line setting and in those who have the T315I mutation.

## Discussion

*Māori impact*

13.5. The Committee discussed the impact of funding asciminib for the treatment of CML on Māori health areas of focus Hauora Arotahi and Māori health outcomes. The Committee noted there is no evidence available to report on inequities regarding health outcomes in this setting.

*Populations with high health needs*

13.6. The Committee discussed the health need(s) of CML among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified

by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding asciminib, and noted or considered:

13.6.1. Tracey & Carter. Am J Hematol. 2005;79:114-8, a New Zealand Cancer Registry analysis, reported the relative risk of CML being 2.31 in Pacific peoples aged 25-49 years and 1.52 in Pacific peoples aged 50-74 years when compared with of NZ Europeans.

13.6.2. There is no evidence available to understand inequities regarding health outcomes in other populations with high health needs.

*Health need*

13.7. The Committee noted chronic myeloid leukaemia (CML), a myeloproliferative neoplasm characterised by uncontrolled growth of myeloid cells in the bone marrow and accumulation of these cells in the blood, accounts for approximately 15%–20% of all cases of leukaemia in adults (Soverini et al. Oncologist. 2016;21:626-33).

13.8. The Committee noted Philadelphia chromosome-positive (Ph+) CML is the consequence of the fusion between the Abelson tyrosine kinase (*AB1*) gene at chromosome 9 and break point cluster region (*BCR*) housekeeping gene at chromosome 22, resulting in the *BCR::ABL1* oncogene and the constitutively active BCR-ABL tyrosine kinase.

13.9. The Committee noted the disease course of CML is divided into three phases (chronic, accelerated and blast), distinguished by the level of abnormal immature white blood (blast) cells present in the blood or bone marrow. The earliest is the chronic phase which can last for months or years and represents the condition of approximately 85% of newly diagnosed patients (Faderl et al. N Engl J Med. 1999;341:164-72). In this stage the disease may have few or no symptoms during this time. Chronic-phase (CP) CML is characterised by the presence of less than 10% blast cells in the peripheral blood and bone marrow (Haznedaroglu et al. Turk J Haematol. 2020;37:42-7).

13.10. The Committee considered that around 1-2% of people with CP-CML will require an allogeneic stem cell transplant.

13.11. The Committee noted following the introduction of TKIs, CML prognosis is estimated by the European Treatment and Outcome Study (EUTOS) score, which predicts for cytogenic response, based on the percentage of basophils in the blood and spleen size.

13.12. The Committee noted that polymerase-chain reaction (PCR) assays are used to determine the *BCR::ACL1* mutation type and the number of copies of BCR::ACL1 mRNA in blood cells compared to a control gene, generating the International Standardised ratio (IS).

13.13. The Committee noted treatment response is measured in logarithmic reduction in leukemic cells. A haematologic response is characterised by the blood cell count returning to normal range, the spleen returning to normal size and a 10-fold reduction in the level of cells with the *BCR::ABL1* gene (10% of cells have the BCR::ABL1 gene). A 100-fold reduction is termed a cytogenetic response. The primary endpoint of the trials is a major molecular response (MMR) meaning there has been a 1000-fold (log 3) reduction.

13.14. The Committee noted that following introduction of imatinib for the treatment of CML, the life expectancy of people with CML normalised to that of the general population (Bower et al. J Clin Oncol. 2016;34:2851-7; Hochhaus et al. N Engl J Med. 2017;376:917-27; Kalmanti et al. Leukemia. 2015;29:1123-32). The Committee

considered that, based on these studies, it is appropriate to use major molecular response as a surrogate marker for overall survival.

13.15. The Committee noted the three tyrosine kinase inhibitors (TKIs) are available on the Pharmaceutical Schedule for the treatment of chronic-phase (CP) CML. Imatinib is used in the first line, dasatinib in the first line for people considered high-risk as per the KISS study (study is currently active but no longer recruiting) otherwise second or third-line, and nilotinib either second or third-line. The Committee considered that around 50% of people with CP-CML will experience MMR and be eligible for a treatment holiday and about 50% of those will not require treatment for a median of seven-years. The Committee considered that looking at the cohort as a whole, the current TKI options are meeting most health needs.

13.16. The Committee considered that there is an unmet health need for a small number of people who experience treatment resistance or intolerance to the currently funded options and have no further TKI treatment options. At this time, interferon therapy and chemotherapy are the available options. The Committee considered these to be obsolete and to have lower efficacy and higher toxicity compared to TKIs.

13.17. The Committee noted Pharmac has received applications for the funding of asciminib and ponatinib for people with CML that is treatment resistant or for whom the currently funded TKI treatments cannot be tolerated and who are not likely to be eligible for stem cell transplant through the Named Patient Pharmaceutical Assessment (NPPA) pathway.

13.18. The Committee considered that as this is a rare disease there is no data available regarding the incidence of Ph+ CML, TKI intolerance/resistance, transplant referral/completion among Māori. Members considered there to be less opportunity for Māori to find a match for an allogenic stem cell transplant, and Māori face barriers to access this treatment including lower referral rates from primary care.

13.19. The Committee noted Tracey & Carter. Am J Hematol. 2005;79:114-8 a New Zealand Cancer Registry analysis which reported that the relative risk of CML is 2.31 in Pacific peoples aged 25-49 years and 1.52 in Pacific peoples aged 50-74 years when compared with the risk of New Zealand Pākehā. Members considered there to be less opportunity for Pacific peoples to find a match for an allogenic stem cell transplant, and Pacific people face barriers to access this treatment including lower referral rates.

13.20. The Committee considered that there is no data on incidence, morbidity, survival inequities among other groups with high health needs.

13.21. The Committee noted a mechanism of resistance is emerging in the *BCR::ABL1* mutation. The *T315I* mutation is among the most frequently identified *BCR::ABL1* mutations, occurring in 2% to 16% of patients with imatinib- or second-generation TKI-resistant CML and increasing in frequency with subsequent lines of therapy.

*Health benefit*

13.22. The Committee noted asciminib is an inhibitor of ABL/BCR::ABL1 tyrosine kinases. Asciminib inhibits the ABL1 kinase activity of the BCR::ABL1 fusion protein by specifically targeting the ABL myristoyl pocket.

13.23. The Committee noted the Hughes et al. N Engl J Med. 2019;381:2315-26 open-label, non-randomised phase 1 study in those with CP (n=141), accelerated phase (n=9) Ph+ CML treated with asciminib 10-200mg once or twice daily to determine maximum tolerated dose and/or recommended dose.

13.23.1. At 12-months the MMR rate was 48%, in those with the T315I mutation the rate was 28%.

13.23.2. 40 patients discontinued treatment and one person died due a blast crisis.

13.23.3. 60% of patients had a grade 3 or 4 adverse event.

13.24. The Committee noted the ASCEMBL multicentre, open-label, 2:1 randomised, phase 3 study in those with CML-CP which was resistant or intolerant to ≥2 TKI treatments. Individuals received either asciminib 40 mg twice daily (*n* = 157) or bosutinib 500 mg daily (*n* = 76).

13.24.1. The Committee noted the Rea et al. Blood. 2021;138:2031-41 publication, which reported ASCEMBL trial results at a median follow up of 14.9 months:

- At 24-weeks the MMR rate was 25.5% with asciminib and 13.2% with bosutinib (adjusted difference 12.2%; 95% CI 2.19, 22.3; 2-sided test p=0.029).

