Record of the Cancer Treatments Advisory Committee Meeting held on 21 July 2023

Cancer Treatments Advisory Committee (CTAC) 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 CTAC Advisory Committee meeting; only the relevant portions of the meeting record relating to CTAC discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

CTAC may:

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

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

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

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

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

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

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

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1. Attendance

Present
Stephen Munn (Chair)
Alannah Kilfoyle
Alice Loft
Anne O'Donnell
Chris Frampton
Chris Hemmings
Matthew Strother
Michelle Wilson
Oliver Brake
Peter Ganly
Richard Issacs
Scott Babington
Vidya Mathavan

Apologies
Lochie Teague

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• Ribociclib within the context of treatments of malignancy	High priority
• Nivolumab and ipilimumab as a combination immunotherapy first-line treatment of clear cell renal carcinoma with **intermediate and poor** International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy	High priority
• Nivolumab and ipilimumab as a combination immunotherapy first-line treatment of clear cell renal carcinoma with **poor, intermediate and favourable** International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy	Low priority
• Cabozantanib and nivolumab as combination tyrosine kinase inhibitor (TKI)/immunotherapy first-line treatment of clear cell renal carcinoma with poor, intermediate and favourable International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy	High priority
• Pembrolizumab for the treatment of metastatic mis-match repair deficient pancreatic cancer	Defer
• Zanubrutinib for the first-line treatment of previously untreated CLL with 17p deletion/TP3 mutation with a within the context of treatment of malignancy	High priority
• Zanubrutinib for the treatment of relapsed/refractory CLL without 17p deletion/TP3 mutation within the context of treatment of malignancy	Cost neutral
• Zanubrutinib for lines of treatment where ibrutinib is currently listed within the context of treatment of malignancy	Cost neutral
• Zanubrutinib for the first-line treatment of Waldenström macroglobulinaemia within the context of treatments of malignancy	Low priority
• Zanubrutinib for the treatment of individuals with relapsed/refractory Waldenström macroglobulinaemia	Medium priority

within the context of treatment of malignancy	
• Zanubrutinib for relapsed/refractory mantle cell lymphoma (MCL) within the context of treatment of malignancy	High priority

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

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

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

4. Record of PTAC meeting held Thursday, February 23, 2023

4.1. The Advisory Committee noted the record of the February 2023 PTAC meeting.

4.2. The Advisory Committee noted PTAC had recommended an application for darolutamide for high risk non-metastatic-castration resistant prostate cancer (nmCRPC) to be funded with a high priority. The Advisory Committee agreed with this recommendation but wished to emphasise the high unmet health need across prostate cancer and the health benefits from this class of medicine. The Advisory Committee considered that its November 2021 considerations for the subsequent use of abiraterone after apalutamide if funded for high risk nmCRPC would also apply to Pharmac's assessment of darolutamide.

4.3. The Advisory Committee considered it appropriate that all future funding applications concerning oncology medicines be reviewed by CTAC initially.

5. Matters Arising

5.1. Assessment of crizotinib and entrectinib for ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS1) non-small cell lung cancer

5.1.1. The Committee noted that the tyrosine kinase inhibitors (TKIs) entrectinib and crizotinib had been previously reviewed by CTAC (April 2021) as first-line treatment options for locally advanced or metastatic ROS Proto-Oncogene 1, Receptor Tyrosine Kinase (ROS1)-rearranged non-small cell lung cancer (NSCLC). The Committee noted that these are currently ranked on Pharmac's options for investment list, and that at the time of assessment, the comparator was platinum-based chemotherapy.

5.1.2. The Committee noted that since this time, Pharmac has funded pembrolizumab, either as combination therapy with chemotherapy (any programmed death ligand -1 (PD-L1) expression) or as monotherapy (for individuals with PD-L1 >50%), as first-line treatment for NSCLC. The Committee noted that in light of this funding decision, the assessment for entrectinib and crizotinib would be updated. To support this update, advice is being sought from Pharmac on the impact of pembrolizumab funding on the outcomes for people with ROS1-rearranged NSCLC. The Committee considered that as ROS1-rearrangement testing is currently not generally utilised in the New Zealand setting, it was appropriate to consider that pembrolizumab +/- platinum-based chemotherapy would now be the comparator for this group.

5.1.3. The Committee noted evidence indicating that people with NSCLC with ROS1-rearrangement experience improved outcomes using pemetrexed-based chemotherapy compared with people with NSCLC without the driver mutation (Chen et al. J Thorac Oncol. 2016;11:1140-52). The Committee considered that outcomes for people with ROS1-rearrangement on pemetrexed were likely substantially inferior to outcomes achieved with targeted therapy (ie TKIs).

5.1.4. The Committee noted the lack of evidence supporting the benefit of immune checkpoint inhibitors (ICIs) in people with ROS1-rearranged NSCLC. The Committee noted that the pivotal clinical trials excluded people with epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutated NSCLC, but not ROS1-rearrangement. The Committee considered that the inclusion of those with ROS1-rearrangement in the trial was likely due to a lack of evidence in the group, rather than suggestive that outcomes would be similar between those with ROS1-rearrangement and NSCLC without driver mutations.

5.1.5. The Committee noted evidence from Mazieres et al. Ann Oncol. 2019;30:1321-28, which described outcomes of 551 individuals with driver mutations including Kirsten rat sarcoma virus (KRAS), EGFR, and ROS1, ICIs. The Committee noted that seven of these individuals had ROS1-rearrangements, and the objective response rate was 17% in this group. The Committee noted that there were too few people with ROS1-rearranged NSCLC to estimate progression free survival.

5.1.6. The Committee considered it unlikely that the addition of ICIs to chemotherapy would provide a clinically significant health benefit for the treatment of ROS1 mutated NSCLC compared to chemotherapy alone. The Committee noted evidence of higher tumour mutational burden (TMB) associated with smoking leading to better outcomes with ICIs (To et al. Front Oncol. 2021;11:635007). The Committee also noted those with driver mutations (including ROS1-rearrangement) often have lower rates of TMB and higher rates of never-smokers, compared to those with NSCLC and no rearrangement. The Committee considered that this may provide a biological rationale to support the lack of efficacy of ICIs in many driver-mutated NSCLCs.

5.1.7. The Committee considered that the reduction in the risk of disease progression and death observed for pembrolizumab in individuals with wild-type ROS-1 in KEYNOTE-189 (Rodríguez-Abreu et al. Ann Oncol. 2021;32:881-95) was unlikely to be applicable for individuals whose cancer has ROS1-rearrangement treated with pembrolizumab. The Committee considered that rates of disease progression and death for those with a ROS1-rearrangement receiving pembrolizumab are likely similar to that experienced on pemetrexed-based chemotherapy alone. The Committee considered that the addition of pembrolizumab in this group was likely to offer small or no reduction in the risk of disease progression or death. The Committee considered that the relative reduction in the risk of progression or death in this group was likely significantly lower than in KEYNOTE-189.

5.1.8. The Committee considered that crizotinib or entrectinib would likely offer a health benefit for those with ROS1-rearrangement compared to ICIs, given the

demonstrated benefit of crizotinib and entrectinib over chemotherapy in this group (Shen et al. Cancer Med. 2020;9:3310-8, Shaw et al. N Engl J Med. 2014;371:1963-71., Chen et al., 2016), and the limited evidence of benefit for ICIs. The Committee noted that there was no direct comparison for these treatments in the population considered, and nor would evidence likely become available. The Committee considered that indirect comparison of data indicated probable superior efficacy with crizotinib or entrectinib compared to ICIs in this population (Rodríguez-Abreu et al., 2021).

Population	Newly diagnosed ROS1 rearranged non-small cell lung cancer
Intervention	Tyrosine kinase inhibitors (crizotinib or entrectinib)
Comparator(s)	Pembrolizumab either as: • Combination therapy with chemotherapy (any PD-L1 expression) or, • Monotherapy (for individuals with PD-L1 >50%)
Outcome(s)	Longer PFS and OS compared to pembrolizumab, based on: • Direct evidence that TKIs offer a significant benefit over chemotherapy • Absence of evidence that pembrolizumab is much more efficacious than chemotherapy in the population • Biological rationale to support a lack of significant efficacy of ICIs in the population
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

5.2. Osimertinib for epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC)

Recommendation

5.2.1. The Committee recommended Pharmac staff defer further analysis until additional overall survival follow-up evidence is reviewed by the Committee.

Discussion

5.2.2. The Committee noted that the osimertinib for the treatment of epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC) post-resection had previously been considered by PTAC in May 2022 (2022-05 PTAC Record), in which it received a medium priority funding recommendation, with PTAC noting the significant disease-free survival benefit, the convenience and suitability of an oral treatment, and the high unmet health need.

5.2.3. The Committee considered that people with resectable EGFRm-positive NSCLC who experience disease progression post-resection are treated the same as those with non-resectable disease and receive erlotinib or gefitinib. The Committee considered that this regimen would apply only to the counterfactual arm of any health economic assessment model. For the intervention arm, those whose disease had progressed while still on adjuvant osimertinib would be more likely to proceed directly to platinum-based chemotherapy. For those with disease progression after completing three years of osimertinib, the Committee was unable to gauge what optimal ongoing treatment would be in the New Zealand setting. If status quo were maintained in terms of funded agents in the advanced setting in New Zealand, the Committee considered many of these individuals would likely receive erlotinib or gefitinib.

5.2.4. The Committee considered that there may be approximately 18 people eligible for osimertinib treatment in the adjuvant setting. This estimate was based on the number

of people diagnosed with adenocarcinoma over the period 2015-18 (Lung Cancer Quality improvement report. Te Aho, 2021. p8), the proportion who can have curative resection, the proportion of those who can have resection who are stage IB-IIIA (Te Aho, 2021), and the proportion who are EGFRm positive (Aye et al. Cancer Epidemiology 2020; 69:101847).

6.2.4.1. In making this estimate, the Committee considered that those with squamous histology are unlikely to be EGFRm positive, and therefore were not included in the estimate of the size of the eligible population.

5.2.5. The Committee considered the supplier uptake estimates based on Australian market data to be conservative, and that uptake may rise faster than the supplier had assumed due to the more mature evidence of overall survival being now available to support prescribing decisions.

5.2.6. The Committee noted that there had been criticism of the key ADAURA trial investigating the use of osimertinib in the adjuvant setting (Wu et al. N Engl J Med. 2020;282:1711-23). The Committee considered the following concerns with the trial:

5.2.6.1. The significant proportion of people in the control arm who did not receive osimertinib at any point in the trial i.e., upon disease recurrence only 43% received osmiertinib upon recurrence in the control arm (Tsuboi et al. N Engl J Med 2023;389(2):137-47, Supplementary Appendix Figure S2 and Table S4) . With 57% of people in the control arm not receiving osimertinib at any point in the trial, it is possible that the OS benefit would be overestimated. Members considered that with the current level of data maturity, it was not clear whether OS gains were attributable to osimertinib use post-resection or for relapsed disease.

5.2.6.2. The Committee considered that it was important to assess whether osimertinib post resection resulted in more people being cured than in the control arm, since this would not be influenced by subsequent treatments. The Committee considered that overall survival data was not yet mature enough to answer this question, given that people were on treatment for up to three years, but data is currently only available through year five.

5.2.6.3. Members noted that in each arm of the trial, 60% of people received adjuvant platinum-based chemotherapy, and considered that this would likely be a greater proportion than currently receive chemotherapy in this setting in New Zealand.

5.2.7. The Committee noted that the ADAURA trial is going through additional follow-up analysis, and that this will be important in assessing the overall survival benefit and likelihood of curative outcomes. The Committee asked to review the application again upon the receipt of additional follow-up evidence, and that the application should be reconsidered in one year's time.

5.2.8. The Committee considered three years to be a significant amount of time on treatment, and considered it likely that additional health system use would be required, such as 6-monthly CT scans and 3-monthly outpatient visits The Committee considered the England/Wales National Institute for Care Excellence (NICE) assumption (NICE TA761 Appraisal Committee papers) that those who survived five years post-treatment initiation are cured to be flawed, but considered the assumption that those who survive eight years are cured to be reasonable. Eight years was considered more reasonable than five years because it allowed for a reasonable period between treatment cessation at three years and the assumption of a cure (two years compared to five years).

Summary for assessment

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

Population	People with EGFRm positive NSCLC who have had tumour resection.
Intervention	Osimertinib, 80mg (tablet) once per day until disease progression or max duration of 3 years (whichever is earlier). On progression, optional: 1) platinum based chemotherapy 2) docetaxel
Comparator(s)	Platinum based chemotherapy On progression: erlotininb or gefitinib
Outcome(s)	Longer disease-free survival (median disease-free survival in the ADAURA trial was 27.5 months for placebo and not reached for Osimertinib). Overall survival is expected to be longer, however data to date is too immature to draw conclusions from. The OS outcome will be assessed upon receipt of additional follow-up evidence
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

5.3. Pertuzumab for neoadjuvant treatment of early breast cancer

Discussion

5.3.1. The Committee noted that pertuzumab for the neoadjuvant treatment of HER2-positive early breast cancer (eBC) has been reviewed at previous committee meetings, most recently in October 2022, where it was recommended for funding with a medium priority.

