Record of the Cancer Treatments Advisory Committee Meeting held on 12 April 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 | Te Pātaka Whaioranga 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)
Alannah Kilfoyle (Online via Zoom)
Alice Loft
Anne O'Donnell
Chris Frampton
Chris Hemmings
Lochie Teague
Matthew Strother (Online via Zoom)
Michelle Wilson
Oliver Brake
Richard Issacs (Online via Zoom)
Scott Babington
Vidya Mathavan (Online via Zoom)

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Apalutamide for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) / metastatic castrate-sensitive prostate cancer (mCSPC), within the context of treatment of malignancy, subject to Special Authority criteria	High Priority
• Atezolizumab subcutaneous formulation and the infusion device within the context of treatment of malignancy, subject to Special Authority criteria	Cost Neutral
• BRAF inhibitor and MEK inhibitor for the treatment of BRAF mutated unresectable metastatic melanoma within the context of treatment for malignancy, subject to Special Authority criteria	Medium Priority
• Pembrolizumab for the adjuvant treatment of resected stage III melanoma	Low 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 cancers 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 cancers that differ from the Cancer Treatments Advisory Committee's, or Specialist Advisory Committees may make recommendations that differ from other Specialist Advisory Committees'.

Pharmac | Te Pātaka Whaioranga 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 cancers.

4. Welcome and introduction

4.1. The chair welcomed the committee with a karakia followed by whakawhanaungatanga.

5. Record of previous meeting held Thursday, October 12, 2023

5.1. The Advisory Committee reviewed the record of the Cancer Treatments Advisory Committee meeting held on Thursday 12th and Friday 13th October 2023 and agreed that the minutes be accepted.

6. Pharmac | Te Pātaka Whaioranga update

6.1. The Committee noted the Pharmac | Te Pātaka Whaioranga update.

6.2. The Committee acknowledged Pharmac's intention to hold more meetings online to aid in reducing carbon emissions and manage expenditure, and provided feedback, such as:

6.2.1. The Committee noted the flexibility of online meetings allows members to manage workloads more effectively.

6.2.2. Members suggested creating smaller ad-hoc committee groups dedicated to specific applications or topics. This may mean not all members need to attend every meeting, allowing for more focused and efficient discussions within specialised subgroups.

6.2.3. The Committee noted that shorter online meetings are more productive and preferable compared to full-day online sessions. Members considered the option of splitting meetings into two 4-hour sessions over consecutive days, allowing for better concentration and reduced fatigue.

6.2.4. Members noted options to explore other ways to seek advice for oncology funding applications will be discussed further with members and Pharmac staff.

7. Correspondence and Matters Arising

7.1. Correspondence: CDK4/6 Inhibitors

Recommendation

7.1.1. The Committee recommended that the eligibility criteria for both palbociclib and ribociclib be amended as follows (additions in **bold**, deletions in ~~strikethrough~~):

Initial application - only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
Either:
1. All of the following:
   1.1. Patient has unresectable locally advanced or metastatic breast cancer; and
   1.2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
   1.3. Patient has an ECOG performance score of 0-2; and
   1.4. Any of the following:

1.4.1. Disease has relapsed or progressed during prior endocrine therapy; or
1.4.2. Both:
1.4.2.1. Patient is amenorrhoeic, either naturally or induced, with endocrine levels consistent with a postmenopausal or without menstrual-potential state; and
1.4.2.2. Patient has not received prior systemic endocrine treatment for metastatic disease; or
1.4.3. Both:
1.4.3.1. Patient has commenced treatment with ribociclib in combination with an endocrine partner prior to 1 July 2024; and
1.4.3.2. There is no evidence of progressive disease; and
1.5. Treatment must be used in combination with an endocrine partner; and
1.6. Patient has not received prior funded treatment with a CDK4/6 inhibitor; **or**

2. **All of the following:**
2.1. Patient has had an active Special Authority approval for XXXX; and
2.2. Patient has experienced a grade 3 or 4 adverse reaction to XXXX that cannot be managed by dose reductions and requires treatment discontinuation; and
2.3. Treatment must be used in combination with an endocrine partner; and
2.4. There is no evidence of progressive disease.

Discussion

7.1.2. The Committee noted it had previously discussed cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors at its July 2023 meeting. The Committee noted they had recommended that ribociclib be listed in the Pharmaceutical Schedule with a high priority, based on differences in reported overall survival between ribociclib and currently funded palbociclib. The Committee noted they had considered that, clinically, the use of ribociclib would be preferred given the apparent overall survival benefits.

7.1.3. The Committee noted that their previous advice and recommendations were based on pivotal phase three clinical trial evidence for ribociclib (MONALEESA trials) and palbociclib (PALOMA trials). The Committee noted the baseline characteristics between the MONALEESA and PALOMA trials were different and therefore cross-trial comparisons could not be made, however noted the reported endpoints.

7.1.3.1. The Committee noted the PALOMA-1 trial reported an absolute PFS difference of 10 months (HR 0.49, 95% CI 0.32-0.75) and an absolute OS difference of 3 months (HR 0.90, 95% CI 0.62-1.30) (Finn et al. Breast Cancer Res Treat 2020;183(2):419-428).

7.1.3.2. The Committee noted the PALOMA-2 trial reported an absolute PFS difference of 10 months (HR 0.58, 95% CI 0.46-0.72) and an absolute OS difference of 3 months (HR 0.96, 95% CI 0.78-1.18) (Slamon et al. JCO 2024;42:994-1000).

7.1.3.3. The Committee noted the MONALEESA-2 trial reported an absolute PFS difference of 9 months (HR 0.57, 95% CI 0.46-0.70) and an absolute OS difference of 12.5 months (HR 0.76, 95% CI 0.63-0.93) (Hortobagyi et al. N Engl J Med 2022;386:942-50).

7.1.3.4. The Committee noted the MONALEESA-3 trial reported an absolute PFS difference of 8 months (HR 0.59, 95% CI 0.48-0.73) and median OS was not reached in the intervention arm (HR 0.72, 95% CI 0.57-0.92) (Slamon et al. N Engl J Med 2020;382:514-24).

7.1.3.5. The Committee noted the MONALEESA-7 trial reported an absolute PFS difference of 10 months (HR 0.55, 95% CI 0.44-0.69) and median OS was not reached in the intervention arm (HR 0.71, 95% CI 0.54-0.95) (Im et al. N Engl J Med 2019;381:307-16).

7.1.4. The Committee noted that in February 2024, Pharmac | Te Pātaka Whaioranga notified its decision to fund ribociclib for HR+/HER2- advanced breast cancer, following consultation in December 2023.

Correspondence from supplier

7.1.5. The Committee noted correspondence from the supplier of palbociclib in response to the July 2023 meeting record.

7.1.6. The Committee noted neither the MONALEESA nor PALOMA trials were powered to detect overall survival benefits, however noted that statistically significant overall survival benefits were observed in the MONALEESA trials. The Committee noted that the progression free survival benefits across the trials were similar.

7.1.7. The Committee noted the differences in toxicity profiles between ribociclib and palbociclib.

7.1.7.1. The Committee noted ribociclib may cause QTc prolongation and potentially increased risks of ventricular arrhythmias. The Committee noted palbociclib is not associated with QTc prolongation. The Committee considered QTc is an extremely variable measure, and the absolute risks of prolongation are extremely small and usually occur early in the treatment course.

7.1.7.2. The Committee noted there is a higher incidence of grade 3 liver function test (LFT) abnormalities reported in clinical trials for ribociclib compared to palbociclib (8% and 3% respectively). The Committee noted that treatment with ribociclib requires LFT monitoring every two weeks for the first two cycle, and at the beginning of each subsequent four cycles, and as clinically indicated. The Committee considered, however, that LFT abnormalities are most likely to occur within the three months of starting treatment.

7.1.7.3. The Committee noted grade 3 myelosuppression is more common with palbociclib compared to ribociclib. The Committee noted that treatment with palbociclib requires complete blood counts prior to the start of therapy and at the beginning of each cycle, as well as on day 15 of the first two cycles, and as clinically indicated.

7.1.8. On balance, the Committee considered that while there are differences in side effect profiles, ribociclib showed a clear overall survival benefit in randomised controlled trials. The Committee reiterated its previous view that most new patients in New Zealand would start on ribociclib, with potential exceptions for those at higher risk of QTc prolongation and with liver conditions.

Correspondence from patient and clinician groups

7.1.9. The Committee noted Pharmac sought advice on changing between CDK4/6 inhibitors, following consultation feedback it had received on the proposal to fund ribociclib. The Committee noted that the funding criteria recommended in July 2024 would not allow people to change between ribociclib and palbociclib.

7.1.10. The Committee considered the toxicity differences between the ribociclib and palbociclib means that some people would have unpredictable adverse reactions which may require treatment discontinuation. The Committee considered that any adverse reaction requiring treatment discontinuation would be grade 3 or 4 and cannot be managed by dose reductions.

7.1.11. The Committee considered that for ribociclib, the main toxicity that would lead to treatment discontinuation is incipient abnormal liver function. The Committee considered any ribociclib-associated irregularities in liver function tests were most likely to occur in the first three months from starting treatment.

7.1.12. The Committee considered that for palbociclib, the main toxicity that would lead to treatment discontinuation is myelosuppression. The Committee noted that myelosuppression can occur at any time during treatment.

7.1.13. The Committee noted there may be other adverse reactions that require treatment discontinuation, such as QTc prolongation, but considered these would be very rare.

7.1.14. The Committee noted the rates of these adverse reactions reported in literature, however considered it would be difficult to quantify discontinuation and switching rates given many reactions can be managed via dose reduction, and any on-target toxicity would require cessation of CDK4/6 inhibitor treatment. The Committee considered that market data in other countries where multiple CDK4/6 inhibitors are funded may be useful in understanding this.

7.1.15. The Committee considered there is currently an unmet health need for people who experience treatment-limiting toxicity to palbociclib. The Committee considered that there would remain an unmet health need for those receiving CDK4/6 inhibitors when ribociclib is funded from 1 July 2024 as the proposed eligibility criteria for CDK4/6 inhibitors would not allow people to transition between funded products should treatment-limiting toxicity be experienced on either agent. The Committee considered that amendments to the criteria would be necessary to enable transitions and address this unmet need. The Committee considered that those who should be eligible to change from ribociclib to palbociclib, or vice versa, would be those with grade 3 or 4 adverse reactions that cannot be managed by dose reductions and require treatment discontinuation.

7.1.16. The Committee considered there would be a cost associated with these amendments, as currently, if someone experiences a treatment limiting adverse reaction to palbociclib, they would not be eligible for ribociclib. As such, people who switch would likely remain on a CDK4/6 inhibitor for a longer time than they would currently. However, the Committee considered this would only affect a small proportion of the overall eligible population but that it was necessary to ensure that people who could benefit would continue to benefit from treatment.

7.2. Bendamustine Special Authority criteria

Recommendations

7.2.1. The Committee recommended the following amendments to Special authority criteria for bendamustine for chronic lymphocytic leukaemia (deletions in ~~strikethrough,~~ additions in **bold**):

> **Initial application — (~~treatment naive~~ CLL)** only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has ~~Binet stage B or C, or progressive stage A~~ chronic lymphocytic leukaemia requiring treatment; and
> 2. ~~The patient is chemotherapy treatment naive; and~~
> 3. ~~The patient is unable to tolerate toxicity of full-dose FCR; and~~
> 4. Patient has ECOG performance status 0-2; and
> 5. ~~Patient has a Cumulative Illness Rating Scale (CIRS) score of < 6; and~~
> 6. Bendamustine is to be administered at a maximum dose of ~~100~~90 mg/m2 on days 1 and 2 every 4 weeks for a maximum of 6 cycles.
>
> Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL). ~~Chemotherapy treatment is considered to comprise a known standard therapeutic chemotherapy regimen and supportive treatments.~~

Discussion

7.2.2. The Committee noted that Pharmac | Te Pātaka Whaioranga staff sought advice to understand the implications of amending the Special Authority criteria for bendamustine in the treatment of chronic lymphocytic leukaemia (CLL).

7.2.3. The Committee noted that bendamustine had been included in the 2023/24 annual invitation to tender. The Committee noted that Pharmac had received feedback on the bendamustine eligibility criteria after its inclusion in the Draft 23/24 invitation to tender. The Committee noted that this feedback related to it currently only being funded for people with CLL that was treatment naïve.