13.24.2. The Committee noted the Hochhaus et al. Leukemia. 2023;37:617-26 publication, which reported the ASCEMBL trial results at a median follow up of 2.3 years:

- At 96-weeks the MMR rate was 37.6% with asciminib and 15.8% with bosutinib (adjusted difference 24.74%; 95% CI 10.53, 32.95; 2-sided test p= 0.001).

13.24.3. The Committee considered that there may be potential bias within the study due to randomised treatment arms not being well balanced.

13.25. The Committee noted the ASC4FIRST multicentre, 1:1 randomised, phase 3 study in those with CML-CP who have not previously received treatment. Individuals received asciminib (*n*=204) or investigator selected TKI (*n*=204).

13.25.1. The Committee noted the Hochhaus et al. N Engl J Med. 2024;391:885-98 publication, which reported the ASC4FIRST trial results at a median follow up of 16.3 months for the asciminib group and 15.7 months for the investigator-selected TKI.

- At 48-weeks the MMR rate was 67.7% with asciminib and 49% with investigator-selected TKI (difference 18.9%; 95% CI 9.6,28.2; adjusted two-sided p< 0.001).
- Discontinuation rate was 13% for asciminib and 30% for investigator selected TKI.
- Grade 3 adverse events rate was 5.5% for asciminib and 10.3% for investigated selected TKIs.

13.26. The Committee considered the asciminib health benefit evidence to be of reasonably high quality, concluding that asciminib is superior to bosutinib (which is known to be effective in individuals exposed to at least two previous TKIs) in the third line setting.

13.27. The Committee considered that individuals who have experienced resistance or intolerance to the currently funded options and those with a T315I mutation would benefit most from asciminib. The Committee considered due to ponatinib unfavourable cardiovascular profile, asciminib would be more preferable.

13.28. The Committee considered that asciminib provides additional health benefit to individuals with CP-CML:

13.28.1. The Committee considered that if an individual starts on imatinib, then third line treatment is nilotinib or dasatinib. The Committee considered asciminib to have comparable efficacy and toxicity to these agents, however notes there are different side effects associated with each agent. The Committee considered that asciminib discontinuation rates are indirectly lower so it may

be more tolerable.

13.28.2. The Committee considered that since dasatinib is used first line for people considered high-risk as per the KISS study there are no other funded second-line TKI treatment options, with alternative treatments including: interferon, chemotherapy, and referring for a allogenic stem cell transplant.

13.28.3. The Committee considered that there are no current TKIs available in the fourth line setting, so asciminib would be compared with interferon therapy and or chemotherapy.

13.29. The Committee considered that while MMR translates into approximately 20 years of OS durable responses, MMR is not able to be translated into an OS advantage in the third and fourth-line setting, as studies would require a long follow up and the treatment in question may become redundant as newer agents come to market. The Committee considered that treatment holidays are agnostic to the agent used, so if a person experiences a log 4.5 reduction in treatment, which remains stable for two years, they would be a candidate for a treatment holiday.

13.30. The Committee considered that due to the rarity of CP-CML and the proposed line of treatment, asciminib should have little impact of the healthcare system if it were to be funded, as there would still be continual treatment reviews by the treating clinician and management if toxicity occurred. The Committee considered that the care of individuals in this setting would be far less onerous when compared to non-TKI options.

13.31. The Committee considered that funding asciminib would reduce the number of referrals for allogenic stem cell transplants, following exhausting all treatment options.

*Suitability*

13.32. The Committee considered asciminib to have a comparable suitability profile to the currently funded TKIs.

*Cost and savings*

13.33. The Committee considered that if asciminib was to be funded in the third-line setting, it may displace use of nilotinib or dasatinib. The Committee considered it is reasonable to assume that no more than 30 people would be eligible in New Zealand to initiate third-line therapy per year.

13.34. The Committee considered that few people survive to the time that they would require fourth-line treatments, and most people would not be receiving funded treatments in this setting. The Committee considered that if asciminib were to be funded in the fourth-line setting, it would mainly displace use of palliative chemotherapy, allogeneic stem cell transplants and certain Named Patient Pharmaceutical Assessment (NPPA) pathway funded therapies.

13.35. The Committee considered that allogeneic stem cell transplants are a resource intensive procedure, which would be associated with very high health sector costs. The Committee considered however that in the total population with CP-CML, very few (1-2%) of individuals would require an allogeneic stem cell transplant. The Committee considered that factors such as having high-risk disease, age and comorbidities were the main determinants of eligibility for stem cell transplant in this setting.

13.36. The Committee noted NPPA funded therapies, such as ponatinib, were generally only funded after people had trialled imatinib, nilotinib and dasatinib, and only if people were using the treatment as a bridge to stem cell transplant. The Committee

considered that this would reflect the subgroup of people who require fourth-line treatment and had high-risk disease.

*Funding criteria*

13.37. The Committee considered the proposed eligibility criteria to be appropriate.

*Summary for assessment*

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

| | |
|---|---|
| Population | People with Philadelphia-mutation positive chronic myeloid leukaemia, in the chronic phase, who have experienced insufficient treatment benefit or unacceptable toxicity with imatinib, nilotinib and dasatinib. |
| Intervention | Asciminib tablets<br><br>• 40mg twice per day<br>• Taken until disease progression and/or unacceptable toxicity.<br>• Some individuals may be eligible to experience treatment-free remission if they experience a cytogenic (major molecular) response that is sustained for at least two years on TKI. |
| Comparator(s) | Best supportive care or palliative chemotherapy.<br><br>Note: Some individuals may be eligible for an allogeneic stem cell transplant (if they have high-risk disease) and/or NPPA pathway funded therapy. |
| Outcome(s) | Increased major molecular response (MMR) rate:<br><br>• ASCEMBL reported that asciminib as a third-line treatment was associated with an MMR rate of 37.6% at 96 weeks (Hochhaus et al. Leukemia. 2023;37: 617-26 [Figure 1])<br>• It is assumed that response rates associated with asciminib would be substantially lower when used fourth line compared to third-line, based on trial evidence in other TKIs (Levy et al. Blood. 2015;126:1588)<br><br>Improved overall survival:<br><br>• Observational evidence suggests that major molecular responses are associated with improved overall survival compared to no response or lower levels of response (Falchi et al. Hematology. 2013;88: 1024-1029).<br>• Improved rates of haematological and molecular response with asciminib may be associated with improved overall survival.<br>• Survival outcomes are poor for those whose disease exhausts the available TKI treatment options (Boddu et al. Leukemia Lymphoma. 2018;59:1312-22). |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 14. Blinatumomab for the treatment of measurable residual disease in B cell lineage acute lymphoblastic leukaemia

### Application

14.1. The Committee reviewed the application for blinatumomab in the treatment of measurable residual disease in B cell lineage acute lymphoblastic leukaemia (B-cell ALL).

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

### Recommendation

14.3. The Committee **recommended** that blinatumomab be listed with a **high priority** for the treatment of measurable residual disease in B cell lineage acute lymphoblastic leukaemia, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application – B-cell acute lymphoblastic leukaemia/lymphoma in complete remission with minimal residual disease**
> Only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for patients meeting the following criteria:
> All of the following:
> 1. Patient has B-cell acute lymphoblastic leukaemia/lymphoma (ALL); and
> 2. Patient has received intensive combination chemotherapy for initial treatment of ALL or for subsequent salvage therapy; and
> 3. Patient has received complete remission; and
> 4. Patient has minimal residual disease (MRD) defined as at least 10-4 (0.01%) blasts based on measurement in bone marrow, documented after an interval of at least 2 weeks from last systemic chemotherapy, measured using polymerase chain reaction or flow cytometry; and
> 5. Patient has ECOG performance status 0-2; and
> 6. Treatment is to be administered for a maximum of 4 cycles.
>
> **Renewal - B-cell acute lymphoblastic leukaemia/lymphoma in complete remission with minimal residual disease**
> Only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for patients meeting the following criteria:
> Both:
> 1. Disease continues to be in complete remission; and
> 2. Treatment is to be administered for a maximum of 4 cycles.