5.3.2. The Committee noted that trastuzumab emtansine (TDM-1) has been funded since July 2022 as adjuvant treatment for HER2-positive eBC in people with residual invasive disease after surgery, and that Pharmac staff were seeking advice on how the magnitude of benefit offered by a pathological complete response (pCR) from neoadjuvant treatment with pertuzumab may be affected by the widening of access to TDM-1.

5.3.3. The Committee was made aware of a study investigating the relationship between pCR and individual prognosis in early HER2-positive breast cancer following neoadjuvant systemic treatment consisting of chemotherapy plus anti-HER2 therapy (Van Mackelenbergh et al. J Clin Oncol 2023;41:2998-3008). The Committee noted that the studies included in this publication were all published prior to the KATHERINE trial (Von Minckwitz et al. N Engl J Med 2019;380:617-28), which investigated the use of adjuvant TDM-1 in early breast cancer. The Committee considered that the evidence suggested that the magnitude of benefit offered by a

pCR is influenced by initial prognostic factors, such as T-stage and nodal status, and that it likely differs across different breast cancer phenotypes. The Committee considered it was important that these initial prognostic factors be factored in when modelling the benefit of a pCR.

5.3.4. The Committee was made aware of a publication assessing the use of pCR as a surrogate for event-free survival (EFS) and overall survival (OS) (Squifflet et al. J Clin Oncol 2023;41:2988-97). The Committee noted that this publication reported strong patient-level associations between pCR and EFS and between pCR and OS, although the trial-level associations were reported to be weak, with low R-squared values.

5.3.5. The Committee considered that the patient-level association between pCR and survival is strong and that experiencing a pCR is associated with a greater likelihood of survival. However, the Committee noted that such a relationship is imperfect and considered there are a large number of confounding factors, including differences in treatments received according to response, differences in prognostic factors, improvements in overall survival outcomes over time, and the time difference between pCR and relapse or death. The Committee noted that these factors, and how they differ in individuals across trials, were important to consider when modelling the benefit of a pCR.

5.3.6. The Committee considered that the large number of other confounding variables influencing survival means the degree to which pCR can predict survival is modest. The Committee considered that at a trial level, the assumption of proportional hazards may not hold, given changes in the hazard rate over time. The Committee therefore considered that odds ratios for response and survival at a patient-level do not necessarily translate to a trial-level EFS or OS benefit.

5.3.7. With the KATHERINE trial of TDM-1 as adjuvant treatment (Von Minckwitz et al. 2019), the Committee noted its participants were generally at a relatively early stage (predominantly stages T1-T3 and node negative), and a high proportion were hormone receptor positive. The Committee considered that this group had a relatively good prognosis compared to other trials, which may make it challenging to compare across trials.

5.3.8. The Committee considered that the overall survival benefits associated with a complete response in the Van Mackelenbergh publication (HR 0.32, 95% CI 0.26-0.41) were larger and more significant than the OS benefits observed in the KATHERINE trial (HR 0.70, 95% CI 0.47-1.05). The Committee noted that the better prognosis among people in the KATHERINE trial may make it harder to detect OS benefits. The Committee considered, based on a naïve comparison of the two studies and the evidence currently available, that there was probably greater certainty of an OS benefit upon a pCR in the neoadjuvant setting, compared to receiving TDM-1 in an adjuvant setting.

5.3.9. The Committee considered that while the funding of adjuvant TDM-1 for those without a pCR in the neoadjuvant setting is likely to reduce the incremental benefit offered by a neoadjuvant pCR, that experiencing a pCR with adjuvant pertuzumab is likely to still provide a health benefit, particularly for survival.

5.3.10. The Committee considered that people who achieve a complete response in the neoadjuvant setting are likely to receive subsequent adjuvant treatment with trastuzumab, while those people who do not experience a complete response are likely to receive adjuvant treatment with trastuzumab emtansine.

5.3.11. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab if it were to be funded in New Zealand for neoadjuvant treatment of

HER2+ breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with HER2 IHC3+ or ISH+ expressing, locally advanced or inflammatory breast cancer which is treatment-naïve
Intervention	Pertuzumab for up to 4 cycles in combination with neoadjuvant trastuzumab and chemotherapy This is followed by adjuvant treatment with: - Trastuzumab emtansine for those without pCR - Trastuzumab for those with pCR
Comparator(s) (NZ context)	Neoadjuvant trastuzumab and chemotherapy As above, followed by adjuvant treatment with: - Trastuzumab emtansine for those without pCR - Trastuzumab for those with pCR
Outcome(s)	Increase in rates of pCR compared to neoadjuvant trastuzumab - Greater rates of tpCR likely to be associated with an improvement in EFS and OS, based on the publication by Van Mackelenbergh et al. J Clin Oncol 2023;41: 2998-3008 - Reduction in TDM-1 use in an adjuvant setting likely to be associated with an increase in the utilisation of TDM-1 in a metastatic setting, owing to the once-per-patient-lifetime restriction on TDM-1 with the current Pharmac funding restrictions Magnitude of benefit offered by pCR likely to be less than that described in the Van Mackelenbergh publication, due to the availability of adjuvant TDM-1 - However, pCR in the neoadjuvant setting is likely to maintain a health benefit over and above the current treatment paradigm

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.

5.4. Cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors

Recommendation

5.4.1. The Advisory Committee **recommended** that ribociclib be listed with a high priority within the context of treatments of malignancy, subject to the following Special Authority criteria (new criteria in **bold**):

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:
All of the following:

1. Patient has unresectable locally advanced or metastatic breast cancer; and
2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
3. Patient has an ECOG performance score of 0-2; and
4. Any of the following:
   - 4.1. Disease has relapsed or progressed during prior endocrine therapy (second or subsequent line setting**)**; or
   - 4.2. (first-line setting) Both:
     - 4.2.1. Patient is amenorrhoeic, either naturally or induced, with endocrine levels consistent with a postmenopausal **or without menstrual-potential** state; and
     - 4.2.2. Patient has not received prior systemic endocrine treatment for metastatic disease;
5. Treatment must be used in combination with an endocrine partner.
6. **Patient has not received prior funded treatment with a CDK4/6 inhibitor**

Renewal - only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Treatment must be used in combination with an endocrine partner; and
2. There is no evidence of progressive disease; and
3. The treatment remains appropriate and the patient is benefitting from treatment.

5.4.2. In making this recommendation, the Committee noted the reported differences in overall survival between ribociclib and the currently funded palbociclib and the health need of people with hormone receptor positive breast cancer.

Discussion

5.4.3. The Committee noted that at its October 2019 meeting, it had considered that, based on the data available at the time, there was a class effect from cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in the treatment of hormone receptor (HR)-positive, HER2-negative locally advanced breast or metastatic breast cancer, such that any agent in this class would be expected to provide the same or similar health benefits.

5.4.4. The Committee noted that following a Request for Proposals (RFP) for CDK4/6 inhibitors, Pharmac approved in March 2020 the funding of palbociclib (brand name Ibrance) for both the first-line and second-line treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer, and that palbociclib was awarded Sole Supply Status until 30 June 2023.

5.4.5. The Committee noted that a generic palbociclib, supplied and manufactured by the same supplier has recently received Medsafe approval.

5.4.6. The Committee noted that since its previous recommendation, there was updated data for both palbociclib and ribociclib and that Novartis had requested a listing of ribociclib alongside palbociclib.

Ribociclib overall survival data

5.4.7. The Committee noted that at the time of its October 2019 recommendation, it considered the overall survival data for ribociclib was immature. The Committee noted that since that time, overall survival data from ribociclib pivotal trials had been published.

5.4.8. The Committee noted the published data of the three pivotal MONALEESA trials that became available following the previous Committee consideration of ribociclib, submitted by the supplier of ribociclib.

5.4.8.1. The Committee noted published data from the MONALEESA 2 phase 3, randomised, double-blind, placebo-controlled trial comparing first-line ribociclib in combination with letrozole to placebo in postmenopausal women with locally confirmed, HR-positive, HER2-negative recurrent or metastatic breast cancer who had not received previous systemic therapy for advanced disease (Hortobagyi et al. N Engl J Med 2022;386:942-50). The Committee noted that following a median follow up of 6.6 years, the median overall survival in the ribociclib group was 63.9 months vs 51.4 months in the placebo group (HR 0.76, 95% CI 0.63 to 0.93).

5.4.8.2. The Committee noted published data from MONALEESA 3 phase 3, double-blind, placebo-controlled trial comparing ribociclib plus fulvestrant to placebo plus fulvestrant in men and postmenopausal women aged 18 years and over with HR-positive, HER2-negative advanced breast cancer, in both a first and second-line setting (Slamon et al. N Engl J Med 2020;382:514-24). The Committee noted the median overall survival in the overall study population was not reached in the ribociclib group vs 40.0 months in the placebo group (HR 0.72, 95% CI 0.57 to 0.92); in the first-line treatment setting median overall survival was not reached for the ribociclib group vs 45.1 months in the placebo group (HR 0.70, 95% CI 0.48 to 1.02); and in the second-line setting median overall survival was 40.2 months in the ribociclib group vs 32.5 months in the placebo group (HR 0.73, 95% CI 0.53 to 1.00).

5.4.8.3. The Committee noted published data from MONALEESA 7 phase 3, randomised, double-blind, placebo-controlled trial comparing ribociclib plus endocrine therapy (goserelin and either a non-steroidal aromatase inhibitor or tamoxifen) compared to placebo plus endocrine therapy in premenopausal or perimenopausal women aged 18 to 59 with HR-positive, HER2-negative breast cancer (Im et al. N Engl J Med 2019;381:307-16). The Committee noted that following a median follow up of 53.5 months, the median overall survival in the overall study population was 58.7 months in the ribociclib group vs 48.0 months in the placebo group (absolute difference +10.7 months, HR 0.76 95% CI, 0.60 to 0.96), in the aromatase inhibitor subpopulation median overall survival was 58.7 months in the ribociclib group vs 47.7 months in the placebo group (absolute difference +11.0 months, HR 0.80, 95% CI 0.62 to 1.04); and in the tamoxifen subpopulation overall survival was not reached in the ribociclib group and 49.3 months in the placebo group (absolute difference incalculable, HR 0.71, 95% CI 0.45 to 1.10).

5.4.9. The Committee considered that, overall, the three trials demonstrated an overall survival benefit for ribociclib. The Committee considered that overall survival improvements from the addition of ribociclib in the MONALEESA trials were unlikely to be due to subsequent therapy, as a significant proportion of the control groups used a CDK4/6 inhibitor on disease progression.

5.4.9.1. The Committee noted in MONALEESA 2, upon progression CDK4/6 inhibitors were used by 21.7% of the ribociclib group and 34.4% of the placebo group, with no difference in the use of chemotherapy.

5.4.9.2. The Committee noted in MONALEESA 3, upon progression CDK4/6 inhibitors were used by 14.0% of the ribociclib group and 30.0% of the placebo group.

Ribociclib and palbociclib class effect considerations

5.4.10. The Committee noted that there are structural differences between palbociclib and ribociclib, culminating in ribociclib being more active against CDK4 than CDK6, and palbociclib equally inhibiting CDK4 and CDK6.

5.4.11. The Committee considered the overall survival benefit reported in the MONALEESA trials exceeded the overall survival benefit reported for palbociclib in the PALOMA 1 and PALOMA 2 pivotal trials (PALOMA 1, 37.5 months palbociclib plus letrozole vs 34.5 months letrozole alone, absolute difference +3 months, HR 0.90, 95% CI 0.62 to 1.29; PALOMA 2, 53.9 months palbociclib plus letrozole vs 51.2 months placebo, absolute difference +2.7 months, HR 0.96, 95% CI 0.78 to 1.18). The Committee noted that these trials did not report statistically significant improvements in overall survival from palbociclib compared to the control arm.

5.4.12. The Committee considered given the updated published data from the MONALEESA trials, there was likely a health benefit from ribociclib over palbociclib. The Committee considered the toxicity profiles of the two medicines remained similar. The Committee considered that, in light of the new evidence (updated ribociclib OS survival), and published data for palbociclib, contrary to its earlier advice, there was not a class effect among CDK4/6 inhibitors and that ribociclib and palbociclib would likely not provide the same or similar health benefits for people with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER-2) negative locally advanced or metastatic breast cancer.

5.4.13. The Committee considered that, clinically, if both were funded, the use of ribociclib would be preferred over palbociclib given the apparent overall survival benefit for ribociclib. The Committee considered that if ribociclib were to be funded, most individuals would be prescribed ribociclib.