7.2.4. The Committee noted the current treatments funded for people with any CLL. The Committee considered that additional use of bendamustine for CLL would be as a second-line treatment for fitter, younger people with IgHV mutated CLL who receive fludarabine, cyclophosphamide and rituximab in first-line and are not eligible for venetoclax (relapsed after more than 36 months). The Committee considered that if the criteria were amended to enable access to this small group, the increase in use of bendamustine would be very low.

7.2.5. The Committee considered that the criteria could be simplified alongside this amendment to enable access for this small group and that it would only a marginal increase in the overall use of bendamustine.

7.3. Open-listing pemetrexed

7.3.1. The Committee noted that pemetrexed had been included in the 2023/24 annual invitation to tender. The Committee noted that Pharmac | Te Pātaka Whaioranga staff sought advice to regarding the potential additional use of pemetrexed if it were to be open listed.

7.3.2. The Committee noted the current eligibility criteria for funding were aligned with the Medsafe approved indications for pemetrexed and considered that this aligns with clinical use of the medicine.

7.3.3. The Committee considered any increase in usage would likely be as a later line treatment across various cancers where other treatments have failed. The Committee considered it would be difficult to quantify these groups, however they would represent a very small proportion of the overall usage.

7.3.4. The Committee noted that there was emerging evidence for use of pemetrexed in the neoadjuvant or adjuvant treatment of lung cancer, particularly in combination with immunotherapy. The Committee considered this may contribute to additional usage in the future.

7.3.5. Overall, the Committee considered any increase in pemetrexed usage would likely be minimal if it was open-listed.

7.4. Pazopanib competitive process

7.4.1. The Committee noted that pazopanib has been funded for the treatment of metastatic renal cell carcinoma, with intermediate or poor prognoses, since April 2012.

7.4.2. The Committee noted that Pharmac | Te Pātaka Whaioranga staff sought advice regarding a competitive process for pazopanib that could result in a brand change for people receiving this treatment.

7.4.3. The Committee noted pazopanib is a small molecule medicine and part of a group called tyrosine-kinase inhibitors (TKI). The Committee noted generics of these are manufactured under the same standards as the innovator medicine and must

demonstrate bioequivalence to gain regulatory approval. The Committee considered it unlikely there would be effects on health benefits if a brand change occurs.

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

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

7.4.6. The Committee considered the annual invitation to tender would be an appropriate way to compete this market, due to the limited clinical risk and appropriateness of the usual transition period (5 months).

7.4.7. The Committee noted that a previous brand changes of sunitinib, another TKI funded for metastatic renal cell carcinoma, had been successful. The Committee considered a brand change for pazopanib would need to be managed the same way and the resource implications would be similar. The Committee considered that implementation activity should focus on communications with clinicians and patients.

7.5. Lanreotide for functional gastroenteropancreatic neuroendocrine tumours and malignant bowel obstruction

7.5.1. The Committee noted a funding application for lanreotide to treat functional gastroenteropancreatic neuroendocrine tumours (GP-NETs) and acromegaly (P-001137) is currently ranked on Pharmac's *only if cost neutral* priority list, after being recommended for funding only if cost-neutral to long-acting octreotide by PTAC in November 2004.

7.5.2. The Committee noted Pharmac | Te Pātaka Whaioranga sought funding proposals from suppliers of lanreotide in the 2023/24 annual invitation to tender. The Committee noted that Pharmac staff were seeking advice on the expected uptake of lanreotide and whether it would be used for malignant bowel obstruction.

7.5.3. The Committee considered there are suitability benefits for lanreotide over long-acting octreotide. The Committee noted that lanreotide is delivered via a prefilled syringe and therefore has the potential for self-administration by patients. The Committee noted long-acting octreotide required up to 15 minutes to prepare vials before administration. The Committee considered it would be useful to have lanreotide funded if comparative pricing to long-acting octreotide was achieved, however it would not address any unmet health need.

7.5.4. The Committee considered prescribing may favour lanreotide over long-acting octreotide in the oncology setting, given its suitability benefits. The Committee considered that many clinicians would still use long-acting octreotide as they are familiar with the medicine and it would provide the same or similar health benefits, however this may change over time. The Committee considered that it would be reasonable to assume half of new patients would be prescribed lanreotide, but noted this was an estimate and would ultimately be dependent on clinician preference.

7.5.5. The Committee noted long-acting octreotide is also funded for malignant bowel obstruction under Special Authority criteria. The Committee recommended Pharmac seek advice from palliative care experts on whether lanreotide should also be funded for this indication.

8. Apalutamide for the treatment of hormone sensitive metastatic prostate cancer (HSmPC)

Application

8.1. The Advisory Committee reviewed an application from the supplier, and a supporting application from Prostate Cancer Foundation New Zealand in collaboration with a consumer for the use of apalutamide for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) / metastatic castrate-sensitive prostate cancer (mCSPC). The application from Prostate Cancer Foundation New Zealand is for Māori and Pacific men, specifically.

8.2. The Committee also reviewed first line treatments for high risk, non-metastatic castration resistant prostate cancer (nmCRPC) and sequencing of treatments across stages of prostate cancer.

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

Recommendation

8.4. The Advisory Committee recommended that apalutamide be funded with a **high priority** for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) / metastatic castrate-sensitive prostate cancer (mCSPC), within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application – (metastatic hormone sensitive prostate cancer)** only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has metastatic prostate cancer; and
> 2. Patient's disease is castration sensitive; and
> 3. Patient has a ECOG performance status of 0 or 1; and
> 4. Patient has not had prior treatment with a third-generation androgen receptor antagonist including apalutamide or with abiraterone; and
> 5. Either:
> 5.1. Apalutamide is to be used in combination with androgen deprivation therapy (a gonadotrophin-releasing hormone [GnRH] analogue); or
> 5.2. Patient has had a bilateral orchiectomy.
>
> **Renewal – (metastatic hormone sensitive prostate cancer)** only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has no evidence of disease progression; and
> 2. Patient's disease remains hormone sensitive; and
> 3. The treatment remains appropriate and the patient is benefitting from treatment.

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

8.5.1. prostate cancer in New Zealand is associated with a high level of unmet health need, metastatic prostate cancer is an incurable illness, and prostate cancer as a disease is causing significant morbidity.

8.5.2. good quality evidence shows apalutamide produces similar benefits to the previously noted benefits from abiraterone in this indication which can impact whānau as well as the person with prostate cancer.

8.5.3. oral agents including apalutamide, other androgen receptor inhibitors (ARIs) and abiraterone may be a more suitable option for people living rurally than docetaxel which is administered via intravenous infusion.

Discussion

Māori impact

8.6. The Committee discussed the impact of funding apalutamide for the treatment of mHSPC on Māori health outcomes. The Committee noted prostate cancer is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. However the committee noted that although and that Māori experience a lower incidence of prostate cancer, after controlling for age (State of Cancer in New Zealand 2020 report, Figure 1.1) but have a higher mortality. However, Māori are less likely to be offered screening and are more often diagnosed at later disease stages (Egan et al. 2020), so may be overrepresented in the group with metastatic prostate cancer. Māori with metastatic prostate cancer are 1.32 times more likely to die of prostate cancer than non-Māori (Obertova et al. 2015). Māori are also less likely to be able to receive medications such as abiraterone, the funded treatment for mCRPC, due to contraindications (CaTSoP, November 2021). Given these factors, there remains an unmet need for a funded treatment for Māori with metastatic prostate cancer, and Māori may be more likely to benefit if funding is not restricted to the group who are hormone-resistant., given their lower access to androgen deprivation therapy (ADT).

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been under-served by the health system

8.7. The Committee discussed the impact of funding apalutamide for the treatment of mHSPC on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been under-served by the health system. The Committee noted that the State of Cancer in New Zealand 2020 report also showed inequitable age standardised mortality for prostate cancer for Pacific people in New Zealand. The Committee noted the report outlining the recommendations from the Prostate Cancer Taskforce reported that mortality rates for prostate cancer increase and survival rates decrease with increasing levels of socioeconomic deprivation.

Background

8.8. The Committee noted that abiraterone is currently funded for metastatic castration-resistant prostate cancer (mCRPC), but has also been recommended for metastatic, hormone naïve/sensitive prostate cancer with a high priority by the then Cancer Treatments Subcommittee (CaTSoP) in July 2019 and a low priority by PTAC in November 2018.

8.9. The Committee noted that apalutamide, and darolutamide have been previously considered by Pharmac | Te Pātaka Whaioranga (separately) for the treatment of high risk, nmCRPC. The Committee noted that both treatments are ranked on the options for investment list (OFI) following recommendations for this indication with a high priority by CTAC in Mar 2022 for apalutamide, and with a high priority by PTAC in February 2023 for darolutamide.

8.10. The Committee noted that an application for enzalutamide for metastatic hormone resistant prostate cancer (mCRPC) (recommended only if cost-neutral to abiraterone by PTAC in August 2016; and CaTSoP March 2017), is currently ranked on the *only if-cost neutral* priority list. The Committee noted Pharmac had recently consulted to decline this proposal as Pharmac considered cost-neutral pricing is not achievable. An application for mCRPC in in individuals contraindicated to abiraterone is ranked on the OFI following a recommendation with a high priority by CTAC in Nov 2021.

Health Need

8.11. The Committee considered that prostate cancer in New Zealand is associated with a high level of unmet health need. The Committee noted that metastatic, hormone-sensitive prostate cancer (mHSPC) is an incurable illness.

8.12. The Committee considered that there was limited patient-reported outcome and impact data available in relation to mHSPC. The Committee noted that the peak incidence for prostate cancer occurs between the ages of 60 and 75 years (Cancer Research UK. Prostate Cancer Statistics), and considered that given the average survival durations, prostate cancer as a disease is causing significant morbidity.

8.13. The Committee considered that there are a limited number of treatment options available for prostate cancer, and that the durability of treatment response particularly in later lines of therapy is often relatively short.

8.14. The Committee noted that all of the treatment options for prostate cancer have associated toxicity. The Committee noted that common toxicities associated with anti-androgen treatments include hot flashes, loss of libido, myopathy, and osteoporosis/osteopenia which can lead to a loss of independence. The Committee considered that toxicity associated with chemotherapy used in prostate cancer includes neuropathy and bone marrow suppression.

8.15. The Committee considered that prostate cancer may cause psychological morbidity due to the incurable nature of metastatic prostate cancer and living with illness over a long duration. The Committee considered that symptoms of progressive disease, specifically pain, fractures and frailty also contribute to morbidity and loss of independence for people with prostate cancer over time.

8.16. The Committee considered that families and whānau of people with prostate cancer also experience unmet health need. The Committee noted a study of physicians in the US and Europe reported that 42% of individuals with mHSPC had a caregiver. Approximately 89% of caregivers were partners/ spouses that provided a mean of 29.0 hours per week of care (Boye et al J. Clin. Oncol.2022;40;54).

8.17. The Committee considered that the loss of productivity due to morbidity for those with prostate cancer, and for their carers, often occurs at a time when people have major professional and whānau responsibilities.

8.18. The Committee noted statistics for prostate cancer from the New Zealand Cancer registry that each year approximately 4000 men in New Zealand will be diagnosed with prostate cancer, and approximately 500 men each year will die from it. (Te Aho O Te Kahu. Prostate Cancer). The Committee noted that this incidence includes people with localised cancer whose disease may progress to be metastatic, and people with metastatic disease at presentation (de novo). The Committee was unable to differentiate these two groups from the data available. The Committee noted the registration data did not capture the number of people for whom their disease relapses/recurs.

8.19. The Committee noted that since prostate-specific antigen screening stopped in the United States, there has been an increase in incident metastatic prostate cancer in men 50 years and older, though it is unknown if this is consistent in magnitude with the expected impact of decreased screening (Nymae et al. JNCI Cancer SPectr. 2021;5:pkaa098). The Committee considered that it was unclear how relevant this in the New Zealand setting, as New Zealand has never had a formal screening programme.