14.4. In making this recommendation, the Committee considered:

14.4.1. the high health need of people with B-cell ALL and measurable residual disease following induction and consolidation chemotherapy

14.4.2. blinatumomab is an effective treatment for minimal residual disease (MRD) in B-cell ALL

14.4.3. the healthcare system must sufficiently resource allogenic haematopoietic stem cell transplant (allo-SCT) services, to ensure people are given the opportunity for potential curative therapy in the appropriate time frame.

### Discussion

*Māori impact*

14.5. The Committee discussed the impact of funding blinatumomab for the treatment of MRD-positive B-cell ALL on Māori health areas of focus and Māori health outcomes. The Committee considered that whilst there is limited evidence regarding Māori and B-cell ALL, the Wong et al. NZ Med J. 2023;136:10-18 publication reported lower EFS and OS for Māori and Pacific people (grouped together in analysis) compared to non-Māori and Pacific people.

*Populations with high health needs*

14.6. The Committee discussed the health need(s) of B-cell ALL among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs. The Committee discussed the impact of funding blinatumomab and considered:

- Due to around 100 people being diagnosed with B-cell ALL per year, of which about 20 are aged 15 or older, there is limited evidence regarding populations identified to have high health needs. Wong et al. NZ Med J. 2023;136:10-18 reported lower EFS and OS for Māori and Pacific people (grouped together in analysis) compared to non-Māori and Pacific people.

*Background*

14.7. The Committee noted in July 2021, access to rituximab was widened to include individuals with newly diagnosed B-cell ALL.

14.8. The Committee noted that in June 2019, dasatinib was funded for the first-line treatment of Philadelphia positive (Ph+) B-cell ALL.

14.9. The Committee noted that inotuzumab ozogamicin for the treatment of relapsed/refractory (R/R) B-cell lineage ALL was assessed by CaTSoP (now CTAC) in November 2021, which recommended inotuzumab be listed for adult patients with R/R CD22-positive B-cell precursor ALL:

14.9.1. with a low priority when ineligible for allogenic hematopoietic stem cell transplant

14.9.2. with a high priority when eligible for transplant.

14.10. The Committee noted that there have been 29 Named Patient Pharmaceutical Assessment (NPPA) applications for blinatumomab since 2019, of which 24 were approved.

*Health need*

14.11. The Committee noted ALL is a cancer of the white blood cells characterised by the overproduction and accumulation of immature white blood cells (lymphoblasts) and inhibition of normal cells in the bone marrow. ALL can also spread to other organs such as the liver and spleen and through the lymphatic and central nervous systems.

14.12. The Committee noted that induction treatment for B-cell ALL is prescribed by age: those aged 15-30 years are more likely to receive a ‘paediatric inspired’ protocol, those aged >30 years old receive the ‘adult’ protocol. The Committee noted that the overall aim of the adult protocol is to achieve measurable residual disease (MRD) - negative status and that a large proportion go on to receive an allo-SCT. Members considered that while the paediatric protocol is much more intensive and with much higher cure rates, less than 10% require an allo-SCT following this treatment.

14.13. The Committee considered that there are approximately 20 people who are aged 15 years or older who are newly diagnosed with B-cell ALL per year. Between 17 and 18 people are candidates for upfront intensive chemotherapy protocol with curative intent. Of these individuals, 20-25% have Philadelphia (Ph) positive disease. Members considered that 75% of those with Ph-positive disease who remain MRD - positive have the T315I mutation.

14.14. The Committee considered there would be ten people per year who have had a complete remission (CR) but have MRD-positive disease following induction chemotherapy.

14.14.1. The Committee considered that almost all people with MRD-positive disease following adult induction chemotherapy will be considered for an allogenic stem cell transplant (allo-SCT); these people receive blinatumomab or ponatinib (T315I mutation present) through the NPPA pathway.

14.14.2. The Committee considered that about 10% of people with MRD-positive disease following paediatric-inspired induction chemotherapy are likely to require a consolidative allo-SCT.

14.15. The Committee noted the Wong et al. NZ Med J. 2023;136:10-18 retrospective analysis of Auckland medical records in those with B-cell ALL (n=52). Māori (n=11) and Pacific peoples (n=7) were combined into a single group in this publication.

14.15.1. Among Māori and Pacific peoples (n=18), the median overall survival (OS) was 27.5 months compared with 42 months among non-Māori and non-Pacific peoples (hazard ratio log-rank: 0.73, 95% CI: 0.3 to 1.7, p=0.087).

14.15.2. Among Māori and Pacific peoples (n=18), the median event free survival (EFS) was 27.5 months compared with 32.9 months among non-Māori and non-Pacific peoples (hazard ratio log-rank: 0.8, 95% CI: 0.4 to 1.7, p=0.015).

14.15.3. Among Māori and Pacific peoples being treated with the adult protocol (n=8), the OS was 11.7 months. Three (38%) had MRD-negative disease following induction phase two, one received an allo-SCT, and six had relapsed/refractory disease, of which five died due to relapse.

14.16. The Committee considered that people with MRD-positive disease cannot be classified as having R/R B-cell ALL (>5% blasts), but in the clinical setting the person would be considered R/R prior to reaching the >5% blast threshold and would be treated accordingly. The Committee considered that if MRD is not addressed then relapse is inevitable.

14.17. The Committee noted the Berry et al. JAMA Oncol. 2017;3:e170580 meta-analysis of 39 studies in those with ALL (n=2076 adults). The 10-year OS for adults who were MRD-positive after induction was 15%, and 60% for adults who were MRD -negative.

14.18. The Committee noted the Pavlu et al. J Haematol Oncol. 2019;12:108 retrospective registry analysis of those who were MRD-positive (n=964) or MRD-negative (n=1816) prior to allo-SCT. Of those who were MRD-positive, lower OS (HR 1.19, 95% CI 1.02,1.39) and leukaemia-free survival (HR 1.26, 95% CI 1.1, 1.44) and higher relapse incidence (HR 1.51, 95% CI 1.26,1.8) were observed when compared to those who were MRD negative. The Committee noted that the disease needs to be considered MRD-negative by flow cytometry tests (<0.01% of cancer cells are detected) to be eligible for an allo-SCT in New Zealand.

14.19. The Committee considered that there is an unmet health need for people with B-cell ALL that is MRD-positive following induction chemotherapy, as there are no funded treatment options. The Committee considered that sadly the majority of people with this type of B-cell ALL will die of the disease.

*Health benefit*

14.20. Blinatumomab is a bispecific T-cell-engaging antibody that engages polyclonal T cells to CD19-expressing B cells. By binding to CD3 and CD19, blinatumomab brings these T cells in close proximity to malignant B cells and causes T-cell-induced cytotoxic killing of the cells (Portell et al. Clin Pharmacol. 2013;5:5-11).

14.21. The Committee noted that the blinatumomab funding application is for people aged 15 years and older, as funding of cancer treatments for people younger than 15 treated in a paediatric hospital setting are supported by the 8.1b rule in the Pharmaceutical Schedule.