5.4.14. The Committee considered there was insufficient evidence to support the use of a second CDK4/6 inhibitor after progression on another CDK4/6 inhibitor and that any Special Authority criteria should limit use of these agents to once per person lifetime.

Palbociclib generic alternatives

5.4.15. The Committee noted that Pharmac sought advice regarding a potential transition to a generic palbociclib. The Committee noted the extensive experience of Pharmac and New Zealand for generic brand changes, for both malignant and non-malignant diseases The Committee considered that there would be no specific concerns with a brand change for palbociclib.

5.4.16. The Committee noted that a generic palbociclib (Palbociclib Pfizer) had recently gained Medsafe approval and that it is manufactured in the same manufacturing plant, to the same specifications, and is packaged similarly, to the currently funded brand, Ibrance.

5.4.17. The Committee considered that Palbociclib Pfizer would be a suitable generic substitute for the currently funded brand of palbociclib if a brand change were to occur. The Committee considered that a brand change for palbociclib could be managed through appropriate communications to and educating both individuals with the disease and health care professionals, similarly to other brand changes. The

Committee considered that if there were a brand change to Palbociclib Pfizer that added confidence would be provided through messaging that it is manufactured by the same company at the same plant.

5.4.18. The Committee did not consider there would be a subset of people who would continue to require access to the Ibrance brand of palbociclib via an Exceptional Circumstances framework.

5.4.19. The Committee considered that if ribociclib was also funded, any savings from changing to generic palbociclib would likely be eroded by the increased share of ribociclib prescribed.

5.5. Special Authority criteria for immunotherapy for melanoma

Recommendation

5.5.1. The Advisory Committee **recommended** that the Special Authority criteria for pembrolizumab and nivolumab, for the treatment of metastatic or unresectable melanoma, is amended as follows (new criteria in **bold**, deletions in ~~strikethrough~~):

Initial application — (unresectable or metastatic melanoma) only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has metastatic or unresectable melanoma (excluding uveal) stage III or IV; and
2. ~~Patient has measurable disease as defined by RECIST version 1.1~~ **Baseline measurement of overall tumour burden is documented clinically and radiologically**; and
3. The patient has ECOG performance score of 0-2; and
4. Either:
   - 4.1. Patient has not received funded nivolumab; or
   - 4.2. Both:
     - 4.2.1. Patient has received an initial Special Authority approval for nivolumab and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and
     - 4.2.2. The cancer did not progress while the patient was on nivolumab; and

~~5. Baseline measurement of overall tumour burden is documented (see Note); and~~

6. Documentation confirming that the patient has been informed and acknowledges that funded treatment with pembrolizumab will not be continued if their disease progresses.

Renewal only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
Either:

1. All of the following:
   - 1.1. Any of the following:
     - 1.1.1. Patient's disease has had a complete response to treatment ~~according to RECIST criteria (see Note)~~; or
     - 1.1.2. Patient's disease has had a partial response to treatment ~~according to RECIST criteria (see Note)~~; or
     - 1.1.3. Patient has stable disease ~~according to RECIST criteria (see Note)~~; and
   - 1.2. **Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period** ~~Patient's disease has not progressed clinically and disease response to treatment has been clearly documented in patient notes~~; and

   ~~1.3. No evidence of progressive disease according to RECIST criteria (see Note); and~~

   - 1.4. The treatment remains clinically appropriate and the patient is benefitting from the treatment; or
2. All of the following:
   - 2.1. Patient has previously discontinued treatment with XXXXX for reasons other than severe toxicity or disease progression; and
   - 2.2. Patient has signs of disease progression; and
   - 2.3. Disease has not progressed during previous treatment with XXXXXXX.

Renewal only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
Both:

1. **Patient's disease has not progressed while on treatment and patient has been on treatment for greater than 2 years; and**
2. **Either:**
   - **2.1. All of the following:**
     - **2.1.1. Any of the following:**
       - **2.1.1.1. Patient's disease has had a complete response to; or**
       - **2.1.1.2. Patient's disease has had a partial response to treatment; or**
       - **2.1.1.3. Patient has stable disease; and**
     - **2.1.2. Response to treatment in target lesions has been determined by comparable radiologic or clinical assessment following the most recent treatment period; and**
     - **2.1.3. The treatment remains clinically appropriate and the patient is benefitting from the treatment; or**
   - **2.2. All of the following:**
     - **2.2.1. Patient has previously discontinued treatment with XXXXXXX for reasons other than severe toxicity or disease progression; and**
     - **2.2.2. Patient has signs of disease progression; and**
     - **2.2.3. Disease has not progressed during previous treatment with XXXXXX.**

Discussion

Long-term survivors

5.5.2. The Committee noted Pharmac had received correspondence from a clinician requesting a review of the requirement for ongoing CT scans in long-term survivors as part of the renewal criteria for immunotherapy (nivolumab and pembrolizumab) for the treatment of metastatic or unresectable melanoma.

5.5.3. The Committee noted that there are resource constraints in radiology departments in New Zealand and considered that there is minimal benefit in using this limited resource to frequently monitor long-term melanoma survivors. The Committee considered that other methods, such as clinical assessment or MRI, are better suited to this and a more appropriate use of resource for the small group of people who have been on treatment with immunotherapy beyond two years.

5.5.4. The Committee considered ‘long-term survivors’ with metastatic melanoma would be those who remain on immunotherapy for two years or more. The Committee considered that there is limited evidence for continuing immunotherapy to treat melanoma beyond two years, however, there is a group of individuals who would prefer to remain on treatment where funding allows it. The Committee considered that less than 5% of people receiving immunotherapy for melanoma would remain on treatment beyond two years. The Committee considered that this change would have little to no impact on the use of immunotherapy for this group of individuals, that this would be a resource sparing change for the sector and that it would reduce unnecessary exposure in those who had been on treatment for over two years.

Baseline assessment of tumour burden and response to treatment

5.5.5. The Committee noted the requirement for clinicians to assess response to treatment via regular CT scanning using RECIST criteria, in order to meet four monthly renewal criteria for immunotherapy for melanoma. The Committee considered that the use of RECIST was inconsistent across the country and often pragmatically not used to establish response to treatment. The Committee noted that Pharmac had not used RECIST criteria for establishing baseline tumour burden or response to treatment for those receiving immunotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC), instead allowing for response to treatment being determined by a comparable radiologic assessment to that used to assess baseline tumour burden. The Committee considered alignment with criteria used for immunotherapy for non-

small cell lung cancer would be appropriate for establishing baseline tumour burden and response to treatment for people with melanoma.

The Committee considered that if alternative monitoring to assess tumour response were permitted under Special Authority renewal criteria, there would not be an increase in the overall use of immunotherapy.

6. Tumour stream review – Renal Cell Carcinoma

Application

6.1. The Advisory Committee reviewed the applications for nivolumab with ipilimumab and cabozantanib with nivolumab for the first line treatment of clear cell renal cell carcinoma (RCC).

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

Recommendation

First-line treatment

6.3. The Advisory Committee **recommended** that nivolumab with ipilimumab be funded with a **high priority** as a combination immunotherapy first-line treatment of clear cell renal carcinoma with **intermediate and poor** International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **INITIATION – Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months
> All of the following:
> 1. The patient has metastatic renal cell carcinoma; and
> 2. The patient is treatment naïve; and
> 3. The patient has good performance status (ECOG grade 0-2); and
> 4. The disease is of predominant clear cell histology; and
> 5. Any of the following:
>   5.1. Haemoglobin level < lower limit of normal; or
>   5.2. Corrected serum calcium level > 10mg/dL (2.5 mmol/L); or
>   5.3. Neutrophils > upper limit of normal; or
>   5.4. Platelets > upper limit of normal; or
>   5.5. Interval of < 1 year from original diagnosis to the start of systemic therapy; or
>   5.6. Karnofsky performance score of less than or equal to 70
>
> **CONTINUATION** -**Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months.
> Both:
> 1. No evidence of disease progression; and
> 2. Treatment remains appropriate.

6.4. The Advisory Committee **recommended** that nivolumab with ipilimumab be funded with a **low priority** as a combination immunotherapy first-line treatment of clear cell renal carcinoma with **poor, intermediate and favourable** International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **INITIATION – Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months
> All of the following:
> 1. The patient has metastatic renal cell carcinoma; and
> 2. The patient is treatment naïve; and
> 3. The patient has good performance status (ECOG grade 0-2); and
> 4. The disease is of predominant clear cell histology.

CONTINUATION -**Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months.
Both:
1. No evidence of disease progression; and
2. Treatment remains appropriate.

6.5. The Advisory Committee **recommended** that cabozantanib with nivolumab be funded with a **high priority** as combination tyrosine kinase inhibitor (TKI)/immunotherapy first-line treatment of clear cell renal carcinoma with poor, intermediate and favourable International Metastatic RCC Database Consortium (IMDC) risk prognoses, within the context of treatment of malignancy, subject to the following Special Authority criteria:

INITIATION – Renal cell carcinoma. Prescribed by any relevant practitioner. Re-assessment required after 3 months
All of the following:
1. The patient has metastatic renal cell carcinoma; and
2. The patient is treatment naïve; and
3. The patient has good performance status (WHO/ECOG grade 0-2); and
4. The disease is of predominant clear cell histology.

CONTINUATION -**Renal cell carcinoma.** Prescribed by any relevant practitioner. Re-assessment required after 3 months.
Both:
1. No evidence of disease progression; and
2. Treatment remains appropriate.

6.6. In making these recommendations, the Advisory Committee considered:

- The high unmet health need of those with clear cell renal cell carcinoma, particularly those with poor and intermediate IMDC risk
- The lack of treatment options for those with favourable IMDC risk
- The high health benefits of these treatments

Second-line treatment

6.7. The Advisory Committee **recommended** that widening access to sunitinib and pazopanib TKIs to allow their use as second-line treatment for RCC (after prior TKI treatment with them first-line) **be declined**.

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

- The lack of evidence supporting a health benefit for use of sunitinib or pazopanib after prior tyrosine kinase inhibitor (TKI) treatment.

6.8. The Advisory Committee recommended that if either nivolumab/ipilimumab immunotherapy or cabozantinib/nivolumab TKI/ immunotherapy were funded in the first-line setting, then widening access to sunitinib and pazopanib TKIs as second-line treatment for RCC should be considered.

Discussion

Māori impact

6.9. The Committee discussed the impact of the current treatment paradigm and available international treatments for the treatment of renal clear cell carcinoma on Māori health areas of focus and Māori health outcomes. The Committee noted the higher incidence of cases in Māori, who also present at an earlier age (at an average of 52 years old compared to 63 years old in the general population) (Delahunt et al Urology. 1994;43:300-9).

Background

6.10. The Committee noted that the sunitinib and pazopanib TKIs were funded in 2010 and 2012 respectively for the first-line treatment of renal cell carcinoma in those with poor and intermediate prognosis.

6.11. The Committee noted it had deferred making a recommendation on an application to widen access to sunitinib and pazopanib to allow their use second-line after prior TKI treatment, pending a review of the disease treatment paradigm.

6.12. The Committee noted it had previously reviewed axitinib, lenvatinib with everolimus, and nivolumab for the second-line treatment of renal cell carcinoma, and that these are currently ranked on Pharmac's Options for Investment list.

6.13. The Committee noted it has also reviewed everolimus and sorafenib for the second-line treatment of renal cell carcinoma, and recommended both of these applications be declined.

Health need

6.14. The Committee noted it had previously reviewed the health need of people with RCC in October 2020.

6.15. The Committee noted that renal clear cell carcinoma can be subdivided by prognostic risk subgroups using International Metastatic RCC Database Consortium (IMDC) risk scores into favourable, intermediate, and poor-risk groups. The scoring system includes six negative clinical prognostic factors. The Committee noted it was a well validated model, with it being a potential guide for selecting therapeutics (Heng et al Lancet Oncol. 2013;1:141-8).

6.16. The Committee noted that cases lacking these negative factors have a good prognosis and may experience longer survival; people presenting with one or two factors have an intermediate risk of death with a median overall survival of approximately 23 months; whilst individuals with three or more factors have an expected poor risk outcome with median survival about 8 months (Guida et al. Oncotarget 2020;11:4582-92).

6.17. The Committee considered that there is a group of people who would be considered having favourable risk using the IMDC score but could benefit nonetheless from pharmaceutical treatment. The Committee considered this group is difficult to define and would be best targeted through access criteria allowing funding for all IMDC risk groups.

6.18. In New Zealand, renal cell carcinoma is more common in men than women, and presents at a younger age in Māori when compared with non-Māori (52.2 years vs. 63.2 years) Delahunt et al. Urology. 1994;43:300-9).