8.20. The Committee considered that Māori experience higher unmet need associated with prostate cancer than non-Māori, noting that non-Māori tāne (men) are twice as likely to be screened by New Zealand general practitioners [Obertova et al 2014], are more likely to be diagnosed at earlier and treatable stages of the disease [Egan et al 2020], are more likely to be closely monitored with active surveillance [Lao et al 2016; Toh et al 2022], and are more likely to receive surgery [Obertova 2015, Toh et al 2022]. The Committee noted that Māori tāne are more likely have metastatic disease at diagnosis than non-Māori (19.1% vs 9.8%; p=0.012; Lao et al 2016). Māori tāne with

distant metastases at diagnosis are 1.32 times more likely than non-Māori men to die of prostate cancer, irrespective of factors such as age, and socioeconomic status [Obertova et al 2015]. The Committee noted that the State of Cancer in New Zealand 2020 report showed large survival disparity between Māori and non-Māori for prostate cancer. The 2020 noted Lao et al 2016 reported that all-cause survival and the cancer-specific survival were both significantly poorer for Māori men than for New Zealand Europeans (log rank test: P = 0.004, 0.006 respectively). The hazard ratio of cancer-specific survival for Māori men was 2.01 (95% CI: 1.21-3.36) compared with New Zealand Europeans.

8.21. The Committee noted that the State of Cancer in New Zealand 2020 report also showed inequitable age-standardised mortality for prostate cancer for Pacific people in New Zealand.

8.22. The Committee noted the report outlining the recommendations from the Prostate Cancer Taskforce reported that mortality rates for prostate cancer increase with increasing levels of socioeconomic deprivation.

8.23. The Committee considered that restricting new funding for agents for prostate cancer to only Māori tāne would not address all the current inequities in health need. The Committee considered that the most appropriate treatment option should be guided by comorbidities and contraindications. The Committee considered that limiting funding by ethnicity in this indication may contribute to generating further inequities, as other populations with similar health need (eg due to comorbidities) would be excluded from accessing the most appropriate treatment option.

8.24. The Committee noted that abiraterone is currently funded in New Zealand for people with metastatic prostate cancer, which is no longer controlled by ADT (sometimes called hormone-resistant, or castrate-resistant). The Committee considered that people for whom abiraterone is contraindicated experience high unmet health need since those contraindicated to abiraterone are also unlikely to be candidates for docetaxel treatment.

8.25. The Committee noted that docetaxel is currently funded in New Zealand for metastatic prostate cancer, at any point in the illness, and noted there is strong evidence for its use as early or late treatment. (Sweeney et al. N Engl J Med. 2015;373:737-46, Kyriakopoulos et al. J Clin Oncol. 2028;36:1080-7, Clarke et al. Amm Oncol. 2019;30:1992-2003). The Committee considered that people whose clinical status contraindicates the use of docetaxel have a high unmet health need with reduced a chance of survival. The Committee considered that there would be more people contraindicated to docetaxel than abiraterone.

8.26. The Committee noted mineralocorticosteroids given in combination with abiraterone are intended to compensate for abiraterone-induced reductions to physiological mineralocorticoid levels. The Committee considered very few people would have contraindications to this. However, the Committee considered a larger group have contraindications to mineralocorticosteroids being given in combination with docetaxel, which are given at a higher dose over a short period of time.

8.27. The Committee noted that liver function test derangement (signalling incipient liver dysfunction) develops in a small number of people treated with abiraterone (approximately 5%), which can lead to treatment discontinuation (Mori et al. BJU In. 2022;129:423-33, Fizazi et al. N Engl J Med. 2017;377:352-50). The Committee considered the impact on the liver can be permanent and may prevent people from receiving subsequent treatments for prostate cancer.

8.28. The Committee considered it likely that approximately 10-15% of the eligible population would not be able to use abiraterone due to contraindication or experiencing intolerance. The Committee considered it difficult to define this group

further given the individualistic nature of determining the most clinically appropriate treatment option.

Application for apalutamide

8.29. The Committee noted that the application was specifically targeting the population of people with metastatic hormone sensitive prostate cancer (mHSPC). The Committee considered that this population experiences good quality of life (QoL) that treatment can help maintain, noting that QoL decreases as metastatic disease progresses. The Committee noted the current funded treatment for this population in New Zealand is ADT. This may be in combination with docetaxel for people with good performance status, and/or bicalutamide/flutamide if the person experiences loss of response to ADT.

Health benefit

8.30. The Committee noted that apalutamide is an ARI which binds to the ligand-binding domain of the AR, and in preclinical studies, this binding led to inhibition of several processes including nuclear translocation, DNA binding and AR-mediated transcription. The Committee noted that the hypothesis is that this blockade combined with ADT may provide a more complete blockade, and thus a more effective treatment that ADT alone (Alkhudair. Saudi Pharm J. 2019;27:368-72).

8.31. The Committee noted results from the TITAN study, a phase 3, randomised, double-blind, placebo-controlled study assessing the safety and efficacy of apalutamide with ADT (*n* = 525) vs placebo with ADT (*n* = 527) in people with mHSPC (*N* = 1052) (Chi et al. N Engl J Med. 2019;381:13-24).

8.31.1. The Committee noted most participants had good performance status and 10% had received previous docetaxel. The Committee noted the majority of participants were classified as ‘white’ or ‘Asian’ ethnicity.

8.31.2. The Committee noted radiographic progression-free survival (PFS) at 24 months: 68.2% apalutamide group vs 47.5% in the placebo group (hazard ratio (HR) for radiographic progression or death, 0.48; 95% confidence interval [CI], 0.39 to 0.60; P<0.001).

8.31.3. The Committee noted that after these results the study was unblinded, and 29.5% of the placebo arm crossed over to receive apalutamide. The Committee noted that at a median follow up of 44 months, apalutamide was associated with a significantly reduced the risk of death of 35% (median OS not reached v 52.2 months; HR, 0.65; 95% CI, 0.53 to 0.79; P < .0001) and of 48% after adjustment for crossover (hazard ratio, 0.52; 95% CI, 0.42 to 0.64; P < .0001). The Committee considered the crossover adjusted analysis to be more applicable. The Committee noted apalutamide delayed second PFS and castration resistance (P < .0001 for both) (Chi et al J Clin Oncol. 2021;39:2294-303).

8.31.4. The Committee noted that there was little difference in discontinuation between the two groups due to adverse events (8% apalutamide group vs 5.3% in placebo group), with rash being a more common cause for discontinuation in the apalutamide group.

8.32. The Committee noted that the effects of prostate cancer-related pain and fatigue on health-related quality of life discussed in the TITAN trial had people receiving apalutamide plus ADT reporting consistently favorable time to deterioration of pain in comparison to people who received placebo plus ADT, and pain and fatigue were not worsened with apalutamide (Agarwal et al. J Urol. 2021;206:914-23).

8.33. The Committee noted results from a systematic review and indirect comparison network meta-analysis of nine studies investigating the effectiveness of systemic therapies for mHSPC (Mori et al. BJU Int. 2022;129:423-33.) The Committee considered the analysis was somewhat limited by publication bias, and noted the included studies had variable inclusion criteria. The Committee considered there was benefit shown across the studies/therapies in regard to OS, PFS (vs each ADT and docetaxel), with more Grade 3 or above adverse events being reported for enzalutamide and abiraterone than apalutamide.

8.34. The Committee noted results of another systematic review and indirect comparison network meta-analysis of new antiandrogen compounds compared to docetaxel for mHSPC which included 13 studies (Marchioni et all. 2020;203;751-59). The Committee considered the analysis by Marchioni et al is likely to be of better methodological quality than Mori et al. However, the Committee noted similar results were reported across the two meta-analyses; abiraterone (HR 0.71, 95% CI 0.59-0.86), enzalutamide (HR 0.61, 95% CI 0.49-0.75) and apalutamide (HR 0.74, 95% CI 0.57-0.95) also reported statistically significant lower disease progression rates than docetaxel. The Committee considered the results indicate that abiraterone and the three ARIs were all comparable in efficacy and safety, and all presented valuable options to add to the New Zealand treatment paradigm.

8.35. The Committee noted evidence for 'triplet therapy' which includes adding abiraterone or an ARI to ADT and docetaxel (Smith et al. N Engl J Med 2022; 386:1132-42, Fizazi et al. Lancet. 2022;399:1695-707, Riaz et al. JAMA Oncol. 2023;9:635-45). The Committee considered there may be an additional benefit to triplet therapy, but that the magnitude of benefit would be over an ARI in combination with ADT is unclear. The Committee considered that the decision to use triplet therapy should be made by the treating clinicians, rather than being constrained by funding restrictions.

8.36. The Committee considered that good quality evidence indicates the previously noted benefits from abiraterone in this indication, including PFS benefit and maintaining QoL, which can impact whānau as well as the person with prostate cancer. The Committee considered skin rash to be the treatment limiting AE most commonly associated with apalutamide, but that with experience clinicians would be able to manage this. The Committee reiterated their consideration that the health benefit is likely greater in those who are unable to receive other treatments due to comorbidities or contraindications.

Suitability

8.37. The Committee noted that apalutamide is administered as four tablets once per day, taken orally with or without food, with the ADT component being an implant inserted with a syringe subcutaneously every 12 weeks.

8.38. The Committee considered that oral agents including apalutamide, other ARIs and abiraterone may be a more suitable option for people living rurally than docetaxel which is administered via intravenous infusion.

Cost and savings

8.39. The Committee considered that apalutamide is likely to require similar monitoring to that modelled previously for abiraterone for mHSPC. The Committee considered that approximately 20% of people may require more frequent management and nursing support for rash.

8.40. The Committee estimated that approximately 60% of the eligible population would be likely to uptake apalutamide + ADT from year 1, and that this uptake rate would likely stay consistent over the following years.

8.41. The Committee considered that the number of people receiving apalutamide should include both people whose disease stage at registration was metastatic as well as those who had less progressed disease at registration and were still sensitive to ADT.

Summary for assessment

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

Population	Individuals with mHSPC
Intervention	Apalutamide, administered orally at a dose of 240 mg daily (as 4 x 60 mg tablets), in combination with ADT. Treatments is ongoing until disease progression, death or unacceptable toxicity.
Comparator(s) (NZ context)	ADT therapy (~85% according to supplier estimates) ADT therapy + docetaxel (~15% according to supplier estimates) *ADT therapy options include:* • Goserelin – 10.8mg subcutaneous injection every 12 weeks • Bicalutamide 50mg in combination with goserelin – 10.8mg subcutaneous injection every 12 weeks plus bicalutamide 50mg od ADT treatment is ongoing until disease progression, death or unacceptable toxicity. *Docetaxel dosing and administration:* 75mg/m^2 – administered via infusion for a maximum of 6 cycles (cycle length of 21 days).
Outcome(s)	Apalutamide plus ADT compared to ADT alone TITAN study (Chi et al. J Clin Oncol. 2021 Jul 10;39(20):2294-2303) reported Superior efficacy compared to ADT monotherapy measured as: • radiographic progression-free survival (rPS): HR: 0.48; 95% CI: 0.39, 0.60; p<0.0001 • overall survival (OS): HR: 0.65; 95% CI 0.53, 0.79; p<0.0001 • time to PSA progression: HR: 0.27; 95% CI: 0.22, 0.33; nominal p<0.0001 • time to mCRPC: HR: 0.34; 95% CI: 0.29, 0.41; nominal p<0.0001 • time to initiation of cytotoxic chemotherapy: HR: 0.39; 95% CI 0.274, 0.558; p < 0.0001 • Side effect profile is manageable (mild to moderate in severity) HRQoL consistent with treatment with ADT monotherapy Apalutamide plus ADT compared to docetaxel plus ADT No direct comparisons available. Systematic reviews and network meta-analysis indicate apalutamide compared to docetaxel may have: • nonstatistically significant lower overall mortality rates: HR 0.90, 95% CI 0.67-1.22 (Marchioni et all. 2020;203:751-9) • statistically significant lower disease progression rates: HR 0.74, 95% CI 0.57-0.95 (Marchioni et all. 2020, Mori et al. 2022) • statistically significant lower rates of high grade adverse events: OR 0.44, 95% CI 0.24-0.79 (Marchioni et all. 2020)
Table definitions:	

Population: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: 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).

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

First-line treatments for prostate cancer

Metastatic Hormone Sensitive Prostate Cancer

8.43. The Committee reviewed evidence for first line treatments for *de novo* mHSPC. The Committee noted that a range of trials have aimed to identify if adding docetaxel, ARIs and/or abiraterone to ADT (the standard of care) improves overall survival for this indication.