14.22. The Committee noted that blinatumomab is used for a maximum of four treatment cycles. One cycle comprises 28 microgram of blinatumomab received as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump per day for 28 days (four weeks) followed by a 14-day (two-week) treatment free period.

14.23. The Committee noted the BLAST trial, a single arm, multi-centre phase II study in those aged ≥18 years with B-cell ALL in first or later CR and with persistent or recurrent MRD $\geq 10^{-3}$ after a minimum of three blocks of intensive chemotherapy. Individuals (n =116) received blinatumomab 15 microgram/m²/day over 28 days followed by an infusion-free period of 14 days for up to four cycles of treatment. At any number of cycles, a person in CR could leave the trial and proceed to allo-SCT.

14.23.1. The Committee noted the Gokbuget et al. Blood. 2018;131:1522-31 publication reporting the BLAST trial results across the treatment cycles:

- Of those who completed cycle one (n=113) 78% of the group were MRD-negative and of those with Ph-positive disease (n =5), three were MRD-negative. Following cycle two, an additional two more people were MRD-negative with no further responses after cycle three or four. Of those who had treatment interruption during cycle one (n=45), 82% were MRD-negative.
- MRD-negative disease was not a requirement to be eligible for an allo-SCT, and 65% (n=74) of the total cohort proceeded to allo-SCT.
- There were similar rates of toxicity across cycle one and two, with all patients experiencing at least one adverse event.
- 29% of grade three and 22% of grade four adverse events were blinatumomab-related.

14.23.2. The Committee noted the Gokbuget at al. Leuk Lymphoma. 2020;61:2665-73 publication reporting the BLAST trial results at a median follow up of 59.8 months:

- 110 were considered evaluable for OS, (five patients with Ph-positive disease and one with >10% blasts at screening were excluded from the survival analyses).
- The median OS was 36.5 months (95% CI 22, NR) and the estimated five-year OS was 43% (95% CI 34, 52).
- Disease relapse occurred in 61% of those who had a complete MRD response but did not have an allo-SCT after treatment.

14.24. The Committee noted that there is insufficient evidence to suggest that achieving MRD negativity with blinatumomab negates the need for a consolidative allo-SCT in those adults with B-cell ALL treated with curative intention on ‘adult’ induction protocols.

14.25. The Committee noted that there is unpublished data reporting that people who are treated on the paediatric-inspired protocol (aged 15 to 30 years) and receive blinatumomab in the induction/consolidation phase regardless of the MRD status experience an OS benefit.

14.26. The Committee noted the NEUF trial, a French retrospective observational study in those with R/R B-cell ALL (n=34 Ph-positive, n=106 Ph-negative) and MRD-positive (n=26 Ph-positive, n=83 Ph-negative). Individuals received blinatumomab through an expanded access programme. The Committee noted the Boissel et al. Blood Cancer J. 2023;13:2 publication reporting the results from the adult cohort of the NEUF trial:

- In those with evaluable MRD after cycle one (n=64), 88% had a complete or partial MRD response, and after cycle two (n=83), 84% had an overall MRD response (91% Ph-negative group, 59% Ph-positive group).
- In those with Ph-negative disease, overall MRD response was achieved in 88% of patients who had no prior salvage therapy (CR1) and 91% of those who had received at least one prior salvage therapy (CR2+). In those with Ph-positive disease, MRD response was achieved in 57% of CR1 patients and 56% of CR2+ patients.

14.27. The Committee also noted the following studies:

- Jabbour et al. Am J Hematol. 2022;97:1135-41
- Topp et al. J Clin Oncol. 2011;29:2493-8
- Topp et al. Blood. 2012;120:5185-7
- Gokbuget. Haematologica.2017;102:132-5
- Martinelli et al. Eur J Cancer. 2021;146:107-14

14.28. The Committee noted the recommendations for Australia (PBAC), Canada (CADTH-pERC), Scotland (SMC) and England/Wales (NICE) regarding the funding of blinatumomab for MRD-positive B-cell ALL following induction/consolidation chemotherapy:

14.28.1. The Committee noted that only Australia (PBAC) has approved funding for blinatumomab for MDR-positive CR in the Ph-positive setting.

14.28.2. The Committee noted that Australia (PBAC) and Canada (CADTH-pERC) have approved funding for blinatumomab for MDR-positive CR in the CR2/subsequent setting.

14.29. The Committee considered there to be evidence of sufficient quality showing that in one to two cycles blinatumomab is effective at converting MRD-positive disease to MRD-negative disease in people who have Ph-negative B-cell ALL following induction chemotherapy. However, there is insufficient evidence to support this treatment in people who have Ph-positive B-cell ALL. The Committee considered it to be unlikely that a phase III trial would be conducted as this therapy is already being used in other countries for these indications.

14.30. The Committee considered that there is increasing evidence showing disease-free survival (DFS) and OS benefit among the MRD-negative, Ph-negative B-cell ALL population (Litzow et al. N Engl J Med.2024;391:320-33). The Committee considered that an application for blinatumomab for this population should be assessed by this Committee in the future, as upfront MRD-negative remission is more likely to negate the need for consolidative allo-SCT.

14.31. The Committee considered that if a person received health benefit(s) from blinatumomab and then experienced relapse, the person would benefit from receiving inotuzumab, if it was funded.

14.32. The Committee considered that if blinatumomab was available, there will be an increase in people who would be eligible for allo-SCT. The Committee considered that the healthcare system is currently insufficiently resourced to provide timely allo-SCT, and there would be a wait time of between nine to 12 months for a person to receive this treatment. The Committee considered that there is a risk of disease escape during a long wait period for an allo-SCT. The Committee considered that there are no appropriate medicines that can be used to hold a person in MRD-negative status during this wait time; although maintenance chemotherapy may be used in an attempt to try hold MRD-negative status. If disease escape occurs, then

the disease will be R/R, resulting in them being ineligible for an allo-SCT. The Committee considered that allo-SCT needs to be sufficiently resourced in the healthcare system to ensure people are given the opportunity for potential curative therapy in the appropriate time frame.

*Suitability*

14.33. The Committee considered that individuals receiving treatment are initially in hospital for one to three days, then managed in the outpatient setting. The Committee noted that treatment in the outpatient setting is dependent on the availability of cassette pumps.

*Cost and savings*

14.34. The Committee considered Pharmac staff's estimate and approach for estimating patient numbers to be appropriate, and specifically considered:

14.34.1. That 75% of ALL cases were of B-cell lineage (Cancer Research UK).

14.34.2. That 41% of patients in CR1 (first remission) are MRD-positive (Greenwood et al. Blood Adv. 2021;5:5574-83).

14.34.3. The majority of patients treated on an adult indication regime with MRD-positive disease would be considered for an allo-SCT, while more than 50% of people with MRD-positive disease treated on a paediatric protocol were likely to require a consolidative allo-SCT after induction chemotherapy.

14.34.4. The majority of patients currently receiving treatment for MRD positive B-cell ALL were treated in an inpatient setting. The Committee considered that the current outpatient costs for these patients would be immaterial.

14.34.5. Currently, people with MRD-positive B-cell ALL would be unlikely to receive an allo-SCT. These people would require further intensive chemotherapy in an attempt to convert their disease to a MRD-negative disease state, to be eligible for a potentially curative allo-SCT. Provided there is no other contraindication, adult patients who are in a MRD-negative state following intensive chemotherapy will proceed to a potentially curative allo-SCT.

14.34.6. It is appropriate to assume that survival outcomes are dependent on complete MRD response, and that 25% of people with MRD positive disease receiving current chemotherapy regimens would achieve a complete MRD response and become MRD negative (Gokbuget et al. 2018).