6.19. The Committee previously noted in 2017 the Effect of Comorbidity on Care and Cancer Survival Inequalities Study – known as the C3 (Quantitative) study – conducted by the University of Otago in 2014 that reported Māori with kidney cancer were 52% more likely to die of their cancer than non-Māori (HR: 1.52; 95% CI, 1.01 to 2.29) (Sarfati et al. 2014. Wellington: University of Otago).

6.20. The Committee considered whilst there was no evidence to suggest a difference in prevalence in Pacific peoples, these individuals may have more comorbidities that exclude them from current therapy options.

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

6.22. The Committee considered that there was a high health need for the whānau of individuals with metastatic renal cell carcinoma due to the severity of the disease, its incurable nature, and the short survival times associated with it.

6.23. The Committee noted that there are many histologically different types of renal cell carcinoma, many of which are divided into clear and non-clear cell types. The Committee considered that these often have different driver mutations and react different clinically. The Committee noted that non clear cell histology renal cell carcinomas are rarer, with less data available. The Committee noted some phase two cohort studies and small randomised trials are available but considered the data strength and quality to be immature. The Committee considered that due to the absence of high-quality evidence in non-clear cell histology, there are limited treatment options in comparison to treatments for clear-cell histology, but this disparity in treatment options does not reflect disparities in health needs.

First-line treatments

6.24. The Committee considered the European Society for Medical Oncology (ESMO) 2021 treatment guidelines (Powles et al. Ann Oncol. 2021;32:1511-9) for first-line treatment of metastatic renal cell carcinoma, which recommended lenvatinib/pembrolizumab, axitinib/pembrolizumab and cabozantinib/nivolumab for combination first-line treatment of all IMDC risk groups, whilst ipilimumab/nivolumab is recommended for those only with intermediate and poor risk.

6.25. The Committee noted the vascular endothelial growth factor (VEGF) TKI sunitinib or pazopanib are funded as a first-line treatment until progression for those with intermediate or poor prognosis disease. The Committee noted that these agents are not part of the current ESMO guidelines for this treatment line.

6.26. The Committee noted the currently funded VEGF TKI options are contraindicated in individuals with poorly controlled hypertension, ischaemic heart disease and significant venous thromboembolic disease. The Committee noted that secondary hypertension commonly occurs in those with renal cell carcinoma due to resection of the tumours through nephrectomy.

First-line therapies in ESMO guidelines

6.27. The Committee considered the following combinations outlined in the ESMO guidelines: axitinib with pembrolizumab, lenvatinib with pembrolizumab, axitinib with avelumab.

6.28. The Committee noted the following studies evaluating the efficacy and/ or safety of first-line treatments for renal cell carcinoma:

- Nocera et al. J Urol. 2022;207:16-24
- Quhal et al. Eur Urol Oncol. 2021;4:755-65
- Riaz et al. Eur Urol. 2021;80:712-23
- Heo et al. J Clin Pharm Ther. 2021;46:35-49
- Lombardi et al. Cancer Treat Rev. 2022;106:102377
- Edwards et al. Health Technol Assess. 2018;22:1-278
- Wallis et al. Eur Urol. 2018;74:309-321

6.29. The Committee noted the Rini et al. 2023. J Clin Oncol 41, 17_suppl LBA4501 study reporting the 5-year follow up of the randomised, open-label, phase 3 KEYNOTE-426 trial comparing axitinib with pembrolizumab to sunitinib. Median study follow-up was 67.2 months (range, 60.0-75.0). For axitinib with pembrolizumab compared to sunitinib, the 60-month overall survival rates were 41.9% vs 37.1%, and the 60-

months progression free survival rates were 18.3% vs 7.3%. The hazard ratio for overall survival when adjusted for subsequent therapy was 0.67 (95% CI, 0.52-0.84).

6.30. The Committee noted Motzer et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4502) that reported the 4 year follow up of the phase 3 CLEAR trial comparing the effects of levatinib with pembrolizumab vs sunitinib. At a median follow-up (IQR) of 49.8 months (41.4–53.1) for levatinib with pembrolizumab and 49.4 months (41.6–52.8) for sunitinib, 149 and 159 deaths occurred, respectively. Overall survival benefit with levatinib with pembrolizumab vs sunitinib was maintained (HR 0.79, 95% CI 0.63–0.99). Overall survival favored levatinib with pembrolizumab across MSKCC risk groups (HR, 95% CI; favorable: 0.89, 0.53–1.50; intermediate: 0.81, 0.62–1.06; poor: 0.59, 0.31–1.12). Progression free survival benefit of levatinib plus pembrolizumab vs sunitinib was maintained (HR, 95% CI; 0.47, 0.38–0.57), including across all MSKCC risk groups. Objective response rate was greater with levatinib plus pembrolizumab (71.3%; complete response [CR], 18.3%) vs sunitinib (36.7%; CR, 4.8%) (relative risk, 95% CI; 1.94, 1.67–2.26). Grade ≥3 treatment-related adverse events occurred in 74.1% and 60.3% in the levatinib plus pembrolizumab vs sunitinib arms, respectively.

6.31. The Committee noted the Motzer et al N Engl J Med 2019; 380:1103-15 multicentre, randomised, open-label, phase three trial comparing avelumab with axitinib to sunitinib. The median progression-free survival was 13.8 months with avelumab plus axitinib, as compared with 7.2 months with sunitinib (hazard ratio for disease progression or death, 0.61; 95% confidence interval [CI], 0.47 to 0.79; P<0.001); in the overall population, the median progression-free survival was 13.8 months, as compared with 8.4 months (hazard ratio, 0.69; 95% CI, 0.56 to 0.84; P<0.001). Adverse events during treatment occurred in 99.5% in the avelumab-plus-axitinib group and in 99.3% in the sunitinib group.

6.32. The Committee considered that there was uncertainty when comparing the effects of different treatment combinations. The Committee considered that time to response was potentially faster for combination treatments that involved a VEGF TKI, and that people requiring a rapid cytoreductive response may therefore benefit more from a VEGF TKI-based treatment. However, the Committee considered that the overall survival data was generally stronger for nivolumab with ipilimumab combination immunotherapy compared to the other combination regimens.

6.33. The Committee considered it would be interested in reviewing other first-line combination therapies outlined in the ESMO guidelines, if applications were received for these agents.

Second-line treatment

6.34. The Committee considered the European Society for Medical Oncology (ESMO) 2021 treatment guidelines (Powles et al. 2021) for second-line treatment of metastatic renal cell carcinoma. The guidelines recommend the use of any VEGF targetted therapy that has not been previously used in combination for individuals previously treated with an immunotherapy, whilst for those previously treated with a TKI they recommend nivolumab or cabozantinib as standard of care, or alternatively axitinib.

6.35. The Committee noted there is no funded second-line therapy in New Zealand, with access confined to participation in clinical trials (which is not possible for many individuals due to ineligibility from frailty or comorbidities, with health need inequity implications). The Committee noted three proposals are ranked on Pharmac's Options for Investment list for second-line therapy: lenvatinib with everolimus, axitinib and nivolumab.

6.36. The Committee noted that international guidelines for second-line treatment may not be applicable to New Zealand as many of the first-line treatments are not funded in

New Zealand. The Committee considered the standard of care in first-line for most countries was a VEGF TKI treatment option.

Second-line treatments in ESMO guidelines

6.37. The Committee considered the following studies evaluating the efficacy of second-line treatments for renal cell carcinoma:

- Motzer et al. Cancer. 2010 .116:4256-65.
- Choueiri et al. N Engl J Med. 2015;373:1814-23
- Choueiri et al Lancet Oncol. 2016;17:917-27
- Powles et al. Br J Cancer. 2018;119:663-9
- Rautiola et al. Acta Oncol. 2014;53(1):113-8
- Xie et al. Eur J Cancer. 2015;51(5):595-603

6.38. The Committee noted the Te Aho o Te Kahu gap analysis (Te Aho o Te Kahu. 2022, Understanding the Gap an analysis of the availability of cancer medicines in Aotearoa) that identified nivolumab and axitinib as gaps in the second-line treatment of renal cell carcinoma.

6.39. The Committee noted it would like to review an application for cabozantinib for the second-line treatment of renal cell carcinoma.

6.40. The Committee considered that among second-line treatment options for renal cell carcinoma, nivolumab had the strongest evidence for a survival benefit. The Committee considered the evidence of benefit was not as strong for other second-line treatment options previously reviewed by the Committee.

6.41. The Committee considered that in individuals where immunotherapy is contraindicated, and have been previously treated with a VEGF TKI, then treatment with cabozantinib, axitinib, lenvatinib or sorafenib would be appropriate.

6.42. The Committee noted the ESMO guidelines (Powles et al. 2021) recommend the use of a different VEGF TKI in individuals who have received a prior VEGF TKI and immunotherapy; however, the Committee considered the health benefit evidence to be weak.

6.43. The Committee considered that second or later line treatment options should not vary depending on IDMC scores but should be based on prior therapy.

Health benefit

First-line treatment - ipilimumab with nivolumab

6.44. The Committee noted that ipilimumab is a CTLA-4 immune checkpoint inhibitor, whilst nivolumab is an antibody that binds to the programmed death (PD-1) receptor.

6.45. The Committee considered that the combination of ipilimumab with nivolumab is clinically suitable when VEGF TKI treatment is contraindicated. The Committee considered that the contraindications to TKI treatment would likely be quite different to contraindications to immunotherapy treatment. The Committee was uncertain for how many people TKIs were contraindicated, but considered the proportion was likely low.

6.46. The Committee noted Motzer Lancet Oncol. 2019;20:1370-85, Motzer et al. N Engl J Med .2018;378:1277-90, Albiges et al. ESMO Open 2020;5:e001079, and Motzer et al J Immunother Cancer. 2020;8:e000891, which reported the results of the CheckMate 214 study, a randomised controlled phase 3 trial comparing ipilimumab with nivolumab versus sunitinib in 1096 individuals.

6.47. The Committee noted Albiges et al. l. ESMO Open 2020;5:e001079, which reported the four year follow up to the trial.

6.47.1. Overall survival (Hazard ratio (HR); 95%CI) was superior with ipilimumab with nivolumab vs sunitinib in intent to treat population (ITT) (0.69; 0.59 to 0.81) and intermediate/poor risk group (I/P) (0.65; 0.54 to 0.78). Four-year progression free survival probabilities were: 31.0% vs 17.3% (ITT) and 32.7% vs 12.3% (I/P), with ipilimumab and nivolumab vs sunitinib. Overall response rate: ipilimumab and nivolumab vs sunitinib in ITT (39.1% vs 32.4%) and I/P (41.9% vs 26.8%). In the favourable group: HRs (95%CI) for overall survival and progression free survival =0.93 (0.62 to 1.40) and 1.84 (1.29 to 2.62).

6.47.2. The Committee noted that in those with favourable risk the progression free survival outcomes favoured sunitinib (HR 1.84; 95% CI 1.29 to 2.62), with 4-year progression free survival probabilities of 25.4% with ipilimumab and nivolumab vs 31.6% with sunitinib. However, the difference in progression free survival probabilities across arms has decreased over time.

6.47.3. The Committee considered that those with intermediate or poor IMDC prognosis gained significant benefit from nivolumab with ipilimumab. The Committee considered that the evidence available suggested that nivolumab with ipilimumab offered no incremental health benefit for those with favourable risk status, and treatment may even be associated with harm given the adverse event profile. The Committee noted that evidence for the favourable risk group was from an unplanned exploratory retrospective subgroup analysis and therefore was subject to a greater degree of uncertainty.

6.47.4. The Committee considered the trial to be well powered, randomised and with the control arm treatment relevant to the New Zealand population and clinical setting.

6.47.5. The Committee noted that treatment related adverse events leading to discontinuation occurred more frequently in the ipilimumab/nivolumab arm (22% vs 12%). No new safety signals were detected in this trial, with the treatment adverse events occurring in line with the expected experience with these agents. The Committee considered that many of the toxicities experienced on first-line sunitinib were relatively straightforward to treat, and that it was uncommon for these adverse events to require hospitalisation. The Committee further considered that the adverse events experienced on first-line sunitinib often resolved upon discontinuation of treatment. The Committee considered that the immune-related adverse events experienced with nivolumab in combination with ipilimumab can be complex and may require treatment even after treatment discontinuation.

6.48. The Committee noted the Cella et al. Lancet Oncol. 2019;20:297-310 publication that reported the patient-reported outcomes (PROs) of those in CheckMate 214. PROs were more favourable with nivolumab plus ipilimumab vs sunitinib up to 103 weeks after baseline. Treatment with nivolumab plus ipilimumab reported significant improvements in 4/5 Functional Assessment of Cancer Therapy Kidney Symptom Index-19 (FKSI-19) domains (including disease-related symptoms, physical disease-related symptoms, treatment side-effects, and functional wellbeing) and Functional Assessment of Cancer Therapy-General physical and functional wellbeing domains. The Committee noted that the evidence from this publication suggested nivolumab with ipilimumab treatment resulted in improved health-related quality of life compared to sunitinib.