8.44. The Committee noted results from the LATITUDE trial; a Phase 3, multicentre (235 sites), randomised (1:1), double-blind trial comparing the efficacy or ADT + abiraterone/prednisone, to ADT alone in people who were newly diagnosed with metastatic disease, received no prior therapy, had no neuroendocrine features, and good performance status (Fizazi et al. Lancet Oncol. 2019;20:686-700). The Committee noted participants were required to have at least two of the following high-risk features: Gleason score of 8 or more, 3 or more bone metastases, visceral metastases (excluding nodes). The Committee noted median OS reported was 53.3 months in the abiraterone/prednisone group, compared with 36.5 months in the control (ADT alone) group (HR 0.66 (0.56-0.78), *P* <0.001). The Committee noted that only 72 of 602 patients in the control arm crossed over to the active treatment arm on progression, and considered the low crossover strengthened the OS results.

8.45. The Committee noted results from the PEACE 1 trial, a phase 3, open label, randomised (1:1:1:1), open label study with a 2 x 2 factorial design, evaluating the efficacy of abiraterone/prednisone, with or without radiotherapy, in addition to standard of care (ADT +/- docetaxel) (*N* = 1172) (Fizazi et al. Lancet. 2022;399:1695-707). The Committee noted that approximately 80% of participants had a high-risk Gleason score of 8 or over. The Committee noted in the overall population, patients assigned to receive abiraterone (n=583) had longer radiographic progression-free survival (hazard ratio [HR] 0·54, 99·9% CI 0·41-0·71; p<0·0001) and overall survival (0·82, 95·1% CI 0·69-0·98; p=0·030) than patients who did not receive abiraterone. Furthermore in the patients who received docetaxel as well as ADT (n=589) in both with abiraterone and without abiraterone groups), the HRs were consistent with those in the overall population (overall survival 0·75, 95·1% CI 0·59-0·95; p=0·017).

8.46. The Committee noted results from the ARASENS phase 3 trial that evaluated the efficacy of darolutamide in combination with ADT and docetaxel (Smith et al. N Engl J Med 2022;386:1132-42). The trial reported that the risk the risk of death was significantly lower, by 32.5%, in the darolutamide group than in the placebo group (hazard ratio 0.68; 95% confidence interval, 0.57 to 0.80; P<0.001). The trial also reported the incidences of the most common adverse events (occurring in ≥10% of the individuals) were highest during the overlapping docetaxel treatment period in both groups.

8.47. The Committee considered that the above studies showed an improvement in overall survival, with similar hazard ratios. The Committee considered the evidence shows the addition of docetaxel to ADT in the treatment of *de novo* metastatic prostate cancer improves overall survival, with the magnitude of benefit correlating with the patient cohort with high volume disease.

8.48. The Committee considered that the evidence showed addition of abiraterone or an ARI to ADT in the treatment of early metastatic disease improves overall survival. The Committee noted that for some agents, the health benefit has only been tested in high-risk disease. The Committee considered the median duration of treatment with these agents in mHSPC to be 25-39 months. The Committee considered that these agents would provide a same or similar health benefit in this context.

High risk, non-metastatic castration-resistant prostate cancer

8.49. The Committee reviewed evidence for first-line treatments for high risk, non-metastatic, castration resistant prostate cancer. The Committee noted that the definition of high risk varies between studies, but typically relates to the PSA doubling time which has been shown to correlate with the risk of metastasis, or death (Smith et al. J Clin Oncol. 2013;31:3800-6). The definition classically will be a PSA doubling time of 6 or 10 months.

8.50. The Committee noted results from the SPARTAN trial; a phase 3, double-blind, placebo controlled trial evaluating the efficacy of apalutamide for non-metastatic hormone-resistant prostate cancer, at high risk for the development of metastasis (PSA doubling time 10 months or less) (*N = 1207*) (Smith et al. N Engl J Med. 2018;378:1408-18). The Committee noted MFS was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo (ADT only) group (HR for metastasis or death, 0.28; 95% CI, 0.23 to 0.35; *P*<0.001). The Committee noted the study was then unblinded and 19% of people in the placebo arm crossed over to receive apalutamide; at a median follow up of 52-month, median OS was 73.9 months (95% CI 61.2-not reached) in the apalutamide arm vs 59.9 months (52.8-not reached) in the placebo arm with an HR for death of 0.78 (0.64-0.96, *P*=0.016).

8.51. The Committee noted results from the PROSPER trial; a Phase 3, double blind, randomised trial evaluating the efficacy of enzalutamide for non-metastatic hormone-resistant prostate cancer, at high risk for the development of metastasis (PSA doubling time 10 months or less (Hussain et al. N Engl J Med. 2018;378:2465-74). The Committee noted at median 18.2 months of follow MFS was 36.6 months (95% CI 33.1 – not reached) in the enzalutamide group and 14.7 months (14.2 – not reached) in the placebo group, with a HR of metastasis or death of 0.29 (95% CI 0.24-0.35, *P*<0.001). The Committee noted the study was then unblinded and 87 people in the placebo arm crossed over to receive enzalutamide; median OS was 67.0 months (95% CI 64.0 to not reached) in the enzalutamide group and 56.3 months (95% CI, 54.4 to 63.0) in the placebo group (HR for death, 0.73; 95% CI, 0.61 to 0.89; *P* = 0.001) (Sternberg et al. N Engl J Med. 2020;382:2197-206).

8.52. The Committee noted results from the ARAMIS trial; a Phase 3, double blind, randomised, placebo controlled trial evaluating the efficacy of darolutamide for non-metastatic hormone-resistant prostate cancer, at high risk for the development of metastasis (PSA doubling time 10 months or less (Fizazi et al. N Engl J Med. 2019;380:1235-46). The Committee noted that median 17.9 months of follow MFS was 40.4 months (95% CI 34.3 – not reached) in the darolutamide group and 18.4 months (95% CI 15.5-22.3) in the placebo group, with a HR of 0.41 (95% CI 0.34-0.50, *P*<0.001). The Committee noted the study was then unblinded and 170 people in the placebo arm crossed over to receive darolutamide; after a median follow up of 29.9 months median OS was not reached in either group (Fizazi et al. N Engl J Med. 2020;383:1040-9).

8.53. The Committee noted results from an arm of the Phase 3 STAMPEDE study which explored the efficacy of abiraterone/prednisone +/- enzalutamide for two years, in comparison to the standard of care (radiation therapy and three years of ADT) (Attard et al. Annals of Oncology. 2021;32:S1283-346). The Committee noted reported 6-year metastasis-free survival (MFS) was 82% for the apalutamide +/- enzalutamide

group, compared to 69% for the standard of care group. The Committee noted a reported 40% reduction in risk of death in the apalutamide +/- enzalutamide group. However, the Committee noted the result that there was no additional benefit of improvement for MFS or OS with the addition of enzalutamide to abiraterone. The Committee considered that this demonstrated benefit from the addition of abiraterone, but adding enzalutamide did not provide additional benefit.

8.54. The Committee considered that the evidence shows the addition of a non-steroidal androgen receptor inhibitor (apalutamide, darolutamide, or enzalutamide), or abiraterone, to ADT in the treatment of non-metastatic hormone-resistant prostate cancer results in statistically significant and clinically meaningful improvements in MFS and OS, while maintaining QoL. The Committee considered the magnitude of health benefit would be the same or similar across the treatments reviewed, and therefore that health benefits estimated with apalutamide and darolutamide would be applicable to abiraterone and enzalutamide in this indication. The Committee considered that the toxicity associated with these treatments is generally manageable. The Committee considered that combining the agents (eg abiraterone + and ARI) does not offer additional benefit.

Metastatic hormone resistant prostate cancer (mCRPC)

8.55. The Committee noted results from the PREVAIL study (Beer et al. NEJM 2014;371:424-33), a phase III, double-blind, randomised, placebo-controlled trial in 1717 chemotherapy naïve patients with histologically or cytologically confirmed adenocarcinoma of the prostate with documented metastases. The Committee noted that at the planned interim analysis with median duration of follow-up of 22 months, median OS was estimated at 32.4 months in the enzalutamide group compared with 30.2 months in the placebo group. In the enzalutamide group 28% of patients had died compared with 35% in the placebo group (HR 0.71; 95% CI, 0.60- 0.84)

8.55.1. The Committee noted that at 12 months of follow-up, the rate of radiographic PFS was 65% in the enzalutamide arm and 14% in the placebo arm and that the median radiographic PFS was not reached in the enzalutamide arm, as compared with 3.9 months in the placebo arm.

8.56. The Committee noted their September 2013 considerations on the evidence for abiraterone in the treatment of mCRPC. The Committee noted that key evidence was from two double blind, randomised controlled, trials in support of the application; COU-AA-301 (de Bono et al N Engl J Med 2011;364:1995-2005 and Fizazi et al Lancet Oncol. 2012;13:983-92) comparing abiraterone versus placebo in 1095 patients who had received prior chemotherapy (taxane pre-treated population) and COU-AA-302 (Ryan et al. N Engl J Med. 2013;368:138-48) comparing abiraterone versus placebo in 1088 patients who were asymptomatic or mildly symptomatic and had not received prior chemotherapy (taxane naïve population).

8.57. The Committee noted previous advice from PTAC that it is reasonable to consider abiraterone and enzalutamide as being clinically equivalent in the treatment of mCRPC. The Committee considered that it would be reasonable to also consider darolutamide and enzalutamide as clinically equivalent, given the similarities in reported efficacies in other areas of prostate cancer.

Sequential treatments

8.58. The Committee considered that, as noted previously in relation to apalutamide and darolutamide, there is limited evidence to support sequential use of abiraterone following an ARI, or vice versa, and noted a prostate specific antigen (PSA) response was rare (approximately 10%) (CTAC April 2022).

Funding options

8.59. The Advisory Committee acknowledged that some people may be contraindicated to abiraterone. However, the Committee considered that abiraterone, apalutamide, enzalutamide and darolutamide have comparable health benefit and safety considerations and should each be considered to have the same or similar health benefit as treatment options in any indication where one or more have been recommended for funding.

8.60. Noting the concerns regarding the limited evidence to support sequential use of abiraterone following an ARI, the Committee considered that due to the comparative efficacy of ARIs and abiraterone, it would be appropriate to limit funding of a single agent of either class to one line of treatment regardless of disease stage – restricting use to one course in a patient care pathway. The Committee considered funding one of these agents, for single use in any stage of disease, would be a significant step in addressing the unmet health need for prostate cancer in New Zealand.

8.61. The Committee considered that if funding to abiraterone was widened to earlier disease stages, there would remain an unmet health need for those contraindicated (as described above). The Committee considered that any of the ARIs reviewed (apalutamide, enzalutamide, or darolutamide) would provide similar health benefit for people contraindicated to abiraterone, regardless of which treatment setting the agent was given in.

8.62. The Committee considered that it would be important to ascertain the level of uptake of treatment across all indications, if funded at the same time or if funded individually.

8.63. The Committee acknowledged that funding treatments in earlier stages would significantly impact health care resource requirements and add to the already stretched New Zealand medical oncology services. The Committee considered Pharmac should seek further advice from prostate cancer treaters to understand who would be best placed to prescribe and manage the introduction of these medicines and the resource requirements that would be needed to implement any new funding.

9. Atezolizumab – comparison of subcutaneous formulation with intravenous formulation

Application

9.1. The Advisory Committee reviewed the application for atezolizumab subcutaneous formulation for non-small cell lung cancer and all other intra-venous atezolizumab indications.

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

Recommendation

9.3. The Advisory Committee recommended that administration of **atezolizumab subcutaneous formulation and the infusion device** be listed if **cost neutral to the administration of atezolizumab intravenous formulation** within the context of treatment of malignancy subject to the following Special Authority criteria:

> Initial application- non-small cell lung cancer
> Applications only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months
> All of the following:
> 1. Patient has locally advanced or metastatic non-small cell lung cancer; and
> 2. Patient has not received prior funded treatment with an immune checkpoint inhibitor for NSCLC; and
> 3. For patients with non-squamous histology there is documentation confirming that the disease does not express activating mutations of
> 4. EGFR or ALK tyrosine kinase unless not possible to ascertain; and

5. Patient has an ECOG 0-2; and
6. Patient has documented disease progression following treatment with at least two cycles of platinum-based chemotherapy; and
7. Atezolizumab is to be used as monotherapy at a dose of 1875 mg every three weeks for a maximum of 16 weeks; and
8. Baseline measurement of overall tumour burden is documented clinically and radiologically.