14.35. Regarding any modelling of cost and savings by Pharmac staff, the Committee considered that:

14.35.1. Blinatumomab would not be used in combination with any other treatments when treating MRD-positive B-cell lineage ALL.

14.35.2. In Aotearoa New Zealand, a larger proportion of patients would receive four cycles of blinatumomab compared to in the BLAST trial, due to the current allo-SCT waitlist.

14.35.3. It was not appropriate to limit treatment to two cycles of blinatumomab for treatment of MRD-positive ALL, due to the current waitlist time for an allo-SCT.

14.35.4. Approximately 80% of patients treated with blinatumomab would become MRD negative and thus eligible for an allo-SCT (Gokbuget et al. 2018).

*Funding criteria*

14.36. The Committee considered the proposed eligibility criteria to be appropriate.

*Summary for assessment*

14.37. The Committee considered that the below summarises their interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for blinatumomab, if it were to be funded in New Zealand for people with B-cell ALL who are in CR but have MRD-positive disease after intensive induction. 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 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 measurable residual disease (MRD) in B cell lineage acute lymphoblastic leukaemia after induction chemotherapy. |
| Intervention | Continuous intravenous infusion of 28 µg blinatumomab per day for 28 days followed by a 14-day treatment free period.<br><br>Maximum treatment course of blinatumomab of 4 cycles. However, the average number of cycles given in Australia is 2 cycles (aligned to BLAST trial). |
| Comparator(s) | Standard chemotherapy regimen for MRD positive B-cell ALL currently used in Aotearoa New Zealand |
| Outcome(s) | 78% of patients receiving a complete MRD response with blinatumomab (Gokbuget et al. Blood. 2018;131:1522-31) compared to 25% receiving a complete MRD response with further or alternate chemotherapy regime (Gökbuget et al. Blood. 2018) . |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 15. Ruxolitinib for acute, corticosteroid-refractory graft versus host disease

### Application

15.1. The Committee reviewed the clinician application for ruxolitinib (Jakavi) for the treatment of acute, corticosteroid-refractory graft versus host disease (aGvHD) in people who have had an allogenic haemopoietic stem cell transplant (HSCT; allograft).

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

### Recommendation

15.3. The Committee **recommended** that the application for ruxolitinib for the treatment of acute corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant be funded with a **high priority,** within the context of treatment of malignancy, subject to the following Special Authority criteria:

**Initial application** (**acute graft versus host disease**) – from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. Person has acute graft versus host disease (grade 2-4) following allogenic haemopoietic stem cell transplant; and
2. Any of the following:
   2.1 Person has received insufficient benefit or their disease has progressed after administration of minimum prednisone 2 mg/kg/day (or equivalent) for at least 3 days; or

2.2 Disease persistence without improvement despite continued treatment with prednisone after administration of minimum prednisone 2 mg/kg/day (or equivalent) for at least 7 days; or
2.3 Person has a recurrence of aGvHD activity during or after corticosteroid tapering to prednisone less than 2 mg/kg/day (or equivalent); or
2.4 Treatment with prednisone cannot be tolerated; and
3. Ruxolitinib not to be used with systemic therapies other than corticosteroids and/or calcineurin inhibitors.

**Renewal (acute graft versus host disease)** - Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. The treatment remains appropriate; and
2. Ruxolitinib not to be used with systemic therapies other than corticosteroids and/or calcineurin inhibitors.

15.4. In making this recommendation, the Committee considered that:

15.4.1. Corticosteroid-refractory aGvHD is associated with very high mortality, and currently funded second-line treatments are insufficiently effective.

15.4.2. There is demonstrated efficacy of ruxolitinib in aGvHD despite the overall survival (OS) benefit reported in REACH2 not being a difference that was statistically significant, where the study was statistically powered for earlier outcomes and treatment crossover was also a factor. Members considered that REACH2 could well have reported a statistically significant result had it been sufficiently powered for OS, and anticipated that those with severe aGvHD who experienced a good response with ruxolitinib would have OS close to that of people without aGvHD.

15.4.3. Ruxolitinib is anticipated to provide health-related quality-of-life (QoL) benefit for people with aGvHD and a decreased duration of hospital stay, due to having less time experienced with GvHD.

## Discussion

*Māori impact*

15.5. The Committee discussed the impact of funding ruxolitinib for the treatment of aGvHD on Māori health areas of focus and Māori health outcomes, as discussed in July 2024.

15.6. The Committee considered that while Māori may not be disproportionately affected by aGvHD, they may experience a disproportionate impact (given the need to stay a long time in or close to the transplant centre for treatment and monitoring for further complications), which may result in disconnection and isolation from whānau and home communities.

*Populations with high health needs*

15.7. The Committee discussed the health need(s) of people with aGvHD among Māori, Pacific peoples, disabled peoples including tāngata whaikaha Māori, and other populations identified by the Government Policy Statement on Health 2024-2027 to have high health needs, as discussed in July 2024.

15.8. The Committee considered that while these groups may not be disproportionately affected by aGvHD, they may experience a disproportionate impact (given the need to stay a long time in or close to the transplant centre for treatment and monitoring for further complications), which may result in disconnection and isolation from whānau and home communities.

15.9. Members further considered that individuals from rural or remote communities would be disproportionately impacted by logistic challenges accessing transplant services.

*Background*

15.10. The Committee noted an application for ruxolitinib for the treatment of chronic corticosteroid-refractory graft versus host disease (cGvHD) following allogenic haemopoietic stem cell transplant (allo-HSCT) was considered at its last meeting in July 2024. The Committee noted that it had recommended that ruxolitinib be funded for the treatment of chronic corticosteroid-refractory graft versus host disease following allogenic haemopoietic stem cell transplant with a high priority, in the context of the treatment of malignancy, subject to Special Authority criteria. In making its recommendation, the Committee had considered:

15.10.1. The health needs of people with chronic graft versus host disease (cGvHD) are high, due to increased mortality and the impacts on their quality of life, and limited effective, evidence-based treatments available in those whose cGvHD is refractory to corticosteroids.

15.10.2. The REACH3 trial was good quality evidence for ruxolitinib being a superior treatment to the currently funded treatments available for the treatment of corticosteroid-refractory cGvHD in New Zealand.

15.10.3. As an orally administered treatment, ruxolitinib has the potential to relieve pressure on hospital outpatient infusion services if it is used for people who would otherwise receive treatments administered via intravenous infusion.

15.10.4. Funding ruxolitinib for the treatment of corticosteroid-refractory cGvHD may reduce long term health sector expenditure through requiring less multi-disciplinary team involvement, reduced hospital stays, and decreased risk of complications associated with current treatments.

15.11. The Committee noted a small number of people are currently receiving funded ruxolitinib for aGvHD through the Named Patient Pharmaceutical Assessment (NPPA) pathway due to being defined as having exceptional clinical circumstances.

*Health need*

15.12. The Committee noted that the health needs of people with corticosteroid-refractory graft versus host disease following allo-HSCT, and the availability and efficacy of currently funded second-line funded therapies for GvHD, were described in the record of its last meeting in July 2024 in the context of chronic GvHD (cGvHD).