6.49. The Committee noted Tannir et al. Clin Cancer Res. 2021;27:78-86, a post hoc analysis of CheckMate 214 that reported efficacy for nivolumab with ipilimumab versus sunitinib in advanced renal cell carcinoma with sarcomatoid features. Progression free survival benefits with nivolumab plus ipilimumab were observed

[median 26.5 vs. 5.1 months; HR, 0.54 (95% CI, 0.33-0.86; P = 0.0093)]. The confirmed objective response rate was 60.8% with nivolumab plus ipilimumab versus 23.1% with sunitinib, with complete response rates of 18.9% versus 3.1%, respectively.

6.50. The Committee considered that if an individual's disease had a sarcomatoid component then clinicians may favour treatment with nivolumab plus ipilimumab due to the health benefit for this population reported in Tannir et al. 2021.

6.51. The Committee noted the following studies:

- Tomita et al. Jpn J Clin Oncol. 2020;50:12-19.
- Atkins et al. J Clin Oncol. 2022;40:2913-23
- Hammers et al. J Clin Oncol. 2017;35:3851-58
- Escudier et al. Eur Urol. 2020;77:449-53.
- Emaekhoo et al. Cancer. 2022;128:966-74
- Hofmann et al. Cochrane Database Syst Rev. 2020;14;10:CD012796.

First-line treatment - cabozantinib with nivolumab

6.52. The Committee noted cabozantinib is a VEGF TKI, whilst nivolumab is a PD-1 inhibitor immunotherapy.

6.53. The Committee noted Motzer et al. Lancet Oncol .2022;23:888-98 and Choueiri et al. N Engl J Med. 2021;384:829-41, which reported the results of the CheckMate 9ER phase 3 clinical trial comparing the efficacy of cabozantinib with nivolumab to sunitinib.

6.53.1. The Committee noted Motzer et al. Lancet Oncol .2022;23:888-98 reported the trial's extended follow-up (median 32·9 months [IQR 30·4-35·9]). Median overall survival was 37·7 months (95% CI 35·5-not estimable) in the nivolumab with cabozantinib group and 34·3 months (29·0-not estimable) in the sunitinib group (HR 0·70 [95% CI 0·55-0·90], p=0·0043) and updated median progression free survival was 16·6 months (12·8-19·8) vs 8·3 months (7·0-9·7; HR 0·56 [95% CI 0·46-0·68], p<0·0001). Grade 3-4 treatment-related adverse events occurred 65% nivolumab plus cabozantinib vs 54% sunitinib.

6.53.2. The Committee noted the Burotto et al J Clin Oncol, 2023. 41, no. 6_suppl; 603 abstract that reported the trial's extended 36.5-month minimum follow-up (median, 44.0 months). Progression free survival and overall survival benefits were apparently maintained with nivolumab plus cabozantinib vs sunitinib in intent-to-treat population. Median progression free survival was 16.6 vs 8.4 months (HR 0.59 [95% CI 0.49–0.71], P < 0.0001) and median overall survival was 49.5 vs 35.5 months (HR 0.70 [95% CI 0.56–0.87], P = 0.0014). Objective response rate (95% CI) was higher with nivolumab plus cabozantinib vs sunitinib (56% [50–62] vs 28% [23–33]), and 13% vs 5% of individuals achieved complete response, respectively. Median duration of response was 22.1 vs 16.1 months for nivolumab plus cabozantinib vs sunitinib. Any-grade treatment-related adverse events occurred in 97% vs 93% of individuals treated with nivolumab plus cabozantinib vs sunitinib (grade ≥ 3, 67% vs 55%).

6.53.3. The Committee considered the trial was well powered, randomised and with the control arm treatment relevant to the New Zealand population and clinical setting.

6.54. The Committee noted Cella et al. Lancet Oncol. 2022;23:292-303 reported the PROs from CheckMate 9ER, with a median follow-up of 23·5 months (IQR 21·0-26·5). Nivolumab plus cabozantinib was associated with decreased risk of clinically meaningful deterioration for FKSI-19 score compared with sunitinib (first deterioration

event HR 0·70 [95% CI 0·56-0·86], nominal p=0·0007; confirmed deterioration event 0·63 [0·50-0·80], nominal p=0·0001).

6.55. The Committee considered that nivolumab with cabozantinib was likely associated with improved health-related quality of life compared to sunitinib, and that these quality of life indicators remained high over the course of treatment.

6.56. The Committee considered the side effects of nivolumab with cabozantinib were similar to the VEGF class effects for sunitinib, including hypertension and diarrhoea.

Second-line treatment

6.57. The Committee considered there was a lack of evidence of health benefit for use of sunitinib or pazopanib after prior TKI treatment and did not see at this stage a role for their use second-line.

6.58. The Advisory Committee considered however that if would be it would be appropriate to consider second-line TKI treatment following immunotherapy if either ipilimumab/nivolumab or cabozantinib/nivolumab were funded in the first-line setting.

Suitability

6.59. The Committee noted that the currently funded first-line treatments are orally administered, and therefore other first or second-line treatments which require intravenous infusion would increase the need for a person to travel to infusion centres. This would also increase the need for infusion service time. The Committee noted there would be an increase in the travel time for the person undertaking treatment and their whānau.

Cost and savings

6.60. The Committee considered that due to the safety profile of the ipilimumab with nivolumab combination, there would be a small subset of people with poorer performance status (ECOG>2) who would not receive this treatment.

6.61. The Committee noted that the currently funded first-line treatments are orally administered, and therefore other first and second-line treatments which require intravenous infusion would increase the need for infusion service time and staff to be able to administer the treatment.

6.62. The Committee considered that while most immune related toxicities would be managed with corticosteroids, there would be a small number of people with refractory or severe toxicity that requires agents such as infliximab for diarrhoea (where <1% would experience diarrhoea, of whom only a small proportion would require infliximab). The Committee considered that there may be a potential increase in the use of radiology imaging if treatments were funded for people with good prognosis (who otherwise would not need imaging clinically).

6.63. The Committee considered there may be an increase in laboratory testing over the current standard of care options.

6.64. The Committee noted that a number of individuals with good prognosis disease would not require immediate treatment and would be observed for a period, but considered that quantifying this number would be difficult.

Funding criteria

6.65. The Committee considered those with intermediate or poor risk status would gain the most health benefit from treatment with nivolumab with ipilimumab, with less evidence available to support clinical benefit for those with favourable risk status. The Committee considered that for nivolumab with cabozantinib, the evidence of benefit

appeared to be strongest for those with poor risk, but that it appeared that those with favourable risk would derive benefit.

7. Eribulin for advanced or metastatic breast cancer (progression following at least two prior lines of chemotherapy)

Application

7.1. The Advisory Committee reviewed the application for eribulin in the treatment of advanced or metastatic breast cancer (progression following at least two prior lines of chemotherapy).

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

Recommendation

7.3. The Advisory Committee **recommended** that eribulin be **declined** within the context of treatment of malignancy.

7.4. The Advisory Committee recommended decline based on:

- The uncertainty of the health benefit based on clinical trial evidence.
- Insufficient evidence to suggest benefit adding to existing treatments.

Discussion

Māori impact

7.5. The Committee discussed the impact of funding eribulin for the treatment of metastatic breast cancer on Māori health areas of focus and Māori health outcomes. The Committee noted Māori had a higher rate of breast cancer, and present at a later stage of disease, than those from European ethnicities. The Committee noted that Māori had a decreased median overall survival compared to European ethnicities (Breast Cancer Foundation National Register report 2003-2020).

Background

7.6. Pharmac sought advice on an application for eribulin for the treatment of advanced or metastatic breast cancer following progression after at least two lines of chemotherapy, which was originally considered by PTAC in November 2022, and received a recommendation to decline. Following this, correspondence was received from the Breast Cancer Aotearoa Alliance (BCAC) and Eisai New Zealand Limited, which was considered by PTAC in May 2023, following which, PTAC maintained its recommendation.

Health need

7.7. The Committee noted the previous PTAC review of the health need of those with advanced breast cancer in May 2023 and November 2022. The Committee agreed with the PTAC's considerations of health need of this population.

7.8. The Committee noted that Māori have a higher incidence of breast cancer than NZ European ethnicity, and present with a more advanced state of disease (Breast Cancer Foundation National Register report 2003-2020).

7.9. The Committee noted that 17.1% of Māori diagnosed with breast cancer were under the age of 45 years (Breast Cancer Foundation National Register 2003-2020), who would be supporting their whānau, often at that age with tāmariki who were young, but whose cancer would not be detectable by 2-yearly mammography screening in the national breast cancer screening programme, risking having even more advanced disease at presentation.

7.10. The Committee noted that in Māori the median overall survival for metastatic breast cancer is decreased compared to NZ Europeans at 12.8 vs 15.7 months respectively (Breast Cancer Foundation National Register 2003-2020).

Health benefit

7.11. The Committee noted that the treatment paradigm is different in New Zealand compared to internationally, with participants in trials having additional prior lines of therapy in comparison to the New Zealand population.

7.12. The Committee noted that there was no cross resistance between eribulin and taxane chemotherapies with similar modes of action (which also target microtubules).

7.13. The Committee noted the Cortes et al. Lancet 2011:377:914-23 international, multi-centre, randomised, open label phase 3 trial in 762 people with advanced or metastatic breast cancer previously treated with 2-5 lines of prior treatment.

7.13.1. The study reported overall survival in those treated with eribulin was a median 13·1 months, 95% CI 11·8-14·3 compared with treatment of physician's choice at 10·6 months, 9·3-12·5; hazard ratio 0·81, 95% CI 0·66-0·99; p=0·041. Serious adverse events occurred in 126 (25%) of those treated with eribulin and 64 (26%) of those on treatment of physician's choice, and adverse events leading to therapy discontinuation occurred in 67 (13%) for eribulin and 38 (15%) of those treated with the treatment of physician's choice. Fatal adverse events occurred in 4% on eribulin and 7% on treatment of physician's choice.

7.13.2. The Committee noted that the treatments received in the treatment of physician's choice group varied, and therefore considered it was hard to compare the two treatment arms. The Committee noted it was not possible to determine from the evidence which of the treatments within the physician's choice group were inferior to eribulin, and whether those treatments were relevant to the NZ treatment environment.

7.14. The Committee noted the Kaufman et al J Clin Oncol. 2015;33:594-601 randomised, open label phase 3 study that compared eribulin with capecitabine. The Committee noted that capecitabine was regularly used in the New Zealand treatment paradigm. The Committee noted that individuals in the trial had 1-3 prior treatments. The Committee noted the median overall survival times for eribulin (n = 554) and capecitabine (n = 548) were 15.9 and 14.5 months, respectively (hazard ratio [HR], 0.88; 95% CI, 0.77 to 1.00; P = .056). Median progression free survival times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (HR, 1.08; 95% CI, 0.93 to 1.25; P = .30). Objective response rates were 11.0% for eribulin and 11.5% for capecitabine.

7.15. The Committee noted the following studies:

- Twelves et al. Breast Cancer (Auckl).2016;10:77-84
- Cortes et al. Breast J. 2020 ;26:1347-1351.
- Chan et al. Asia Pac J Clin Oncol. 2022;18:201-208
- Maeda et al. Breast. 2017;3:66-72
- Watanbe et al Invest New Drugs. 2017; 35: 791–799
- Inoue et al. Invest New Drugs. 2020; 38: 1540–1549.
- Adamo et al. Ther Adv Med Oncol.2019;11:1758835919895755
- Krasniqi et al, Int J Med Sci.2021;18:2245-2250
- Garrone et al. Springerplus.2016;5:59
- Pedersini et al. Oncology.2018;94 Suppl 1:10-15

- Sabatier et al. Cancer Res Treat. 2018 50: 1226–1237.
- Mougalian et al. Cancer Med.2018;7:4371-4378.
- Mougalian et al Adv Ther. 2021; 38: 2213–2225.
- Pivot et al. Ann Oncol. 2016 ;27:1525-31
- Jafri et al. Oncology.2022;100:666-73
- Tsurutani et al. Breast Cancer.2019 ;26:235-243
- Yuan et al. Eur J Cancer. 2019;112:57-65
- Leo et al. Oncologist. 2019;24:e232-e240.
- Aftimos et al Eur J Cancer. 2016;60:117-24
- Lorusso et al. Future Oncol.2017;13:971-978
- Kimura et al Cancer Chemother Pharmacol,2018 ;81:923-33.
- Barni et al Future Oncol. 2019;15:33-44
- Kikuchi et al. Asia Pac J Clin Oncol. 2018;14:e231-e237
- Perez-Garcia et al. Expert Opin Drug Saf.2019;18:347-355

7.16. The Committee considered the quality-of-life data to be limited, however, there was no data to suggest the negative effects were worse than the currently funded treatments. The Committee considered the toxicity profile of eribulin to be similar to that of other chemotherapeutic treatments used in New Zealand to treat breast cancer.