9.4. In making this recommendation, the Committee considered:

- the evidence that 1875mg SC atezolizumab every 3 weeks is a non-inferior treatment option compared to 1200mg IV atezolizumab every 3 weeks for the treatment of locally advanced or metastatic NSCLC.
- the frequency of in-person clinical review required for the second-line treatment of NSCLC and the travel a person and or their whānau/family will need to undertake associated with these hospital appointments.
- whether current community health care infrastructure would be able to support the administration of atezolizumab.

Discussion

Māori impact

9.5. The Committee discussed the impact of funding atezolizumab SC for the second line treatment of NSCLC. The Committee noted that Māori are disproportionately impacted by lung cancer with higher incidence rates and presenting at a younger age compared with non-Māori. The Committee noted Māori face access inequity to funded medicines, access barriers to receiving health care, transportation and structural barriers. The Committee considered a community delivered treatment may contribute positively to reducing these barriers for people requiring second line treatment for NSCLC.

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been under-served by the health system

9.6. The Committee discussed the impact of funded atezolizumab SC for the second line treatment of NSCLC for Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been under-served by the health system.

- The Committee noted that Pacific peoples face access inequity to funded medicines, access barriers to receiving health care, transportation and structural barriers.
- The Committee noted people living in rural areas also experience inequities accessing health care including increased travel time compared to people living in urban areas.
- The Committee considered a community delivered treatment may contribute positively to reducing barriers for people requiring atezolizumab for second line treatment of NSCLC. However, the Committee considered that community health care infrastructure is currently insufficiently resourced to support administration of atezolizumab outside of a hospital setting. More investment would be needed to realise these benefits.

Background

9.7. The Committee noted Pharmac | Te Pātaka Whaioranga staff sought advice regarding the benefits for the health system and those requiring treatment if the

subcutaneous formulation of atezolizumab were funded, and if it provides the same benefits as the currently funded intravenous infusions. The Committee noted Pharmac also sought advice to whether this could be extrapolated to other funding proposals for atezolizumab under consideration.

9.8. The Committee noted that IV atezolizumab is funded for the second line monotherapy treatment of metastatic NSCLC.

9.9. The Committee noted that atezolizumab has been previously considered for the:

- second line treatment of locally advanced or metastatic urothelial carcinoma
- adjuvant treatment for NSCLC that is PD-L1 positive
- first-line treatment of extensive-stage small cell lung cancer in combination with chemotherapy
- treatment of advanced or metastatic triple negative breast cancer with >1% PD-LD1 expression in combination with chemotherapy
- first line treatment of unresectable hepatocellular carcinoma in combination with bevacizumab.

9.10. The Committee noted that intravenous atezolizumab has a variable approved maintenance dosing schedule of 840 mg every 2 weeks or 1200 mg every 3 weeks or 1680 mg every 4 weeks. The Committee noted atezolizumab IV formulation is delivered over 60 minutes, with subsequent infusions administered over thirty minutes if the first dose is tolerated.

Health need

9.11. The Committee noted it had previously reviewed the health need for those with NSCLC.

9.12. The Committee noted that Māori are disproportionately impacted by lung cancer with higher incidence rates and presenting at a younger age compared with non-Māori and noted the previous considerations for the health need of Māori with lung cancer for agents for funding in this context (non-small cell lung cancer).

9.13. The Committee noted that Māori are known to face access inequity to funded medicines, access barriers to health care (including costs associated with primary care appointments, prescriptions, as well as access to and cost of transportation and obtaining time off work or childcare cover) and structural barriers (accessing appointments and waiting times) (Achieving access equity in Aotearoa New Zealand: towards a theory of change. Pharmac | Te Pātaka Whaioranga, 2019 and New Zealand Health Survey. Ministry of Health | Manatū Hauroa, 2022). The Committee noted that Māori living in rural areas have a shorter life expectancy than urban Māori, with 1.2 years difference for women and 1.5 years difference for men (Rural health: challenges of distance, opportunities for innovation. National Health Committee, 2010).

9.14. The Committee noted many of the same access barriers to health care (including costs associated with primary care appointments, prescriptions, as well as access to and cost of transportation and obtaining time off work or childcare cover) and structural barriers (accessing appointments and wait times) affect Pacific people (Pharmac, 2019).

9.15. The Committee noted that people in rural areas experience inequities accessing health care, including increased travel time. The Committee noted the National Health

Committee reported that many people in rural areas are concerned about access to health and disability services. (National Health Committee, 2010).

9.16. The Committee considered a community delivered treatment may contribute positively to reducing these barriers for people requiring second line treatment for NSCLC.

9.17. The Committee considered the frequency of in-person clinical review required for the second-line treatment of NSCLC, and the travel a person and or their whānau/family will need to undertake associated with these hospital appointments, will remain similar regardless of the formulation of treatment.

Health benefit

9.18. The Committee noted atezolizumab is a humanised immunoglobin monoclonal antibody that targets programmed cell death protein 1 ligand 1 on tumour infiltrating immune cells or tumour cells. Atezolizumab binds directly and selectively to PD-LD1, thus preventing it from binding to its receptor PD-1 and B7.1 both of which function as inhibitory receptors expressed on activated T-lymphocytes and other immune cells.

9.19. The Committee noted atezolizumab SC formulation contains a fixed dose of 1875 mg of atezolizumab which is administered in a volume of 15mL into the thigh manually or with SC injection device over seven minutes.

9.20. The Committee noted that at the time of the meeting an application for atezolizumab SC had been submitted to Medsafe seeking approval for a fixed dose administered once every 3 weeks across all approved indications for treatment with IV atezolizumab.

9.21. The Committee noted that results of the IMscin001 trial which, following dose determination, was an open label multicentre trial that compared the SC and IV atezolizumab formulations for the treatment of locally advanced or metastatic NSCLC.

9.21.1. The Committee noted Burotto et al. J. Ann Oncol. 2020;31;s820-s821 reported the results of the dose finding study that, at a range of 11-56.1 days, the pharmacokinetics and safety of atezolizumab SC were comparable to IV administration.

9.21.2. The Committee noted Burotto et al. Ann Oncol. 2023;34:693-702, reporting the results of the Phase 3 IMscin001 trial at a median follow up of 4.7 months, indicated that SC dosing regimen of 1875mg every 3 weeks was non-inferior to IV dosing regimen of 1200mg IV every 3 weeks.

9.22. The Committee considered there was sufficient evidence for the non-inferiority of 1875mg SC every 3 weeks compared to 1200mg IV atezolizumab every 3 weeks for locally advanced or metastatic NSCLC.

9.23. The Committee considered that the evidence provided for non-inferiority in NSCLC could be extrapolated to other indications.

9.24. The Committee considered that from the evidence provided they are not aware of any risks associated with people changing from IV to SC atezolizumab.

Suitability

9.25. The Committee noted that greater adherence to treatment is associated with treatments given subcutaneously when compared with intravenously (O'Shaughnessy et al. Eur J Cancer. 2021:223-32). The Committee considered the reduced pain/discomfort, shorter administration time and reduced time in clinic contribute to this outcome. The Committee considered the evidence for improved adherence associated with SC treatments related to different agents in different (ie non-

oncology) settings with lower injection volumes able to given subcutaneously as a single injection by patients themselves in their own homes easily, often unassisted, rather than higher injection volumes via subcutaneous infusion often needing administration by health professionals or the assistance of others.

9.26. The Committee noted the closed syringe of atezolizumab SC can be stored at ≤ 30°C for up to 8 hours in diffuse daylight and in the refrigerator (2°C to 8°C) for up to 30 days.

9.27. The Committee noted the injection volume of atezolizumab SC is 15 mL and this may be unsuitable for some people, such as those with port-a-caths or PICC lines *in situ*.

9.28. The Committee noted that the SC injection devices that can be used to administer SC atezolizumab, however these are single use and carry an expense for the delivery of treatment.

Cost and savings

9.29. The Committee considered that SC atezolizumab would be administered at a fixed dose every 3 weeks.

9.30. The Committee noted subcutaneous treatments are time saving in regard to preparation and administration. The Committee noted there are currently a small number of people requiring atezolizumab for NSCLC and the associated effect on hospital oncology services' infusion capacity overall would be small.

9.31. The Committee considered that if SC atezolizumab was funded, it could be administered in the community by primary care clinics or community health nurses. The Committee considered this may alleviate resource pressures in hospital oncology services. The Committee considered that there would need to be a proactive implementation plan supported by Health New Zealand | Te Whatu Ora to provide training and resources in less urban locations to administer subcutaneous treatment and monitor for and manage any adverse effects. The Committee considered that if not adequately supported, introduction of SC treatments would compete with resources available for IV treatment, and not necessarily save resource to the extent possible.

9.32. The Committee noted there are limited community-based studies on cost and time savings from subcutaneous treatments. Those that have been done had wide confidence intervals and were for different drugs with smaller injection volumes.

9.33. The Committee considered that, if appropriate community-based administration services were in place, SC atezolizumab would primarily be used by people that have to travel long distances to hospital infusion centres, those with limited venous access and those with maintained remission living in rural areas.

9.34. The Committee considered that management of people in the community would require significant oncology nurse input, and this is not available in all districts. The Committee considered in rural areas, primary health care teams would support these people and there is currently limited resource to do so.

10. BRAF and MEK inhibitors for the treatment of unresectable BRAF mutated metastatic melanoma

Application

10.1. The Advisory Committee reviewed the treatment paradigm for unresectable BRAF mutated metastatic melanoma

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

Recommendation

10.3. The Advisory Committee recommended that a BRAF inhibitor and a MEK inhibitor be funded for the treatment of BRAF mutated unresectable metastatic melanoma with a **medium priority**, within the context treatment for malignancy, subject to the following Special Authority criteria:

> **Initiation (metastatic melanoma)** only from a medical oncologist, radiation oncologist, or medical practitioner on the recommendation of a medical oncologist, radiation oncologist. Approvals valid for 6 months from applications meeting the following criteria:
> All of the following
> 1. Patient has metastatic or unresectable melanoma stage III or IV; and
> 2. Baseline measurement of overall tumour burden is documented clinically and radiologically; and
> 3. The patient has ECOG performance score of 0-2; and
> 4. The patient has confirmed BRAF mutation; and
> 5. Patient has received treatment for metastatic melanoma with a funded immune checkpoint inhibitor and has experienced disease progression, or has experienced intolerable side effects or is not able to take an immune checkpoint inhibitor due to contraindication.
>
> **Continuation –** only from a medical oncologist, radiation oncologist, or medical practitioner on the recommendation of a medical oncologist, radiation oncologist. Approvals valid for 4 months from applications meeting the following**:**
> Both
> 1. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
> 2. The treatment remains clinically appropriate, and the patient is benefitting from the treatment.

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

- the unmet health needs of people with unresectable or metastatic BRAF mutated melanoma in New Zealand, particularly people who are ineligible for, intolerant to, or whose disease progresses following treatment with PD-1 inhibitor immunotherapy.

- there generally appears to be similar efficacy and treatment benefit between dual agent targeted therapies (BRAF/MEK inhibitors) for the treatment of advanced BRAF mutated melanoma, but the toxicity profiles vary between the combinations.

- Suitability considerations that it unlikely that there would be an overall reduction in the use of infusion resource, as many people would be expected to also receive immune therapy treatment for their melanoma.

10.5. The Committee did not support the funding of BRAF/MEK inhibitors for the first-line treatment of unresectable or metastatic BRAF mutated melanoma, as results the DREAMseq study suggest that OS is worse for targeted therapy than immunotherapy in the first-line setting.

Discussion

Māori impact

10.6. The Committee discussed the impact of funding BRAF/MEK inhibitors for the treatment of unresectable BRAF mutated metastatic melanoma on Māori health outcomes. The Committee noted melanoma is not one of Pharmac's five Hauora Arotahi - Māori Health Areas of Focus. The Committee considered that given the much lower incidence of melanoma in Māori in comparsion to non-Māori in New Zealand, the funding of BRAF/MEK inhibitors would likely have a relatively limited impact on health outcomes for Māori. The Committee considered that it was,

however, worth noting that that despite a much lower incidence, Māori are more than twice as likely to die from their melanoma (2020 report by Te Aho O Te Kahu).