15.13. The Committee noted that all individuals proceeding to allograft are given preventative treatments against GvHD, with options depending on individual risk and donor factors. The Committee noted that while aGvHD occurs generally within the first 100 days following allograft and that there is overlap between acute and chronic GvHD, both occur on a spectrum but can have differences in organ effects. The Committee considered that individuals with GvHD theoretically can get GvHD again (as either breakthrough refractory disease or recurrence during treatment tapering) and that those with aGvHD are more likely to get cGvHD than those who did not have aGvHD, with the risk of developing cGHD increasing the longer an individual has aGvHD.

15.14. The Committee noted that aGvHD affects both children and adults in similar proportions and therefore considered Pharmac staff should double their patient number estimates (which were based on adults only) to include treatment of children. Members considered that aGvHD occurs in approximately 50% of all allografts for children under 12 years of age where there was a matched unknown donor (which is common practice currently).

15.15. The Committee noted that aGvHD typically involves the skin, gastrointestinal tract (causing anorexia, pain and diarrhoea) and liver, with significant effects on the individual no matter which underlying disease led to the allograft. Members considered that the impact of aGvHD can range from causing highly unpleasant and painful symptoms to being so severe that it can cause death or lead directly to palliative care.

15.16. The Committee noted that staging of aGvHD disease sites and grading of overall disease severity is standard in clinical practice, meaning that the health need of people with aGvHD is known to be very high and is well documented. The Committee noted that grade two or higher aGvHD is associated with high morbidity, high mortality and a significant decrease in quality of life. The Committee noted that severe (ie grade two to four) aGvHD occurs in 15-20%, or about one in six people receiving an allograft.

15.17. The Committee noted that those with grade one GvHD typically have the skin affected and are managed with topical high-dose corticosteroids, while level two or higher aGvHD requires systemic treatment. The Committee noted that the initial approach for grade two or higher aGvHD is to optimise levels of calcineurin inhibitor therapy (although this provides a meaningful benefit only infrequently), and corticosteroids are added at doses depending on grade and organ involvement (typically 2 mg/kg/day prednisone-equivalents given in divided doses).

15.18. Members noted that many cases of aGvHD do not respond to corticosteroids, where they considered that up to 60% with grade two and 30-40% with grade four aGvHD would be likely to respond. Members considered that a third of cases in children 12 years of age and under do not respond to corticosteroids. The Committee noted that corticosteroid-refractory aGvHD is associated with very high morbidity and mortality of approximately 80%.

15.19. Members considered that many therapies are either ineffective in this setting or are used in upfront conditioning pre-allograft and therefore are not used in the treatment of corticosteroid-refractory aGVHD (ie anti-thymocyte globulin [ATG], mycophenolate, methotrexate, pentostatin, and extracorporeal photopheresis [ECP] which is not available in all regions). Members agreed with the applicant's views that there are no robustly evidence-based effective second-line funded treatments for corticosteroid-refractory aGvHD in New Zealand. Members considered that infliximab would be the most used, albeit insufficiently effective, second-line treatment for corticosteroid-refractory aGvHD in approximately 50-85% of cases (etanercept might also be used, although rarely).

15.20. Members considered that people who have previously had aGvHD and develop cGvHD would be treated with corticosteroids in the first instance followed by ruxolitinib (if funded), with subsequent treatments (for example imatinib, infliximab) being considered on an individual basis. Members considered that calcineurin inhibitors are generally not used in this context.

*Health benefit*

15.21. The Committee noted that the evidence for ruxolitinib in aGvHD comes from the phase 3, multicentre, randomised (1:1), open-label, REACH2 trial in 309 patients aged 12 years or older with glucocorticoid-refractory aGvHD after allogenic stem cell transplant (Zeiser et al. N Engl J Med. 2020;382:1800-10).

15.21.1. The Committee noted that participants received either oral ruxolitinib 10 mg twice daily or 'Investigator's choice' of therapy from nine options (control arm), but considered many of control arm options were not relevant to the New Zealand context. Members considered that the group of participants would have initially tapered off high-dose corticosteroid treatment and

ciclosporin, then commenced ruxolitinib no earlier than four weeks post-allograft to receive a total of about six months of ruxolitinib treatment. The Committee noted that crossover from control to ruxolitinib therapy was permitted and that this occurred in a significant proportion of participants.

15.21.2. The Committee noted that the primary endpoint of REACH2 was overall response at day 28 (either complete response [CR] or partial response [PR]), which was reported in 62% (96/154) with ruxolitinib including CR in 34% (53/154) vs 39% (61/155) in the control arm, of which CR was reported in 9% (30/155); odds ratio, 2.64; 95% confidence interval [CI], 1.65, 4.22; P<0.001).

15.21.3. The Committee noted the durable overall response at day 56 was 40% (61/154) with ruxolitinib vs 22% (34/155) in the control arm (odds ratio, 2.38; 95% CI, 1.43, 3.94; P<0.001). The Committee noted that the estimated cumulative incidence of loss of response at six months was 10% with ruxolitinib vs 39% in the control arm.

15.21.4. The Committee noted the median treatment failure-free survival was 5.0 months with ruxolitinib vs 1.0 month in the control arm, with a hazard ratio (HR) for relapse or progression of hematologic disease, non–relapse-related death, or addition of new systemic therapy for aGvHD of 0.46 (95% CI, 0.35, 0.60).

15.21.5. The Committee noted the median overall survival (OS) was 11.1 months with ruxolitinib vs 6.5 months in the control arm, and the authors reported a hazard ratio for death of 0.83 (95% CI, 0.60, 1.15), although the study was statistically powered for earlier outcomes (ie days 28, 56) and treatment crossover was also a factor. Members considered that the study could well have reported a statistically significant result had it been sufficiently powered for OS. Members further considered that:

- Response type (to treatment) is an appropriate surrogate outcome to use for modelling OS in this setting.
- Proceeding to a much more effective second-line therapy such as ruxolitinib early in treatment would be expected to be beneficial, based on the observation that early effective therapy reduces the risk of increased resistance to subsequent treatment options, which are known to be insufficiently effective.
- For those with severe aGvHD, obtaining a good response to treatment for aGvHD would be anticipated to result in overall survival that is close to (ie only slightly less) than that of people who did not experience aGvHD.
- Ruxolitinib is anticipated to provide health-related quality-of-life (QoL) benefit for people with severe corticosteroid-refractory aGvHD and a decreased duration of hospital stay, due to having less time experienced with GvHD.
- Infliximab would be broadly as effective as the REACH2 control arm.

15.21.6. The Committee noted that treatment discontinuation occurred in 111 (72%) with ruxolitinib vs 132 (85%) in the control arm, with lack of efficacy being the most common reason for this (in 32 [21%] and 68 [44%], respectively).

15.21.7. The Committee considered that the safety profile of ruxolitinib in REACH2 was similar to what would be expected based on its current use in treating myeloproliferative disorders, and adverse effects included anaemia, thrombocytopaenia and a higher risk of viral illness. Members considered

that in most cases, ruxolitinib side effects are manageable with supportive care although some individuals might stop treatment with ruxolitinib due to severe thrombocytopenia.

15.22. The Committee noted that the REACH2 study was the only randomised controlled trial investigating ruxolitinib in aGvHD, and considered it was a high-quality supplier-funded randomised study with no apparent design issues and no specific concerns about bias.

15.23. The Committee considered that evidence from case series suggests broadly similar outcomes from ruxolitinib for children under 12 years of age with corticosteroid refractory aGvHD compared with the adult population. The Committee considered that, while this was relatively new data, no new safety signals were identified. The Committee noted the following evidence for ruxolitinib in children with aGvHD:

15.23.1. Results from a compassionate use programme involving 1180 patients with acute, chronic or non-specified GvHD (Pattipata et al. Bone Marrow Transplant. 2024;59:637-46). The Committee noted that this involved 8% of patients aged eight to 12 years who received a 56% best response rate of grade one to two (ie reverting severe disease back to grade one or two), suggesting rapid and positive effects in a real-world setting.