7.17. The Committee considered that data to support the use in people with brain metastases was limited to case reports that were small, retrospective and uncontrolled, and therefore there was no good evidence to support its use in this group compared to other groups.

7.18. The Committee considered that the trials to support health benefit were heterogeneous in the number of prior treatment lines, which confounded the assessment of the effect of eribulin and impeded those trials' relevance to the New Zealand population and clinical setting. The Committee considered there was also heterogeneity in the control arm of the trials, which impacted on assessing benefit. The Committee considered that if the trials were undertaken now, the design would likely be different with results more likely to detect any health benefit where it might exist. The Committee considered that overall, it was difficult to draw conclusions from the available evidence and there was uncertainty about the quality of health benefit and whether this would result in health outcomes that were clinically meaningful.

Suitability

7.19. The Committee noted that eribulin is administered as an intravenous infusion and therefore individuals will need to travel to infusion services for treatment.

Cost and savings

7.20. The Committee noted that should eribulin be funded it would be an additional treatment option, rather than replacing an existing one.

7.21. The Committee considered that the number of individuals treated would be less than 300 a year.

8. Pembrolizumab for metastatic mis-match repair deficient pancreatic cancer

Application

8.1. The Advisory Committee reviewed the application for pembrolizumab for the treatment of metastatic mis-match repair deficient pancreatic cancer.

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

Recommendation

8.3. The Advisory Committee **recommended** that pembrolizumab for the treatment of metastatic mis-match repair deficient pancreatic cancer be **deferred** until additional information has been reviewed for other similar tumours where more mature data is available.

Discussion

Māori impact

8.4. The Committee discussed the impact of funding pembrolizumab for the treatment of mismatch repair deficient pancreatic cancer on Māori health areas of focus and Māori health outcomes. The Committee noted there was no specific evidence on rates of mismatch repair deficient pancreatic cancer in Māori, but the incidence of pancreatic cancer overall was higher in Māori, with Te Whatu Ora cancer registry data providing age standardised five- year cumulative incidence rates for pancreatic cancer registered between 2016 and 2020 of 13.57 per 100,000 for Māori, 10.04 for Pacific people, 5.12 for Asian, and 7.48 for New Zealand European/ others (Te Whatu Ora Cancer Register data, accessed 2023).

8.5. The Committee also noted that studies in those with pancreatic cancer, and all cancers respectively, reported Māori were less likely to receive palliative chemotherapy, and that those with no comorbidity were more likely to die than non-Māori (Camburn & Das, J. Clin. Oncol. 2021;39(15_suppl):e18554), Gurney et al. JCO Glob Oncol. 2020;6:766-74).

Background

8.6. The Committee previously considered pembrolizumab as a second-line treatment of all adults and children with unresectable or metastatic microsatellite instability-high or mismatch repair deficient cancers that have progressed following prior treatment, regardless of tissue of origin, and had deferred making a recommendation pending publication of the KEYNOTE 158 trial (July 2021). The Committee had considered that there was insufficient valid, mature data for pembrolizumab as a tumour-agnostic treatment, with further assessment to be considered following evidence for individual tumour entities.

8.7. Pharmac sought advice on the use of pembrolizumab for the treatment of mismatch repair deficient pancreatic adenocarcinoma.

Health need

8.8. The Committee noted that pancreatic cancer can be broadly divided into exocrine and neuroendocrine forms. The majority of diagnoses are for pancreatic ductal adenocarcinomas (PDAC), a form of exocrine tumour, which accounts for approximately 90% of all pancreatic cancer diagnoses (Orth et al, Radiat Oncol. 2019;14:141), with other subtypes including acinar carcinoma, pancreaticoblastoma, and neuroendocrine tumours (Park et al, JAMA. 2021;326:851-62).

8.9. The Committee noted that at presentation, 50% of affected individuals have metastatic disease, whilst 10% to 15% have localised disease amenable to surgery,

and the remainder (30%-35%) have locally advanced mostly unresectable disease due to the extent of tumour-vascular involvement (Park et al, 2021).

8.10. The Committee noted that pancreatic cancer has a very poor prognosis, with a median survival of approximately 10 to 12 months with treatment, and 5 to 6 months without treatment due to the advanced stage of diagnosis for many at presentation, and the low percentage of those affected eligible for surgical resection (Wood et al, Gastroenterology 2022;163:386–402).

8.11. The Committee noted the risk of developing pancreatic cancer is correlated with age, with approximately 80% of those with pancreatic cancer aged over 60 years and the average age at diagnosis being 71 years of age (Mario et al, Acta Biomed. 2018; 89: 141-6).

8.12. The Committee noted pancreatic cancer is reported to have a 5-year prevalence of 10.87 per 10,000 in New Zealand (The Global Cancer observatory, 2021). In New Zealand, 8.5 per 100,000 people were diagnosed with pancreatic cancer in 2020, and 6.3 per 100,000 people died of the condition in 2018 (Te Whatu Ora, 2022).

8.13. The Committee noted the five year pooled incidence of pancreatic cancer registered between 2016 and 2020 was higher in Māori and Pacific people compared to Asian and New Zealand European ethnicities, with age-standardised rates of 13.57, 10.04, 5.12 and 7.48 per 100,000 respectively (standardised to the World Health Organization standard world population) (Te Whatu Ora Cancer Register data, accessed 2023).

8.14. The Committee noted the mismatch repair system plays a pivotal role in the repair of DNA sequence mismatches during replication. Defects in the mismatch repair system (mis-match repair deficient), or loss of function of one of the mismatch repair proteins, causes errors in DNA replication leading to mutations that accumulate in microsatellites, resulting in microsatellite instability (Macherla et al, Int J Mol Sci. 2018 Nov; 19: 3505).

8.15. The Committee noted that mis-match repair deficiency in pancreatic cancer is rare, affecting approximately 0.3-3% of those with pancreatic cancer (Luchini et al, Gut. 2021 Jan;70:148-56, Laghi et al. PLoS One. 2012; 7: e46002, Ahmad-Nielsen et al. Pathol Res Pract. 2020;216:152985).

8.16. The Committee noted a single centre trial investigated whether mis-match repair deficiency in pancreatic cancer affected survival, which reported those with mis-match repair had a longer overall survival time than those without. The Committee noted that the trial was small with 46 people included, of whom eight had mis-match repair deficiency (Nataka et al, Clin. Cancer Res. 2002;8:2536–40).

8.17. The Committee noted a retrospective analysis of the Finland Lynch Syndrome registry data between 1982-2020, which identified 23 individuals with pancreatic cancer (Zalevskaja et al. Front Oncol. 2023;13:1123901). The 5-year overall survival was reported to be higher in those with mis-match repair deficiency compared to general population survival times at 13.6% versus <8% respectively. The Committee considered that it was unclear if this was due to the molecular characteristics of the cancer, or due to these individuals being monitored frequently and their cancers being diagnosed at an earlier and resectable stage.

8.18. The Committee noted a study of 6342 individuals from 147 families with MMR gene mutations, which reported that these individuals had an 8.6 fold increase (95% CI, 4.7-15.7) in the risk of developing pancreatic cancer compared with the general population *(*Kastrinos et al. JAMA. 2009;302:1790-5*).*

8.19. The Committee noted those with a family history of pancreatic cancer, defined as having two pancreatic cancer cases in first degree relatives, were reported to have an

increased risk of developing pancreatic cancer, with familial pancreatic cancer accounting for approximately 5-10% of pancreatic cancer cases *(*Matsubayashi, Diagnostics (Basel). 2019;9:169*).*

8.20. The Committee noted surgical resection is the only potential curative treatment for PDAC, but that at diagnosis only 15-20% of tumours are considered surgically resectable. Adjuvant chemotherapy has been reported to increase median survival compared to surgery alone (20.1 versus 15.5 months, P = 0.009) (Ducreux et al, Ann Oncol. 2015;26:v56-68).

Health benefit

8.21. The Committee noted pembrolizumab is an immune checkpoint inhibitor, which binds to the PD-1 receptor on T-lymphocytes, blocking the effects of the PD-L1 and PD-L2 ligands. This exposes the tumour cell to the immune system.

8.22. The Committee considered the KEYNOTE 158, phase 2 non-randomised non-controlled open label, multisite observational longitudinal follow-up study including 233 people with mis-match repair deficient non colorectal cancer treated with pembrolizumab, of whom 22 had pancreatic cancer *(*Marabelle et al, J Clin Oncol. 2020;38:1-10*).*

8.22.1. The Committee noted the study reported that four individuals had achieved complete or partial response (one and three respectively). In these four individuals the following endpoints were reported: overall response rate (ORR) of 18.2% (5.2 to 40.3 95%CI)*, m*edian duration of response (months) 13.4 (range 8.1 to 16.0+) (+ no progression of disease by the time of last disease assessment), median progression-free survival (months) 2.1 (1.9 to 3.4, 95%CI) median overall survival (months) 4.0 (2.1 to 9.8, 95% CI).

8.22.2. The Committee considered the study's results were limited by:

- variation in methods to diagnose *mis-match repair deficiency in the trial,*
- small numbers of people with mis-match repair deficient pancreatic cancer,
- no active treatment control arm or use of historical controls.

8.23. The Committee noted that people with mis-match repair deficient pancreatic cancer have longer overall survival in comparison to those without the deficiency, and therefore in single arm trials it is challenging to compare the health benefit of the drug.

8.24. The Committee noted pembrolizumab is an immunotherapy and therefore is associated with a risk of immune related adverse effects.

8.25. The Committee considered noted that evidence of health benefit was limited, but that it was unlikely further clinical trial evidence would be generated due to small numbers of people with the condition, with any additional evidence likely to be limited to observational cohort data.

8.26. The Committee noted the following studies:

- Cox et al. Cureus 2021, 22;13:e14640
- Castro and Goldstein. J Immunother Cancer. 2015 15;3:58
- Zhao et al. J Med Cases, 2022;13;240-3
- Maio et al Ann Oncol 2022;33:929-38

8.27. The Committee considered that more mature, randomised control trial data is being generated as a single therapeutic and in combination with other therapeutics, in other more common mis-match repair deficient cancers including endometrial cancer. The

Committee considered that as the mechanism of action is likely to be the same, that this evidence could be generalised to rarer tumour types.

8.28. The Committee considered it would be helpful to see data from trials that compare pembrolizumab with other standard of care therapeutics in mis-match repair deficient cancers.

Suitability

8.29. The Committee noted that pembrolizumab is administered every 3 or 6 weeks at 200mg or 400mg respectively, as an intravenous infusion over 30 minutes, and this would be a reduction in infusion number and time compared to other second-line treatments gemcitabine and irinotecan, folinic acid and fluorouracil (FOLFIRNOX).

8.30. The Committee has previously noted that immunohistochemistry to confirm mis-match repair deficient status is required but this is not currently routinely performed, and therefore, additional testing may be required to identify individuals with the deficiency.

Cost and savings

8.31. The Committee noted that most people would proceed to treatment with FOLFIRNOX following progression, whilst in those with poor Eastern Cooperative Oncology Group (ECOG) scores would proceed to treatment with gemcitabine.

8.32. The Committee considered that, in the current treatment paradigm, perhaps 50- 75% would receive FOLFIRINOX, with the remainder receiving gemcitabine.

8.33. The Committee noted that additional testing would be necessary to identify those with mis-match repair deficient pancreatic cancer. The Committee considered this is likely to be limited to immunohistochemistry, which is the technique performed to identity mis-match repair deficiency in other cancer types including colorectal in New Zealand. The Committee noted that testing for mis-match repair deficiency is not common practice in New Zealand currently in the absence of targeted treatment options. The Committee considered that, due to the rarity of the deficiency a significant increase in the amount of testing would be required to identify the small number of eligible individuals. The Committee noted that this testing may be performed in if the is a possibility the person has Lynch Syndrome.

8.34. The Committee noted that in New Zealand, the majority of pancreatic cancers are diagnosed late and therefore low numbers of tumours are resectable. The Committee noted that for those with resectable tumours, there is a high recurrence rate, and would therefore likely require treatment upon recurrence.

Summary for assessment

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

Population	People with metastatic mis-match repair deficiency or microsatellite instability-high pancreatic cancer, who have received prior chemotherapy for their metastatic disease

Intervention	Pembrolizumab 200mg every 3 weeks or 400mg every 6 weeks, administered via a 30-minute intravenous infusion, until treatment progression, unacceptable toxicity or death.
Comparator(s)	Mixed comparator consisting of: • Gemcitabine 1,000mg/m^2 each week, for the first 7 weeks, followed by a week of rest, then 3 of every 4 weeks. Administered via 30-minute intravenous infusion. • Fluorouracil in combination with irinotecan and folinic acid (FOLFIRINOX), administered via intravenous infusion over 3 hours. The fluorouracil component is administered at home over 46 hours, after which people return to hospital for a 30-minute inspection and pump removal.
Outcome(s)	• Reduced burden on hospital infusion services due to shorter duration and less frequent infusions • Potential longer overall and progression-free survival compared to current treatments
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the target population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

9. Zanubrutinib for treatment of chronic lymphocytic leukaemia

Application

9.1. The Advisory Committee reviewed the application for zanubrutinib in the treatment of chronic lymphocytic leukaemia (CLL).