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been under-served by the health system

10.7. The Committee discussed the impact of funding BRAF/MEK inhibitors for the treatment of unresectable BRAF mutated metastatic melanoma on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been under-served by the health system. 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.

Background

10.8. The Committee noted that a range of B-Raf proto-oncogene, serine/threonine kinase (BRAF) or mitogen-activated protein kinase (MEK) inhibitors have been considered for the treatment of BRAF V600 mutated metastatic melanoma.

10.9. The Committee note that dabrafenib monotherapy and in combination with trametinib, and vemurafenib monotherapy and in combination with cobimetinib have considered at various times for melanoma stage III/IV with BRAF V600. The relative ranking of these proposals has previously been completed. However, the Cancer Treatments Subcommittee (CaTSoP, which is now CTAC) indicated that it would like to review new published evidence for these agents when it became available.

10.10. The Committee noted a range of immune checkpoint inhibitors (PD-1 inhibitors) were also considered by for the wider group of metastatic melanomas. The Committee noted nivolumab, and pembrolizumab have been listed for the treatment of melanoma (previously unresected or metastatic) since 2016.

10.11. The Committee noted that the targeted therapies, BRAF/MEK inhibitors and immune checkpoint inhibitors (immune therapy), were developed and received FDA approvals over a similar time period. The Committee considered this has led to many countries including Australia, Canada, and the United Kingdom, considering either therapy as a reasonable first option for BRAF mutated metastatic melanoma. The Committee considered that due to the tandem development of BRAF/MEK inhibitors and immune therapy, it is very unlikely that future trials will further explore BRAF/MEK inhibitors compared to placebo in this setting, or other sequencing considerations.

10.12. The Committee considered it important to consider the role of BRAF/MEK inhibitors in the first line setting in the context of funded immune therapy, and to understand the benefit of BRAF/MEK inhibitors in the second line setting (following immune therapy).

Health need

10.13. The Committee noted in 2021, registrations of melanoma were reported at a rate of 35.2 per 100,000 (age-standardised to the World Health Organization's standard world population [ASI]) in New Zealand, with 2831 people diagnosed in 2021(Health New Zealand | Te Whatu ora, cancer web tool); between 2017 and 2021, rates of registrations were 46.53, 0.98, 8.67, 2.52 per 100,000 ASI in European/Other, Asian, Māori and Pacific people respectively (Health NZ. cancer web tool). The Committee noted approximately 10% of cases are metastatic at diagnosis (McHugh et al. J Clin Neurosci. 2020;73:144-9).

10.14. The Committee noted activating mutations in BRAF are present in approximately 40% to 60% of advanced melanomas, and in 80% to 90% of cases, this activating mutation consists of the substitution of glutamic acid for valine at amino acid 600

(V600E mutation) with most of the remainder consisting of an alternate substitution (lysine for valine) at the V600 locus (V to K). The Committee noted individuals with BRAF positive melanoma tend to be younger and have poorer survival than people with wild-type melanoma at diagnosis (Normanno. BRAF in Melanoma: ESMO Biomarker Factsheet. 2015) this is due to BRAF-mutated melanomas tending to be more aggressive and are more likely to metastasise to the brain, and are associated with shorter survival in individuals with stage IV tumours than BRAF wild-type (WT) melanomas (Castellani et al.2023).

10.15. The Committee 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. The Committee considered that it was, however, worth noting that that despite a much lower incidence, Māori are more than twice as likely to die from their melanoma (2020 report by Te Aho O Te Kahu).

10.16. The Committee noted a New Zealand study reported that in Pacific peoples, acral lentiginous melanoma (22.9%) was the most common subtype (Sneyd et al. Cancer Epidemiol Biomarkers Prev. 2009;18:1706-13), and therefore less likely to have a BRAF mutation, 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.

10.17. The Committee considered that previously considerations by Pharmac's Advisory Committees for BRAF and MEK inhibitors for melanoma have often focussed on the population with rapidly progressive disease and poor performance status who are ineligible for or have been perceived to not experience sufficient survival time to benefit from immunotherapy. The Committee considered this group represents one group in this disease type with an unmet health need. The Committee considered the other group with unmet health need are people who have progressed on immunotherapy or had to stop treatment due to toxicity and have no other viable systemic treatment options under current the publicly funded treatments.

10.18. The Committee considered that the current treatment paradigm in New Zealand is out of step with the international standard of care due to the lack of availability of BRAF/MEK inhibitor at any stage, noting that both the ESMO and NCCN guidelines recommend consideration of BRAF/MEK inhibitors for people with BRAF mutated advanced melanoma.

Health benefit

10.19. The Committee noted BRAF and MEK inhibitors were developed to to target the cell signalling pathway which mutation of BRAF over-activates, and were initially used as monotherapy. The Committee noted that using BRAF/MEK inhibitors in combination is a strategy to avoid/delay the re-activation of MAPK pathway which leads to the development of resistance to targeted therapy. The Committee noted that despite rapid and high response rates, half of the people treated with BRAF inhibitor monotherapy relapse within six months due to drug resistance (Hauschild et al. Lancet. 2012;380:358-65).

10.20. The Committee noted multiple meta-analyses have been conducted assessing the relative efficacies of BRAF/MEK inhibitors with other melanoma treatment combinations in the first line

10.21. The Committee noted results from Franken et al Eur J Cancer. 2019:123:58-71, an indirect comparison network meta-analysis of 28 Phase 3 randomised controlled trials

of 14,376 people examining 19 first line treatment options for advanced melanoma. The Committee noted for progression-free survival (PFS), dabrafenib plus trametinib (hazard ratio [HR] PFS: 0.21) and vemurafenib plus cobimetinib (HR PFS: 0.22) were identified as most favourable treatments but both had less favourable safety profiles compared to the other treatments. The Committee noted five other treatments were dabrafenib [HR PFS: 0.30], nivolumab plus ipilimumab [HR PFS: 0.34], vemurafenib [HR PFS: 0.38], nivolumab [HR PFS: 0.42], and pembrolizumab [HR PFS: 0.46]). The Committee noted that in contrast, for overall survival (OS), nivolumab plus ipilimumab (HR OS: 0.39), nivolumab (HR OS: 0.46) and pembrolizumab (HR OS: 0.50) appeared more favourable than dabrafenib plus trametinib (HR OS: 0.55) and vemurafenib plus cobimetinib (HR OS: 0.57). The Committee noted another indirect comparison network meta-analysis reported similar results (Zoratti et al. Cancer Treat Rev. 2019:74:43-8).

10.22. The Committee noted results from Wu et al. J Comp Eff Res. 2021;10:267-80, an indirect comparison network meta-analysis of 15 Phase 2 and 3 trials comparing the efficacy of dabrafenib plus trametinib (dab/tram) to other treatments doe the first line treatment of advanced melanoma. The Committee noted, PFS appeared superior in the dab/tram arm compared with monotherapies and compared with immune therapy (PD-1 inhibitors). The Committee noted combination nivolumab plus ipilimumubab appeared statistically significantly superior in terms of OS to dab/tram. The Committee noted high rates of Grade 3 and 4 adverse events (AEs) of 50-70% for dab/tram, and 73% for vemurafenib plus cobimetinib (vem/cobi). The Committee noted the most common AEs with dab/tram were pyrexia, nausea, vomiting, diarrhoea, headache, fatigue and hypertension and the most common AEs with vem/cobi were rash, arthralgia, diarrhoea, fatigue, nausea, pyrexia, derranged LFTs and retinopathy.

10.23. The Committee noted results from Corrie et al Cancer Treat Rev. 2022:110:102463, an indirect comparison network meta-analysis of 43 publications including 15 targeted therapy trials for monotherapy, dual therapy, and triplet therapy with a PD-1 inhibitor. The Committee noted results suggested PFS and OS superiority with dual targeted therapy over monotherapy. The Committee noted triple therapy appeared superior OS to doublet targeted therapy, but this was not statistically significant. The Committee noted another meta-analysis also reported superiority of combination targeted therapy over monotherapy (in regard to PFS and OS) (Kim et al. J Dermatolog Treat. 2018;29:314-21).

10.24. The Committee considered that the meta-analysis evidence indicated PFS improved with dual targeted therapy (BRAF/MEK inhibitors) compared with BRAF inhibitor monotherapy, but dual therapy was also associated with an increased rate of toxicity. The Committee considered PFS was improved with BRAF/MEK inhibitor combination compared with immunotherapies (ie PD-1 inhibitors), but this was also associated with increased toxicity. The Committee considered that OS was generally superior for immunotherapy in comparison to targeted therapies. The Committee considered that there generally appears to be similar efficacy between dual agent targeted therapies, but the toxicity profiles vary between the combinations.

10.25. The Committee reviewed evidence for treatment sequencing in the treatment of BRAF mutated advanced melanoma. The Committee considered there has been long term debate regarding the optimal sequencing of targeted and immunotherapy in this indication. The Committee considered benefits of first-line treatment with targeted therapy is that most people experience a rapid response to treatment, with about a 95% rare of stable disease or better on initial response in the landmark studies (Ascierto et al. Clin Cancer Res. 2021;27:5225-35), showing very few people are refractory to combination targeted therapy. The Committee considered combination targeted therapies are reasonably well tolerated, with manageable toxicity in most

cases. However, the Committee noted resistance to combination targeted therapy usually occurs by 12-18 months on the treatment (Ascierto et al. Clin Cancer Res. 2021;27:5225-35. Conversely, the Committee considered benefits of first-line treatment with immunotherapy were that it more commonly leads to durable responses, but approximately 40% of people have disease refractory to the treatment, and time to response is longer than with targeted therapy (Robert et al. Lancet Oncol. 2019;20:1239-51).

10.26. The Committee noted results from the DREAMseq study, a Phase 3, randomised (1:1) study comparing first line immune therapy (ipi/nivo) to first line targeted therapy (dab/tram) for BRAFV600 m mutated metastatic or unresectable melanoma (*N* = 157) (Persa et al. Dtsch Dermatol Ges. 2021;19:902-04). If a participant's disease progressed on their first treatment, then they moved to 'Step 2' of the trial where they received the other type of treatment.

10.26.1. The Committee noted at a median follow up of 27.7 months, the two-year OS rate was 71.8% in the first-line ipi/nivo arm and 51.5% in the first-line dab/tram arm; the Data and Safety Monitoring Committee (DSMC) considered this result clinically meaningful and recommended the study be closed, and people receiving dab/tram be given the option to switch to ipi/nivo. The Committee noted the overall response rate (ORR) to first-line ipi/nivo was 46%, and to first-line dab/tram was 43%. The Committee noted the ORR for dab/tram was similar whether used first- or second-line, whereas ORR for ipi/nivo was 46% first-line but only 29.6% second-line. The Committee considered this result relevant, although noted that the ipi/nivo combination is not currently funded in New Zealand.

10.26.2. The Committee noted the authors' conclusions from the DREAMseq study were that first-line immunotherapy (with ipi/nivo) followed by dabrafenib/trametinib showed superior 2-year OS than the inverse sequence, which applied across all subgroups in the trial, including those purported to have 'worse' outcomes with immunotherapy. The Committee considered this result was likely due to the improved response when receiving BRAK/MEK treatment in the second line, in comparison to immunotherapy. The Committee noted that participants who died within 10 months in both arms were notable for having poorer prognostic factors. The Committee noted the authors argued that rather than considering induction targeted therapy for poor risk patients, better therapeutic outcomes may be attained by lowering the threshold for switching second line therapy (ie not strictly waiting for disease progression if there are signs first-line immune therapy is failing).

10.26.3. The Committee considered limitation of the DREAMseq study included that the population included a higher-than-expected occurrence of V600K BRAF mutations, which are thought to be more resistant to targeted therapy; relatively strict crossover criteria; and that the conclusions cannot be applied to people with a very high tumour burden or untreated brain metastases, as they were excluded from the study population.