15.23.2. A recent meta-analysis based upon similar data suggesting that ruxolitinib is an effective and safe treatment for corticosteroid refractory aGvHD and that both children and adults could benefit (Fan et al. Front Immunol. 2022;13:954268).

15.23.3. The Committee was made aware of newly published data from the REACH4 trial, a phase I/II open label, single arm multicentre study in 45 children with grade two to four corticosteroid-refractory or treatment naïve aGvHD (Locattei et al. Blood. 2024:blood.2023022565. Online ahead of print). Members noted that the age-appropriate initial doses in phase I were recommended as phase II doses for participants under 12 years of age. The median duration of ruxolitinib exposure was 3.8 months (range 0.3-11.2) and the overall response rate (ORR) in all patients was 84.4% (90% CI, 72.8, 92.5) at day 28, with a durable ORR at day 56 of 66.7% (90% CI, 53.4-78.2). Members considered this study reported similar overall response rates and clinically meaningful effectiveness of ruxolitinib with no new safety signals. Members considered that the evidence in corticosteroid-naïve patients suggested that ruxolitinib would be used in combination with (not replacing) corticosteroids.

15.24. The Committee noted the following additional meta-analyses and considered that these also support the survival and health-related QoL benefits of ruxolitinib in aGvHD.

- Zhang et al. PLoS One. 2022;17:e0271979
- Baccelli et al. Bone Marrow Transplant. 2024;59:765-76

15.25. The Committee noted the clinical guidelines and additional evidence provided by the applicant and identified by Pharmac staff in a literature search:

- Jagasia et al. Blood. 2020;135:1739-49
- Wei et al. Drug Des Devel Ther. 2021;15:4875-83
- Levine et al. Biol Blood Marrow Transplant. 2010;16:1693-9
- Penack aet al. Lancet Haematol. 2024;11:e147-59
- Hamad et al. Intern Med J. 2023;53:2319-29.

15.26. The Committee considered that the evidence indicates those with aGvHD who would benefit most from ruxolitinib would be people with severe (ie grade two to grade four) systemic corticosteroid-refractory disease, and that this would include both adults and children.

15.27. The Committee noted that ruxolitinib's Medsafe approval is for the treatment of GvHD in patients aged 12 years and older (Medsafe data sheet). However, Members did not consider this should be a barrier clinically, given that children are often treated with medicines that are not Medsafe-approved for use in children (due to absent regulatory studies in those age groups). Members considered there is evidence of ruxolitinib being safe and effective in children under 12 years of age, and noted the serious consequences of not providing younger children effective treatment for what is a potentially fatal disease. Members further noted that internationally, ruxolitinib is given as second-line treatment for aGvHD in paediatric transplant services, analogous to adult transplant services.

*Suitability*

15.28. The Committee noted that ruxolitinib is an easily administered oral tablet that is well absorbed even in cases of aGVHD where the gastrointestinal tract is heavily affected.

15.29. The Committee noted that ruxolitinib dosing of 10 mg twice-daily is recommended based on pharmacokinetic data, therefore a once-daily dose (using a 20 mg formulation) would not be recommended, and Members did not support having a 20 mg formulation in this setting.

15.30. The Committee considered that ruxolitinib is equally suitable for children under 12 years of age based on the appropriate age-banded doses in the REACH4 trial.

*Cost and savings*

15.31. Regarding any modelling of cost and savings by Pharmac staff, Members considered that:

15.31.1. For people who experience GvHD recurrence while on treatment with ruxolitinib, the time on treatment with ruxolitinib would be extended by a minimum of six months before there would be consideration of tapering ruxolitinib.

15.31.2. Corticosteroid treatment would remain the first-line treatment if ruxolitinib were funded for aGvHD. Members considered that ruxolitinib would be used in combination with corticosteroids and calcineurin inhibitors for aGvHD.

15.31.3. For people who have previously received a good response with ruxolitinib for aGvHD and subsequently develop cGvHD, it would be clinically appropriate to consider ruxolitinib treatment again for cGvHD. Members considered it difficult to estimate the number of people who might experience overlap and develop cGvHD following initial treatment with ruxolitinib for aGvHD, but considered it might be reasonable to assume that a response to ruxolitinib for aGvHD could halve the risk of developing cGvHD subsequently.

15.31.4. The main comparator for assessment of ruxolitinib for aGvHD would be infliximab, given at a weekly dose of 10 mg/kg, and ruxolitinib would replace most of its use.

15.32. The Committee was made aware of unpublished REACH2 study outcomes indicating that ruxolitinib was associated with a shorter length of hospital stay (personal communication described by the applicant), and agreed that this was a reasonable inference. Members considered that a reduced hospital stay duration would be associated with a decreased cost of care, due to people requiring less nutritional support, pain relief, laboratory testing, and healthcare professional care (transplant

staff and staff from other services eg surgical, gastrointestinal, dermatological, pathology, liaison psychiatry, and palliative care services).

15.33. The Committee considered that health sector impacts of funding ruxolitinib for aGvHD were unlikely to be substantial, although it was unclear whether there would be an increase in the number of blood product transfusions (ie red cells and typically, platelet transfusions). Members considered that while severe thrombocytopaenia was a concern, this side effect might be managed for a longer time than in the chronic setting given the lethality of aGvHD, and the fact that thrombocytopaenia could also be a disease complication as opposed to a medicine adverse effect. However, Members considered that ruxolitinib would likely be discontinued in individuals whose severe thrombocytopenia requires platelet transfusion, and/or whose severe thrombocytopenia is considered related to ruxolitinib.

15.34. Members considered that the studies of ruxolitinib did not report increased cases of CMV infection with ruxolitinib and considered that standard of care monitoring occurs for this.

*Funding criteria*

15.35. The Committee considered the proposed Special Authority criteria to be generally reasonable, and that ruxolitinib for aGvHD should not be funded for use with systemic therapies other than corticosteroids and/or calcineurin inhibitors.

15.36. Members considered that the most appropriate daily dose of corticosteroids to include in the Special Authority criteria for ruxolitinib for aGvHD (ie to define 'corticosteroid refractory' aGvHD) was 2 mg/kg (not 2.5 mg/kg) minimum prednisone equivalents, as per current practice.

*Summary for assessment*

15.37. The Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ruxolitinib if it were to be funded in New Zealand for corticosteroid-refractory aGvHD. 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 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 treated with allogeneic stem cell transplant who have developed severe (ie grade two to four) acute graft-versus-host disease (aGvHD) and received an inadequate response to systemic corticosteroids. |
| Intervention | Ruxolitinib (tablet) at starting dose of 10mg twice daily (BD), for at least 28 days.<br><br>If a response is experienced, then taper systemic corticosteroids first. If the response is sustained after 56 days of ruxolitinib – start tapering ruxolitinib (reduce by 50% every 2 months).<br><br>Adjunctive to corticosteroids with or without calcineurin inhibitors |
| Comparator(s) | Predominantly infliximab (in approximately 50-85% of cases).<br><br>Adjunctive to corticosteroids with or without calcineurin inhibitors |

| | |
|---|---|
| Outcome(s) | REACH2 trial:<br>• Overall response rate at day 28 (62% ruxolitinib vs 39% best available therapy (OR 2.64; 95% CI, 1.65 to 4.22).<br>• Median treatment failure-free survival (5.0 months vs. 1.0 months; HR 0.46; P<0.001).<br>• Median overall survival was 11.1 months in the ruxolitinib group and 6.5 months in the control group (hazard ratio for death, 0.83; 95% CI, 0.60 to 1.15).<br><br>Likely HRQoL gain and decreased hospital stay duration if less time experienced with aGvHD. |
| Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data. | |

## 16. Exceptional circumstances (NPPA) discussion

16.1. The Committee noted the challenges applying the NPPA policy to cancer treatments and Pharmac staff sought advice from the Committee on how cancer treatment NPPA applications would be best assessed under the current Policy.