9.2. The Committee made recommendations for the following lines of treatment:

9.2.1. Previously untreated CLL with 17p deletion/TP3 mutation

9.2.2. Relapsed/refractory CLL without 17p deletion/TP3 mutation

9.2.3. Lines of treatment where ibrutinib is currently funded (second-line for CLL with 17p deletion/TP3 mutation, and third line for CLL without 17p deletion/TP3 mutation)

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

Recommendation

9.4. The Advisory Committee **recommended** that zanubrutinib be listed for the first-line treatment of previously untreated CLL with 17p deletion/TP3 mutation with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** (untreated chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation) – from any relevant practitioner. Approvals valid for 6 months.
> Both:
> 1. Patient has previously untreated CLL; and
> 2. It is confirmed the patient has 17p deletion or TP53 mutation
>
> **Renewal application** (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate, and the patient is benefiting from treatment

9.5. In making this recommendation, the Advisory Committee considered

9.5.1. There is currently a high unmet health need in the first-line treatment of CLL with 17p del/ TP53 mutation in New Zealand, as no BTK inhibitor is currently funded for this line of treatment.

9.5.2. There are several reasons a BTK inhibitor may provide additional health benefit compared to venetoclax monotherapy for the treatment of previously untreated CLL with 17p del/ TP53 mutation, including the SEQUOIA trial evidence, and removing the need for hospital admission for tumour lysis syndrome prophylaxis. Additionally a BTK inhibitor at this line of treatment aligns with international guidelines,

9.5.3. Comparative evidence of efficacy for venetoclax monotherapy vs fixed duration venetoclax with rituximab in relapsed CLL with 17p deletion/TP53 mutation is lacking. There may be a preference among prescribers for continuous therapy and therefore uptake for zanubrutinib for previously untreated CLL with 17p del/ TP53 mutation would likely be high (perhaps 90+%) if venetoclax monotherapy was available second-line, with uptake slightly lower (perhaps closer to 70%) if only venetoclax with rituximab were available second-line.

9.6. The Advisory Committee **recommended** that zanubrutinib be listed for the treatment of relapsed/refractory CLL without 17p deletion/TP3 mutation only if cost-neutral to venetoclax with rituximab, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** (relapsed/refractory chronic lymphocytic leukaemia (CLL)) – from any relevant practitioner. Approvals valid for 6 months.
> All of the following:
> 1. Patient has chronic lymphocytic leukaemia requiring treatment; and
> 2. Patient has received at least one prior therapy for chronic lymphocytic leukaemia; and
> 3. Patient has not previously received funded BTK inhibitor therapy; and
> 4. Patient's disease has relapsed within 36 months of previous treatment
>
> **Renewal application** (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) - from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment

9.7. In making this recommendation, the Advisory Committee considered

9.7.1. As noted in some of the previous Committee discussions referenced above (CTAC – September 2018; CTAC – July 2019), individuals with CLL without 17p del/ TP53 currently have access to venetoclax which provides a reasonable treatment option for this group.

9.7.2. A BTK inhibitor would provide similar health benefit to venetoclax with rituximab for second-line treatment of CLL without 17p del/ TP53 mut, with the added health benefits of no hospital admission for tumour lysis syndrome prevention, and a full oral regimen.

9.7.3. If both zanubrutinib and venetoclax with rituximab were available, it is anticipated that zanubrutinib uptake would be 50% with the main determinant being split patient desire for fixed duration vs continuous therapy.

9.8. The Advisory Committee **recommended** that zanubrutinib be listed for lines of treatment where ibrutinib is currently listed only if cost-neutral to ibrutinib within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** (previously treated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – from any relevant practitioner. Approvals valid for 6 months.
> Any of the following:
> 1. Both:

1.1.1. There is documentation confirming that patient has 17p deletion or TP53 mutation; and
1.1.2. Patient has experienced intolerable side effects with venetoclax monotherapy or CLL is refractory to or has relapsed within 36 months of a venetoclax regimen; or

2. All of the following:
2.1 Patient has received at least one prior immunochemotherapy for CLL; and
2.2 Patient's CLL has relapsed within 36 months of previous treatment; and
2.3 Patient has experienced intolerable side effects with venetoclax in combination with rituximab regimen; or
3. Patient has developed intolerable side effects from other BTKi therapy.

Renewal application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) - from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria:
Both:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate, and the patient is benefiting from treatment

9.9. In making this recommendation, the Advisory Committee considered

9.9.1. Ibrutinib is currently funded in New Zealand for the second-line treatment of CLL with 17p del/ TP53 mutation, and the third line treatment of CLL without 17p del/ TP53 mutation.

9.9.2. Zanubrutinib would provide similar health benefit to ibrutinib for the lines of treatment where ibrutinib is already funded, due to the considered class effect of BTKis.

9.9.3. If zanubrutinib were to be funded alongside ibrutinib in lines of treatment where ibrutinib is funded, uptake would likely to 100% due to the favourable safety profile of zanubrutinib, and potentially slightly increased efficacy.

Discussion

Māori impact

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

Background

9.11. The Committee noted previous considerations for treatment for CLL by Pharmac committees, including ibrutinib (CaTSoP – July 2020, CaTSoP – April 2019, CTAC-April 2023), venetoclax in combination with rituximab (CaTSoP – April 2019), venetoclax monotherapy (CaTSoP – September 2018 , PTAC – February 2019), venetoclax with Obinutuzumab (CaTSoP – July 2020), and acalabrutinib (CTAC-April 2022).

9.12. The Committee noted that zanubrutinib is a second-generation Bruton tyrosine kinase (BTK) inhibitor, and ibrutinib is a first generation BTK inhibitor.

9.13. The Committee noted that the current treatment paradigm for CLL in New Zealand was split into lines of treatment for CLL with, and CLL without 17p deletion/TP3 mutation (17p del/ TP53 mut). The Committee noted that ibrutinib is currently funded in New Zealand for the second-line treatment of CLL with 17p del/ TP53 mut, and the third line treatment of CLL without 17p del/ TP53 mut.

9.14. The Committee considered that currently funded treatment options for CLL are limited compared to several other countries where there is widespread use of BTK inhibitors and venetoclax. The Committee considered that fixed-duration therapies should be considered for funding as they provide good outcomes with more predictable cost

than continuous therapies such as BTKis. The Committee considered that there was currently no evidence to suggest that continuous therapy resulted in superior outcomes compared to fixed term therapy.

Health need

9.15. The Committee considered that the health need of individuals with CLL has been well established and widely discussed at previous PTAC and CTAC meetings, including discussion in the context of various treatments in both the treatment-naïve and relapsed/refractory (R/R) settings.

9.16. The Committee considered there was currently a high unmet health need in the first-line treatment of CLL with 17p del/ TP53 mut in New Zealand, who do poorly with chemo-immunotherapy based regiments and currently have no BTK inhibitor funded for this line of treatment.

9.17. The Committee considered that an increase in CLL registration in New Zealand may reflect the ageing population, and possibly increased rates of diagnosis, but that an increase in individual registrations would not necessarily correlate with increased treatment requirements. The Committee considered that the number if people requiring treatment in all four indications could be estimated by analysing Special Authority individual numbers in the first instance, with reference to the supplier estimates if required. The Committee considered that 10% was a reasonable estimate of the proportion of people with newly diagnosed CLL who have 17p del/TP53 mutation but that a higher proportion may have these mutations in the subgroups who access treatment at each successive treatment line.

Health benefit

9.18. The Committee noted the results of the SEQUOIA trial (Tam et al. Haematologica. 2020;106:2354-63, Tam et al. Lancet Oncol. 2022;23:1031-43),: a Phase III open-label, randomised ongoing, international trial providing the primary evidence for the health benefits of zanubrutinib for the first-line treatment of CLL, with a subgroup providing evidence for people with 17p del/ TP53 mut CLL (*N*=110). The Committee noted that efficacy measures included overall response rate (ORR), progression free survival (PFS), and complete response rate (CR). The Committee noted the following results: PFS: 88.9% (95% CI:81.3,93.6) at 24 months, ORR: 99/110 (90.0%) (95%CI:82.8-94.9), CR: 7(95%CI:2.6,12.7). The Committee also noted patient reported outcomes from the trial (Ghia et al. Hemasphere. 2022; 6:560-1).

9.19. The Committee noted the results of the ALPINE trial:, a phase 3 direct head-to-head, randomised (1:1), open label, multinational providing the primary evidence for zanubrutinib in comparison to ibrutinib for relapsed or refractory CLL (Brown et al. N Engl J Med. 2023;388:319-32, Hillmen et al. J Clin Oncol. 2023;41:1035-45). The Committee noted efficacy and safety results, including OR (investigator assessed): zanubrutinib 83.5%, ibrutinib 74.2%, 24-month, event-free response investigator assessed: zanubrutinib 79.5%, ibrutinib 71.3%, 24-month PFS zanubrutinib 78.4% (95% CI, 73.3 to 82.7), ibrutinib 65.9% (95% CI, 60.1 to 71.1), atrial fibrillation/flutter: lower in the zanubrutinib group (in 17 of 324 [5.2%] vs. 43 of 324 [13.3%] in the ibrutinib group).

9.20. The Committee considered that there was a class-effect for efficacy of BTK inhibitors including zanubrutinib and ibrutinib. The Committee referred to the ELEVATE (Sharman et al. Lancet. 2020;395:1278-91) and ALPINE (Brown et al. N Engl J Med. 2023;388:319-32, Hillmen et al. J Clin Oncol. 2023;41:1035-45) trials as evidence indicating this class effect. The Committee considered that zanubrutinib would provide similar health benefit to ibrutinib for the lines of treatment where ibrutinib is already funded, due to this class effect. The Committee considered that for this reason, the same economic modelling for ibrutinib could be used for zanubrutinib for

all indications, with ibrutinib as an equally efficacious comparator to zanubrutinib in indications where ibrutinib is funded. The Committee noted that zanubrutinib may be slightly more efficacious and cause fewer cardiac adverse events, but that these differences were likely insufficient to warrant separate economic modelling.

9.21. The Committee considered the strength of evidence for BTK inhibitors including zanubrutinib and ibrutinib to be good.

9.22. The Committee considered that there were several reasons a BTK inhibitor may provide additional health benefit compared to venetoclax monotherapy for the treatment of previously untreated CLL with 17p del/ TP53 mut, as reflected in the SEQUOIA trial evidence, and via removing the need for hospital admission for tumour lysis syndrome prophylaxis. The Committee also commented that this would align with international guidelines.

9.23. The Committee reiterated its support for the April 2023 recommendation of removing the restriction on accessing usage of ibrutinib or venetoclax with rituximab to people who experienced a disease relapse within 36 months of prior line of treatment. The Committee considered that if a BTK inhibitor were to be funded for the first-line treatment of 17p-/del TP53mut CLL, then on progression these people who receive first-line BTK inhibitor treatment would then access venetoclax with rituximab as fixed duration therapy. Members considered that some haematology oncologists may prefer in 17p/TP53mut CLL to utilise venetoclax monotherapy upfront (first-line) and a BTK inhibitor on progression if venetoclax was only available once.

9.24. The Committee considered that a BTK inhibitor would provide similar health benefit to venetoclax with rituximab for second-line treatment of CLL without 17p del/ TP53 mut, with the added health benefits of no hospital admission for tumour lysis syndrome prevention, and a full oral regimen. The Committee estimated that if funded alongside venetoclax with rituximab there would be a 50/50 split across both therapies at both second and third line ie that half of people would receive a BTK inhibitor first followed by venetoclax, and half would receive it in the reverse order.

9.25. The Committee considered that some people with CLL may prefer to receive a continuous oral regimen, especially if they were of older age, and therefore less likely to utilise later (three or more) lines of treatment. The Committee considered that due to prolonged progression free survival obtained with these oral regimens, some people of older age would not need to utilise further lines of therapy.

Suitability

9.26. The Committee considered that there do not appear to be any suitability issues relating to the use of zanubrutinib that have not been previously discussed in considerations of ibrutinib and acalabrutinib.

Cost and savings

9.27. The Committee considered that it was difficult to estimate the number of people who may discontinue continuous treatment if the 36-month Special Authority limitation were removed, but that on balance a broad estimate of 50% was not unreasonable, and this should be varied widely in sensitivity analysis (20-80%) and refined with further advice if highly material to economic modelling.