10.27. The Committee reviewed results from the SECOMBIT study, a randomised (1:1:1), three arm, non-comparative, Phase 2 trial in untreated, metastatic BRAFV600 mutant melanoma (N=209) (Ascierto et al. J Clin Oncol. 2023;41:212-21). Arm A (n=69) received encorafenib plus binimetinib (enco/bini) until progressive disease [PD] the received ipi/nivo every 3 weeks for four cycles then nivolumab every 2 weeks, arm B (n=71) received ipi/nivo until PD then enco/bini and arm C (n=69) received encorafenib plus binimetinib for 8 weeks (induction targeted therapy) then ipilimumab plus nivolumab until PD, then enco/bini.

10.27.1. The Committee noted at a median follow-up of 32.2 (IQR, 27.9-41.6) months, median OS was not reached in any arm and > 30 patients were alive in all arms; assuming a null hypothesis of median OS of ≤ 15 months, the OS end point was met for all arms. The Committee noted the 2-year, and 3-year OS rates were 65% (95% CI, 54 to 76) and 54% (95% CI, 41 to 67) in arm A, 73% (95% CI, 62 to 84) and 62% (95% CI, 48 to 76) in arm B, and 69% (95% CI, 59 to 80) and 60% (95% CI, 58 to 72) in arm C.

10.27.2. The Committee noted that although not formally compared, the overall response rate (ORR) for ipilimumab plus nivolumab was numerically higher when given first in the sequence (ie, arm A ORR for ipilimumab plus nivolumab = 25.7%, arm B ORR for ipilimumab plus nivolumab = 44.9%, and arm C ORR for sandwich ipilimumab plus nivolumab = 57.9%).

10.27.3. The Committee noted conclusions from the SECOMBIT study were that clinical benefit was demonstrated from all three approaches, and comparing the approaches was not possible in the trial design. The Committee considered that generally the results aligned with the findings from the DREAMseq study.

10.28. The Committee considered that the available evidence (including the DREAMSeq study) suggests that BRAF/MEK inhibitors are likely no more effective, and potentially associated with shortened overall survival, relative to the currently funded PD-1 inhibitors. The Committee considered that while BRAF inhibitors were associated with a faster time to response, there was no prospectively identifiable subgroup of people who may derive more benefit from a BRAF/MEK inhibitor than from a PD-1 inhibitor. The Committee considered that people with the worst prognosis are often not represented within the clinical trials, and the evidence from DREAMSeq suggested that people with rapidly progressive disease were likely to have a poor prognosis regardless of the treatment administered. The Committee considered that it was therefore appropriate to not recommend BRAF/MEK inhibitors in a first-line setting.

10.29. The Committee considered that there would likely be a small group of people who are currently unable to receive funded PD-1 inhibitor treatment. The Committee considered that for these people with an absolute contraindication to funded PD-1 inhibitors, it may be appropriate for a BRAF/MEK inhibitor to be made available. and who may benefit from a BRAF/MEK inhibitor if it were to be funded. The Committee considered that this was likely a very small group of people with severe immune conditions (e.g. colitis) or have recently undergone transplant, though it was also considered that some people would still receive PD-1 inhibitors post-transplant.

Suitability

10.30. The Committee noted that BRAF/MEK inhibitors are orally administered, and so at an individual level there would be a decrease in the need for intravenous infusions whilst the person is on target therapy. However, the Committee considered it unlikely that there would be an overall reduction in the use of infusion resource, as many people would be expected to also receive immune therapy treatment for their melanoma.

Cost and savings

10.31. The Committee considered that funding BRAF/MEK inhibitors for the second-line treatment of unresectable or metastatic melanoma with confirmed BRAF mutation following immunotherapy with a PD-1 inhibitor is like to be associated with improved PFS and OS relative to best supportive care, but that the magnitude of this benefit is uncertain at this time. The Committee noted that due to the similar timed evolution of immunotherapy and targeted therapy in this indication, there are no studies comparing second-line targeted therapy to best supportive care following immunotherapy. The Committee noted that targeted therapy (BRAF/MEK inhibitors) is

standard of care internationally for people with BRAF mutated advanced melanoma who progress following immunotherapy (Gonzalez-Cao et al. Ann Transl Med. 2023;11:270).

10.32. The Committee considered it would be challenging to estimate the likely magnitude of benefit offered by a second-line BRAF/MEK inhibitor in this setting. The Committee considered that people with BRAF-mutated melanoma likely had a worse prognosis than those without a BRAF mutation, and therefore that using information on an 'all-comers' population to estimate survival on best supportive care was likely to overestimate survival in this setting. The Committee considered that the evidence from SECOMBIT suggested that the rate of response with a BRAF/MEK inhibitor was relatively high, and likely better than the response rate observed with supportive care. However, it was uncertain what the response rate would be with second-line supportive care, or the extent to which a tumour response was likely to be associated with longer survival relative to no tumour response.

10.33. The Committee considered that there was no evidence available for targeted BRAF/MEK treatment in a second-line cohort only, and that there was also no evidence reporting the outcomes with immunotherapy in a BRAF-positive cohort. The Committee considered it was also difficult to establish whether prior treatment with immunotherapy is likely to result in different outcomes with either BRAF/MEK treatment, or best supportive care. The Committee considered that there is some information on outcomes on second-line BRAF/MEK treatment from international registries, which may inform outcomes in intervention arms. However, the Committee considered it was highly difficult to estimate how much more effective a BRAF/MEK inhibitor may be relative to supportive care.

10.34. The Committee considered data from SECOMBIT (Ascierto et al. 2023) could be used to inform what proportion of people progressing onto immunotherapy receive targeted therapy, to estimate the population who may receive BRAF/MEK inhibitors if they were to be funded in the second-line setting. The Committee considered that duration of treatment would also be available from the SECOMBIT study. The Committee considered that SECOMBIT study to be more representative of the real-world population than DREAMseq, but may still overestimate the eligible population as the trial population would have been less unwell than people often presenting in a New Zealand clinical setting.

10.35. The Committee noted BRAF testing is not currently routine in the setting of melanoma. The Committee considered uptake of testing is likely to rise if BRAF/MEK inhibitors were to be funded, although the speed and magnitude of this uptake is uncertain.

Summary for assessment

10.36. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for BRAF/MEEK inhibitors if they were to be funded in New Zealand for unresectable or metastatic melanoma in a second line setting. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant.

10.37. The Advisory Committee noted that elements of in the PICO (population, intervention, comparator, outcomes) for this application is unclear/uncertain at this time. The PICO may develop based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with unresectable or metastatic melanoma, with confirmed BRAF mutation, **who have previously received a PD-1 inhibitor in the metastatic setting**
Intervention	One of the following BRAF/MEK inhibitor regimens: • Trametinib capsules 150mg twice daily with trametinib capsules 2mg twice daily (eviQ - Melanoma metastatic daBRAFEnib and tRAMEtinib) • Vemurefinib capsules 960mg twice daily for across days 1 to 28 of a 28-day cycle and cobimetinib capsules 60mg once daily for days 1 to 21 of a 28-day cycle (eviQ - Melanoma metastatic cOBIMEtinib and vemurafenib) Treatment continued until disease progression or unacceptable toxicity
Comparator(s) (NZ context)	Best supportive care
Outcome(s)	Likely improved rate of response • Response rates in the SECOMBIT trial reported to be 58% in Arm B (second-line BRAF/MEK inhibitor after first-line PD-1), compared to 26% in Arm A (second-line PD-1 after first-line BRAF/MEK) • This response rate is assumed to be higher than that experienced by people receiving no targeted treatment second-line Improved rate of response assumed to be associated with greater survival • Magnitude of potential overall survival benefit uncertain given lack of direct trial evidence • Survival benefit may be approximated using a number of approaches, including international registries, first-line PD-1 evidence, and the evidence from the SECOMBIT trial; however, all of these approaches contain limited information and a high degree of uncertainty
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 patient 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.	

11. Neoadjuvant and adjuvant treatment of resectable Stage III melanoma

Application

11.1. The Committee noted that Pharmac | Te Pātaka Whaioranga staff sought advice regarding:

- Adjuvant and neoadjuvant treatment with pembrolizumab for resected or resectable stage III melanoma. This advice was requested following new information received from the supplier of pembrolizumab, Merck Sharpe and Dohme in September 2023 and recently published American Society of Clinical Oncology (ASCO) guidelines update for melanoma treatments.
- BRAF +/- MEK inhibitors (eg adjuvant dabrafenib and trametinib) alone or in combination for resectable/resected stage III melanoma. While no applications have been received for these treatments in the resected stage III setting, the Committee noted the combination features in the treatment paradigm for resectable/resected stage III melanoma within recent international treatment guidelines (ASCO 2023).

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

Recommendation

11.2. The Committee reiterated its previous recommendation to fund pembrolizumab for the adjuvant treatment of resected stage III melanoma with a **low priority**.

11.3. In making this recommendation, the Committee considered:

- The unmet health need of people with resected/resectable stage III melanoma, including those with BRAF mutations.
- The overall clinical benefit of adjuvant pembrolizumab is uncertain with no evidence of overall survival improvements
- The toxicity risk associated with adjuvant pembrolizumab
- Adjuvant pembrolizumab is expected to incur a high cost to the pharmaceutical budget and health system resources.

11.4. The Committee noted it would welcome a future application for BRAF +/- MEK inhibitors (eg adjuvant dabrafenib and trametinib) alone or in combination for resectable/resected stage III melanoma.

Discussion

Māori impact

11.5. The Committee discussed the impact of funding treatments for resected or resectable stage III melanoma, with and without BRAF mutations, on 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).

Impact on Pacific peoples, disabled people, tāngata whaikaha Māori, and other people who have been under-served by the health system

11.6. The Committee discussed the impact of funding adjuvant and neoadjuvant treatment with pembrolizumab for resected or resectable stage III melanoma, and BRAF/MEK inhibtors (eg adjuvant dabrafenib and trametinib) alone or in combination for resectable/resected stage III melanoma on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been under-served by the health system. The Committee were not aware of not aware of any population groups experiencing health inequities who are disproportionately affected by resectable melanoma.

Background

11.7. The Committee noted that an application for Pembrolizumab has been considered for the adjuvant treatment of resected stage III melanoma.

11.8. In August 2019 and October 2019, respectively, PTAC and the Cancer Treatments Subcommittee (CaTSoP, which is now CTAC) had recommended it be deferred pending further data to support the benefit of use of pembrolizumab in this setting.

11.9. The Committee noted that CaTSoP recommended it be funded with low priority in the context of treatment of malignancy in November 2021, however, in making this

recommendation the CaTSoP had considered that an overall survival benefit with adjuvant pembrolizumab is uncertain and unlikely to become clear due to substantial crossover within the clinical trial.

11.10. The Committee noted previous comments regarding:

11.10.1. The change in tumour staging from American Joint Committee on Cancer (AJCC) 7th Edition to 8th Edition with the introduction of stage 3D disease and prognostic implications of this.

11.10.2. The subtle difference in standard of care with a change from pathological to radiologic staging.

Health need

11.11. The Committee noted stage III melanoma is a malignant skin cancer that has spread locally, regionally or is in transit to a lymph node. About half of all cases of stage III melanoma present de novo at stage III, while the other half progress from stage I/II disease to stage III. Malignant melanomas are genetically highly heterogeneous, acquiring numerous mutations when metastasising (Czarnecka et al. Int J Mol Sci. 2020;21:4576).

11.12. The Committee noted in 2021, 2831 New Zealanders were diagnosed with melanoma corresponding to a registration rate of 35.2 per 100,000 (age-standardised to the World Health Organization's standard world population [ASI]) (Health New Zealand | Te Whatu Ora, cancer web tool, accessed February 2024). The Committee noted there has been an annual 1.8% increase in registrations observed since 2011, and in 2025 there could be an estimated 3,045 cases of melanoma in New Zealand (Ministry of Health. Cancer Registry - New Cancer Registrations [ICD Code C43 - Melanoma]. 2023. Accessed via Qlik on 10 March 2024).

11.13. The Committee noted non-Māori, predominantly New Zealand Europeans, are more than five times more likely to be diagnosed with melanoma than Māori even after adjusting for age (Te Aho o Te Kahu, 2021). However, the Committee noted that Māori are more than twice as likely to die of 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). The Committee noted males with melanoma are at higher risk of disease progression, as are patients with a higher stage of disease within the first 2 years after diagnosis (PTAC, 2019).