## Discussion

### Assessment of cancer applications under the principles of the NPPA Policy

16.2. The Committee noted the current Named Patient Pharmaceutical Assessment (NPPA) Policy and the assessment process for an NPPA application. The Committee noted the core principles of the policy are:

- *The NPPA Policy is intended to meet the needs of those exceptional cases which are not currently feasible to consider through the Pharmaceutical Schedule listing process. This may be due to the urgent clinical need of the person, or the unusual nature of their particular clinical circumstances.*

- *Treatments funded through NPPA must be 'end of spectrum' in the sense that other currently funded options are not clinically suitable for the individual. This ensures that the NPPA process does not undermine the Pharmaceutical Schedule through providing a competing alternate pathway to access funded treatment.*

- *The NPPA Policy is designed for individual assessment but it must be determined how the individual's clinical circumstances are 'different' to the wider patient population, and the implications of funding this individual in the context of the wider patient population must also be considered.*

16.3. The Committee noted that three guiding questions are used to help assess whether applications meet the core principals the NPPA policy. The Committee noted that Pharmac does not assess applications that are inconsistent with these core principles.

16.4. The Committee noted there was no fixed population size that Pharmac uses to define exceptionality. The Committee considered Pharmac could improve clinician understanding of the process by making it clearer that exceptionality is defined through a patient's individual clinical circumstances being unable to be met via the Pharmaceutical Schedule, that inability being a combination of various factors including, but not limited to, rarity of the condition.

16.5. The Committee noted that Pharmac needs to consider how many other people could have similar clinical circumstances in the future and the precedence setting of

determining a group's clinical circumstances to be 'exceptional'. The Committee noted that the availability of new information may change the outcome of a group previously defined as exceptional under the NPPA policy.

*Challenges in defining exceptional circumstances*

16.6. The Committee noted there are challenges in defining exceptional circumstances in the context of cancers:

16.6.1. The Committee noted that many cancers could be broken down into small population subsets, particularly where genetic mutations are involved. The Committee considered this is likely to become more complex as many tumour types are moving towards molecular definitions and some of these may become considered as distinct cancer entities. The Committee noted some mutations can be somatic or germline, and the type of mutation can be used to guide treatment selection in some instances.

16.6.2. The Committee noted that there is a clinical desire to use the most effective treatments upfront, but this can be at odds with the NPPA policy that requires all suitable funded alternatives to be used. The Committee noted that progressing through all funded treatment lines is different for cancer than many other conditions, with poorer outcomes as an individual progresses through treatment lines. The Committee considered that most individuals progress through multiple lines of treatments and therefore exceptionality should not be defined through how many prior lines have been received.

16.6.3. The Committee noted it can be difficult to differentiate between cancer that is insensitive to chemotherapy, rather than poorly responsive, when determining whether all funded alternatives have been trialled or ruled out. The Committee considered that this needs to be considered on a case-by-case basis, based on the evidence presented and the plausibility of that evidence in its applicability to the application being considered.

16.6.4. The Committee noted that sometimes funded alternatives are not able to be used, for reasons such as hypersensitivity reaction, and in such situations, where someone is unable to be treated with what is considered a funded alternative, this can be a rationale for approval via NPPA. The Committee considered that it would be helpful if there was a simplified process for these types of applications.

*Challenges regarding equity via NPPA*

16.7. The Committee considered that the NPPA process exacerbates health inequities. There are a number of factors that are needed to develop a successful NPPA application, including access to end-of-line specialist care and clinicians that are familiar with the process. This can be influenced by an individual's geographical location, socioeconomic circumstances and general access to health care. The Committee considered that those with the highest unmet health needs would be the least likely to successfully access medicine funding through the NPPA process.

16.8. The Committee considered the NPPA process risked creating other inequities in access to funded treatments:

16.8.1. The Committee noted they consider Pharmaceutical Schedule funding applications for small groups of people, and this can, at times, be smaller than those groups of people Pharmac determines meet the principles of the NPPA policy. The Committee considered this risked an inconsistent approach, with some groups being assessed via the Pharmaceutical

Schedule and often having to wait for funded access, while others were assessed via the NPPA process with rapid access to treatment.

16.8.2. The Committee noted that where certain genetic tests are not available in the public health system, the testing can be accessed privately. The Committee considered that this can be used to define exceptional clinical circumstances and/or identify targeted treatment options. The Committee considered this advantaged those with access to private testing, as other people without those means would not be able to access these treatments through NPPA. The Committee considered that a nationally consistent testing platform would be required to avoid this inequity and noted that this inequity of access to testing was commonplace in the New Zealand health system. The Committee considered that the availability of a test or a target that has a pharmaceutical intervention should not be considered in isolation as rationale for meeting the principles of the NPPA policy, and that such interventions would be better considered for funding via the Pharmaceutical Schedule.

*Bridge to transplant*

16.9. The Committee considered that NPPA had a role to play in funding treatments in the bridge to transplant setting and was supportive of this treatment modality continuing in the future due to the small numbers, exhaustion of funded alternatives and potentially curative nature of the intervention.

16.10. The Committee noted the significant delays and under resourcing of transplant centres in New Zealand, which can result in substantial waitlists. The Committee considered that this does put Pharmac in a difficult place as there is limited certainty of progression to a transplant in a timeframe that would previously been considered reasonable as a bridge. Given this, the Committee considered:

16.10.1. if it is confirmed for an individual that the therapeutic intent is as bridge to transplant, and the individual meets criteria to be eligible for a transplant, then that should be enough to satisfy the bridge to transplant criteria

16.10.2. it would be reasonable to request a letter of confirmation from the relevant Health NZ hospital transplant committee prior to progressing an application in the bridge to transplant setting

16.10.3. that Pharmac should discuss these transplant delays with the transplant centres directly.

16.11. The Committee noted that some of the treatments now available for some indications can be provided with the intention to avoid a transplant altogether. In these cases, the preferred treatment option would enable individuals to stay on treatment without the requirement for transplant. The Committee considered that in such cases, it may not be appropriate to consider these people to have the same clinical circumstances as the above.

**Process considerations**

16.12. The Committee requested it receive detailed summaries of NPPA applications at meetings going forward. Members noted this was an important feedback loop, ensuring consistent advice and decision-making on NPPA applications. The Committee considered that while there are privacy issues with the information that could be shared publicly, there is a lack of national awareness on what is approved via NPPA, which can create regional inequities. These summaries could improve visibility of approvals across regions.

16.13. The Committee noted that when Pharmac staff have sought clinical advice on an application and an alternative treatment has been identified, it would be appropriate for staff to confirm whether this would be appropriate with the applicant via email. In addition, it would be important to be clear with the applicant that if the application was considered not to meet the principles of the NPPA policy that if the reasons for this outcome were addressed, applicants could do so via email and that there would not be the need to submit a new application. The Committee considered that there was an impression that in such situations a new application could be required, which may act as a deterrent.