11.14. The Committee was made aware of data from Environmental Health Intelligence New Zealand (EHINZ) reporting that deaths due to melanoma in New Zealand decreased from 2015 to 2018. The Committee considered this is likely in part due to the funding of pembrolizumab and nivolumab for metastatic or unresectable melanoma from August 2016.

11.15. The Committee noted activating mutations in the B-raf proto-oncogene (BRAF) gene are present in approximately 40% to 60% of advanced melanomas and in 80% to 90% of cases, the BRAF mutation consists of the substitution of glutamic acid for valine at amino acid 600 (V600E mutation) with most of the remainder consisting of an alternate substitution (lysine for valine) at the V600 locus (V to K).The Committee noted BRAF mutations are more frequent in young patients who are only occasionally exposed to the sun than in chronically sun-exposed individuals (Castellani et al. Cancers (Basel). 2023;15:4026). The Committee noted these melanomas tend to be more aggressive than BRAF wild-type (WT) melanomas and are more likely to metastasise to the brain (Czarnecka et al. 2020).

Health benefit

Pembrolizumab - adjuvant treatment

11.16. The Committee noted result from the EORTC 1325-MG/KEYNOTE-054 trial; a double-blind, randomised (1:1), placebo-controlled, phase 3 trial (*N*=1019) assessing the efficacy of adjuvant pembrolizumab (vs placebo) in stage IIIA-IIIC (AJCC 7th Edition) cutaneous melanoma with metastasis to regional lymph nodes (Eggermont et al. N Engl J Med. 2022;1).

11.16.1. The Committee noted at a median follow up of 4.9 years, 532 participants experienced disease recurrence or death – 40.4% of the pembrolizumab group, and 60.2% of the placebo group.

11.16.2. The Committee noted in the overall intention-to-treat population, pembrolizumab was associated with longer recurrence-free survival (RFS) than placebo (5-year rate of RFS, 55.4% [95% CI, 50.8 to 59.8] vs. 38.3% [95% CI, 33.9 to 42.7]; hazard ratio for recurrence or death, 0.61 [95% CI, 0.51 to 0.72]) and a longer distant metastasis-free survival (DMFS) (5-year rate of DMFS, 60.6% [95% CI, 56.0 to 64.9] vs. 44.5% [95% CI, 39.9 to 48.9]; hazard ratio for distant metastasis or death, 0.62 [95% CI, 0.52 to 0.75]).

11.16.3. The Committee noted that following first recurrence, a PD-1 inhibitor-based treatment was given to 59 (27.2%) people in the pembrolizumab group, and 195 (64.6) people in the placebo group, and a BRAF/MEK inhibitor combination treatment was given to 40 (18.4%) people in the pembrolizumab group and 30 (9.9%) people in the placebo group.

11.16.4. The Committee considered the evidence showed a durable response in the metastatic setting and considered it likely this would be the same population benefiting in the early setting. However, the Committee considered there was no evidence for overall survival benefit from giving pembrolizumab treatment earlier in the treatment paradigm.

11.17. The Committee noted results from the SWOG S1401 trial; a randomised Phase 3 trial to evaluate whether adjuvant pembrolizumab for one year (*n* = 647) improved recurrence-free survival (RFS) or overall survival (OS) in comparison with high-dose interferon alfa-2b (IFNα-2b) for one year or ipilimumab for up to three years (*n* = 654) in people with stage IIIA-IIIC (AJCC 7th Edition) resected melanoma (Grossman et al. Cancer Discov. 2022;12:644-53). The Committee noted that at a median follow up of 4 years compared with either IFNα-2b 2b or ipilimumab, adjuvant pembrolizumab improved relapse-free survival (HR 0.77, 99.62% CI 0.59-0.99) but not OS (HR 0.82, 96.3% CI 0.61-1.9) in the total study population. The Committee noted Grade 3 or higher treatment-related toxicity was less for pembrolizumab (20%) than ipilimumab (49%) or IFNα-2b (72%).

11.18. The Committee considered the association between recurrence free survival and distant metastasis free survival with overall survival to be uncertain in this setting. The Committee noted that pembrolizumab provides a durable response in the metastatic setting but considered there was insufficient evidence at this time that earlier treatment in the adjuvant setting would improve survival outcomes with certainty. The Committee considered that based on the evidence available, it was plausible that the benefits observed for RFS may have no significant impact on overall survival. However, the Committee also considered that the evidence base translating RFS to OS was highly uncertain and that the likely range of possible scenarios should also include the possibility that RFS does have a material relationship with OS.

11.19. The Committee considered that an improvement in RFS associated with adjuvant treatment has an uncertain effect on health-related quality of life (HRQoL) and health system costs. The Committee considered that the available evidence does not yet

support a HRQoL improvement from adjuvant pembrolizumab treatment, and that the presence of recurrence or distant metastases may not necessarily be associated with significant symptoms. The Committee considered that most people who relapse in the New Zealand setting often may not actually realise they have relapsed as they lack relevant symptoms, and the lack of a systematic approach to health sector melanoma surveillance is a key reason for non-symptomatic relapses not being detected. The Committee considered it is plausible that an improvement in RFS may in fact have no meaningful benefit in terms of HRQoL in this setting. The Committee considered that immune checkpoint inhibition can also be associated with significant toxicities, which would also be important to consider when estimating potential net HRQoL impacts of adjuvant treatment.

11.20. The Committee noted adjuvant pembrolizumab would represent a high cost to both pharmaceutical expenditure and the overall health system without clear associated benefits for cancer survival outcomes.

11.21. The Committee considered that a trial powered to show improvements in overall survival from adjuvant immunotherapy compared to standard of care would be important to understand its clinical utility overall and appropriate place in melanoma treatment paradigms.

Pembrolizumab - neoadjuvant treatment

11.22. The Committee noted the following published evidence for neoadjuvant treatment with pembrolizumab for resectable stage III melanoma:

11.22.1. SWOG 21801, a Phase II, randomised (1:1), open-label study where people were given 3 doses of neoadjuvant pembrolizumab as well as 15 adjuvant doses, compared to adjuvant treatment alone (Patel et al. N Engl J Med. 2023;388:813-23). The Committee noted that at a median follow up of 14.7 months, 2-year event free survival was 72% for the neoadjuvant group compared to 49% for the adjuvant only group (P = 0.004). The Committee noted the overall survival HR: 0.63, 95% CI 0.32 to 1.24). The Committee considered pembrolizumab to be fairly well tolerated in this population, noting 11 people (7%) in the neoadjuvant group experienced grade 3-4 surgical toxicity, and 5 people (4%) in the adjuvant group experienced grade 3 surgical toxicity (no grade 4).

11.22.2. An investigator initiated, single centre, phase 1b clinical trial (N = 29) (Huang et al. Nat Med. 2019;25:454-6) where people received a single dose of neoadjuvant pembrolizumab followed by complete resection and adjuvant therapy or up to 1 year, and the long term outcomes of this study (Sharon et al. Ann Oncol. 2023;34:806-12). The Committee noted at a median follow up of 61.9 months there were no deaths in people that experienced a major pathological response (*n* = 8), compared to an overall survival of 72.8% for the remainder of the cohort (*P* = 0.12).

11.23. The Committee considered that current evidence for neoadjuvant therapy that is followed by adjuvant therapy was of a weak strength and low quality. The Committee considered there was also insufficient evidence currently available to support the use of neoadjuvant therapy alone. The Committee considered that the evidence suggests neoadjuvant treatment followed by adjuvant treatment may plausibly offer a benefit in RFS over adjuvant treatment alone, but that this was uncertain. The Committee considered that there is also insufficient evidence to suggest whether neoadjuvant treatment followed by adjuvant treatment is associated with a significant overall survival benefit over adjuvant treatment.

11.24. The Committee noted that melanoma is often detected and many resections are performed in a primary care setting. Because of this, the Committee considered that

many patients who may be eligible for neoadjuvant treatment would likely still receive all cycles as adjuvant treatment. The Committee considered that a shift in the initial care of melanoma would be required to support the use of neoadjuvant immunotherapy in treating melanoma.

BRAF/MEK inhibitors

11.25. The Committee noted results from the five-year analysis of the COMBI-AD trial, a double-blind, randomised (1:1), placebo-controlled trial (*N* = 870) assessing the efficacy of adjuvant dabrafenib plus trametinib (a BRAF/MEK combination) in Stage III melanoma (Dummer et al. N Engl J Med. 2020;383:1139-48). The Committee noted that at a median follow up of 60 months for combination group and 58 months for the placebo group, 52% (95% CI, 48 to 58) of the combination group were alive without relapse vs 36% (95% CI, 32 to 41) of the placebo group (Hazard Ratio [HR] for relapse or death: 0.51, 95%CI 0.42 to 0.61). The Committee noted 65% (95% CI 61 to 71) were alive without distant metastasis in the combination group compared to 54% (95% CI 49 to 60) with placebo (HR 0.55 for distant metastasis or death, 95% CI 0.44 to 0.70). The Committee noted no significant difference in incidence or severity of serious adverse events during follow up.

11.26. The Committee noted patient-reported outcomes from the COMBI-AD trial (Schadendorf et al. Lancet Oncol. 2019;20:701-10). At a median follow up of 34 months, the Committee noted that patient reported outcomes were not adversely affected by combination therapy for health-related quality of life, and all other assessments.

11.27. The Committee noted results from the BRIM8 trial; a negative phase III trial of adjuvant vemurafenib monotherapy for BRAF mutation-positive resected stage III melanoma (BRIM8). The primary endpoint was not met (Maio et al. Lancet Oncol. 2018;19:510-20) and treatment was associated with clinically meaningful worsening in some treatment- or disease-related symptoms (Schadendorf et al. Eur J Cancer. 2019:123:155-61).

11.28. The Committee also noted the following published evidence for adjuvant treatment with BRAF/MEK inhibitors for resectable stage III melanoma:

- Long et al. N Engl J Med. 2017;377:1813-23
- Hauschild et al. J Clin Oncol. 2018;36:3441-9
- Dummer et al. Lancet Oncol. 2020;21:358-72
- Atkinson et al. Eur J Cancer. 2022:163:79-87
- Maio et al. Lancet Oncol. 2018;19:510-20
- Schadendorf et al. Eur J Cancer. 2019:123:155-61

11.29. The Committee noted the updated American Society of Clinical Oncology (ASCO) guidelines for systemic therapy for melanoma (Seth et al. J Clin Oncol. 2023;41:4794-820) recommend adjuvant therapy for BRAF-mutated melanoma consists of either one year of immunotherapy with either nivolumab or pembrolizumab, or one year of treatment with dabrafenib plus trametinib, with both of these options being regarded as effective, with different toxicity profiles. However, the Committee considered that the optimal therapy has not been established since these treatment options have not been directly compared in randomised clinical trials.

11.30. The Committee noted the following published evidence for neoadjuvant treatment with BRAF/MEK inhibitors for resectable stage III melanoma:

- Amaria et al. Lancet Oncol. 2018;19:181-93
- Long et al. Lancet Oncol. 2019;20:961-71
- Zippel et al. J Surg Oncol. 2017;116:856-61
- Hieken et al. Nat Commun. 2024;15:1430
- Bai et al. eClinicalMedicine. 2023; 65: 102290
- Mazano et al. Melanoma Res. 2023; 33: 388–97

Suitability

11.31. The Committee noted that immunotherapies (eg pembrolizumab) are administered as intravenous infusions in hospital infusion clinics, and considered that treatment with these therapies will require travel and additional time for travel, administration and on-treatment monitoring, potentially affecting an individual's work, family and finances, and may particularly impact people living in rural settings.

11.32. The Committee considered that BRAF and MEK inhibitors as oral medications would be expected to have a lesser impact and greater suitability for individuals with resectable stage III melanoma and their whānau compared with stage IV treatments. However, the Committee noted that as these treatments are targeted to mutation positive disease, they therefore would not be suitable for the broader group of people with resectable stage III melanoma.

Cost and savings

11.33. The Committee considered uptake of (neo)adjuvant therapies for stage III melanoma (i.e., BRAF/MEK inhibitors and/or PD-1 inhibitors) would be high if they were to be funded in New Zealand, although members noted that some people may elect to not receive therapy due to the risk of lifelong toxicities.

12. Other Business

12.1. There was a brief discussion about committee membership.