9.28. The Committee also noted that if the 36-month Special Authority restriction was removed for all BTK inhibitors, nobody would use obinutuzumab-chlorambucil at second-line. This change was made to the PICO table below.

9.29. The Committee considered that evidence of comparative efficacy for venetoclax monotherapy vs fixed duration venetoclax with rituximab in relapsed CLL with 17p deletion/TP53 mutation is lacking. There may be a preference among treaters for

continuous therapy and therefore uptake for zanubrutinib for previously untreated CLL with 17p del/ TP53 mut would likely be high (perhaps 90+%) if venetoclax monotherapy was available second-line, and lower (perhaps closer to 70%) if venetoclax with rituximab was the only venetoclax-containing treatment available second-line.

9.30. The Committee noted that individuals whose disease progresses on a BTKi would be subsequently treated with another class of drug in preference to a second BTKi. Further data on retreatment with second generation BTKi in disease resistant to first generation BTKi is awaited and may influence future treatment practices.

9.31. The Committee considered that if zanubrutinib were to be funded alongside ibrutinib in lines of treatment where ibrutinib is funded, uptake would likely be 100% due to zanubrutinib's favourable safety profile and slightly increased efficacy. The Committee also considered 100% uptake would be likely if zanubrutinib were to be funded alongside venetoclax with rituximab for relapsed/refractory CLL without 17p del/TP53 mut due to the same benefits of zanubrutinib.

Funding criteria

9.32. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for zanubrutinib if it were to be funded in New Zealand for CLL in the included indications. 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	CLL or SLL, 17p deletion or TP53 mutation, first-line	CLL or SLL, relapsed or refractory, 17p deletion or TP53 mutation, second-line	CLL or SLL, relapsed or refractory, no 17p deletion or TP53 mutation, second-line	CLL or SLL, relapsed or refractory, no 17p deletion or TP53 mutation, third line
Intervention	Zanubrutinib, 320 mg daily oral dose (four total 80 mg capsules) until disease progression or unacceptable toxicity.			
Comparator(s) (NZ context)	Venetoclax monotherapy	Ibrutinib monotherapy, 420 mg daily oral dose until disease progression or unacceptable toxicity	Venetoclax-rituximab (six cycles max. rituximab)	Ibrutinib monotherapy, 420 mg daily oral dose until disease progression or unacceptable toxicity
Outcome(s)	The therapeutic intent of treatment for CLL is to prolong PFS and OS, with minimal toxicity.			
	SEQUOIA trial (zanubrutinib): • PFS at 30.5 months: 86% • OS at 24.0 months: 93.6%	ALPINE trial: • PFS 72.6% vs. 54.6% at 24 months zanubrutinib vs. ibrutinib, with a hazard ratio of 0.53 (95% CI 0.31-0.88) • OS 85.3% vs 81.5% alive at the end of follow up with zanubrutinib vs. ibrutinib, with a hazard ratio overlapping 1 (0.76 95% CI 0.51-1.11)		

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.

10. Zanubrutinib for treatment of Waldenströms macroglobulinaemia

Application

10.1. The Advisory Committee reviewed the application for zanubrutinib in the treatment of Waldenström macroglobulinaemia (WM).

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 zanubrutinib for the first-line treatment of Waldenström macroglobulinaemia be listed with a **low** priority, within the context of treatments of malignancy, subject to the following Special Authority criteria:

> **Zanubrutinib**
> **Initial application – Waldenström macroglobulinaemia (Lymphoplasmacytic Lymphoma)**
> Applications from any relevant practitioner. Approvals valid for 12 months.
> **Prerequisites** (tick boxes where appropriate):
> 1. The patient has Waldenström macroglobulinaemia/Lymphoplasmacytic Lymphoma requiring treatment; and

2. The patient is treatment-naïve; and
3. Patient has good performance status.

Renewal application
Applications from any relevant practitioner. Approvals valid for 12 months.
Prerequisites (tick boxes where appropriate)
1. No evidence of clinical disease progression and
2. The treatment remains appropriate, and the patient is benefiting from treatment.

10.4. In making this recommendation, the Committee considered:

- The health need for individuals with symptomatic WM requiring first-line therapy, where bendamustine-rituximab (BR) is not a suitable option.
- The health benefit evidence and improved tolerability and safety of zanubrutinib compared to currently funded treatments for people with WM, although the Committee noted the limited number of treatment-naïve individuals participating in the clinical trials.
- The suitability of the oral administration of zanubrutinib for individuals.

10.5. The Advisory Committee recommended that zanubrutinib for the treatment of individuals with relapsed/refractory Waldenström macroglobulinaemia be listed with a **medium** priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Zanubrutinib
Initial application – relapsed/refractory Waldenström macroglobulinaemia (Lymphoplasmacytic Lymphoma)
Applications from any relevant practitioner. Approvals valid for 12 months.
Prerequisites (tick boxes where appropriate):
1. The patient has Waldenström Macroglobulinaemia/Lymphoplasmacytic Lymphoma requiring treatment; and
2. Patient has relapsed after, or is refractory to, previous line of treatment; and
3. The patient is zanubrutinib naïve; and
4. Patient has good performance status.

Renewal application
Applications from any relevant practitioner. Approvals valid for 12 months.
Prerequisites (tick boxes where appropriate)
1. No evidence of clinical disease progression and
2. The treatment remains appropriate, and the patient is benefiting from treatment.

10.6. In making this recommendation, the Committee considered:

- The health need for those experiencing relapsed/refractory (R/R) WM including those experiencing early relapse/refractory disease who have fewer treatment options following first line treatment.
- The health benefit evidence and improved tolerability and safety of zanubrutinib compared to currently funded treatments for peoples with WM.
- The improved suitability of an oral treatment option for individuals if used as a monotherapy.

Discussion

Māori impact

10.7. The Committee noted that, based on the supplier-provided analysis of Manatū Hauora- New Zealand Cancer Registry data, Māori comprised roughly 3% of registered cases of WM between 2010 to 2020. The Committee considered there to be a lack of evidence to suggest there was a difference in age-standardised incidence or disease biology for Māori individuals compared to non-Māori individuals with WM in New Zealand.

Background

10.8. The Committee noted that at the November 2021 CaTSoP (now CTAC) meeting an application for ibrutinib, a first-generation Bruton's tyrosine kinase inhibitor (BTKi) which is used as a continuous monotherapy for the treatment of WM was assessed and two recommendations were made. The Committee noted that CaTSoP recommended that ibrutinib for the treatment of first line and R/R WM be listed with a low and medium priority, respectively.

10.9. The Committee noted that at the October 2022 CTAC meeting an application for bortezomib, a proteosome inhibitor, which is used for a fixed duration in combination with other drugs for the treatment of WM, was assessed and bortezomib for the treatment of WM in the R/R setting was recommended to be listed with a medium priority.

Health need

10.10. The Committee noted that WM is an incurable lymphoplasmacytic lymphoma infiltration of lymphoplasmacytic cells into the bone marrow and immunoglobulin M (IgM) monoclonal gammopathy. The Committee noted that WM is a relatively uncommon blood cancer, representing 2% of blood cancer cases. The Committee noted a supplier-provided analysis of Manatū Hauora- New Zealand Cancer Registry data, which suggested that in 2020, there were 40 newly diagnosed cases of WM in New Zealand.

10.11. The Committee noted that the mean age of diagnosis with WM was roughly 68 years. The Committee noted that treatment is not required until the individual is experiencing symptoms, with a median time between diagnosis and treatment can be up to 5 to 10 years (Kyle et al. Blood. 2012;119:4462-6). The Committee noted that there is an unmet health need for individuals who are unable to receive bendamustine-rituximab (BR) therapy, a relatively effective treatment for the condition but one that is typically reserved for people experiencing good performance status.

10.12. The Committee noted that the currently funded treatment options for WM include BR, cyclophosphamide-dexamethasone-rituximab (CDR), rituximab-cyclophosphamide-vincristine-prednisone (R-CVP), cyclophosphamide-doxorubicin, vincristine, prednisone + rituximab (R-CHOP), rituximab-chlorambucil (R-Chlorambucil) and rituximab monotherapy. The Committee noted that BR is the preferred and most efficacious current treatment option for people experiencing good performance status, the other treatment regimens used in situations where BR is not a suitable option.

10.13. The Committee noted that, based on the supplier-provided analysis of Manatū Hauora- New Zealand Cancer Registry data, Māori comprised roughly 3% of registered cases of WM between 2010 to 2020. The Committee considered there to be a lack of evidence to suggest there was a difference in age-standardised incidence or disease biology for Māori individuals compared to non-Māori individuals with WM in New Zealand.

Health benefit

10.14. The Committee noted the following evidence of the progression-free survival (PFS) that the currently funded treatment options can provide:

- BR can provide a median PFS of up to 69.5 months (Rummel et al. Lancet. 2013;381:1203-103).
- CDR can provide a median PFS of up to 34 months in the first-line setting (Kastritis et al. Blood). 2015;126:1392-4) and up to 35 month in the R/R setting (Paludo et al. Br J Haematol. 2017;179:98-105).

- R-CVP/R-CHOP can provide a median PFS of up to 30 months in the upfront setting (Rummel et al. Lancet. 2013;381:1203-103).
- R-monotherapy can provide a median PFS of up to 20 months in the upfront setting and 20 months in the R/R setting (Dimopoulas et al N Engl J Med. 2018;378:2399-2410).

10.15. The Committee noted that zanubrutinib is a second-generation inhibitor of Bruton's tyrosine kinase (BTKi). Zanubrutinib binds with high affinity to the BTK target site, forming an irreversible covalent bond, thus preventing further BTK-mediated activity, hindering malignant B-cell proliferation and differentiation.

10.16. The Committee noted that there is limited evidence to support the use of zanubrutinib in the first-line setting, with only 20 of the 201 participants in ASPEN receiving zanubrutinib in the first-line setting and the remaining participants having relapsed/refractory disease (Tam et al. Blood. 2020;136:2038-50; Trotman et al. Blood. 2022;136:2027-37).

10.17. The Committee previously considered there to be a class effect between BTKi therapies for the treatment of WM. The Committee considered that, based on the available evidence, both ibrutinib and zanubrutinib appeared to provide similar magnitudes of health benefit and similarly favourable safety profiles compared to funded chemotherapies.

10.18. The Committee noted that there is no evidence of a difference in efficacy between zanubrutinib and ibrutinib. The Committee noted that there were greater rates of partial response rates when the individuals received zanubrutinib compared with ibrutinib, however the Committee considered that the response rate measure is not prognostic in WM and therefore did not translate into the PFS or OS benefit.

10.19. The Committee noted the supplier's proposed treatment paradigms for individuals requiring first-line and R/R treatment for WM but considered both to be unsuitable. In regard to first line, the Committee considered that treatment options depend on whether BR is either going to be suitable or unsuitable for the individual, and that if BR was deemed unsuitable alternative options for individuals could include CDR, R-CVP, R-monotherapy or a BTKi if it was available. In regard to the R/R treatment setting, the Committee noted that less than 10% of individuals would receive retreatment of BR and that the preferred option for all individuals following first line immunochemotherapy would be a BTKi if it was available.

10.20. The Committee noted that the ASPEN trial was a phase III randomised, double-blind, placebo-control trial comparing zanubrutinib monotherapy with rituximab monotherapy in 201 individuals with WM previously untreated (n=37) and treated (n=164) (Tam et al. Blood. 2020; 146:2038-50).

10.20.1. The Committee noted that individuals participating in the trial had to have received at least one prior line of treatment, or if individuals were treatment naïve, it was due to immunochemotherapy being inappropriate, and were reported to be due to cardiac, renal, infection or other reasons. Individuals had the *MYD88* mutation which is representative of over 90% of those with WM, however individuals with the wildtype gene or genetic testing were indeterminate received zanubrutinib in a non-randomised arm of the study (Dimopoulos et al. Blood Adv. 2020:4 6009-18).

10.20.2. The Committee noted the results of the final analysis of the ASPEN trial, where after a median follow up of 19.4 months, 79% of individuals remained on study treatment, and 89% remained on study. No individuals experienced a complete response. Overall 28% zanubrutinib group and 19% ibrutinib group (2-sided, p=0.09), 29% zanubrutinib group and 20% ibrutinib group (p =0.12) of the R/R group and 26% zanubrutinib group and 17% ibrutinib group (p =0.54) TN group

were reported to experience a very good partial response, which was defined as monoclonal IgM detectable, ≥90% reduction in serum IgM level from baseline or normal serum IgM values, improvement in lymphadenopathy/splenomegaly if present at baseline, no new signs, or symptoms of active disease. The median time to experience the very good partial response was 4.7 months zanubrutinib and 5.1 months ibrutinib (p=0.17) for the R/R group and 5.6 months zanubrutinib and 22.1 months ibrutinib (p=0.35) for the TN group. The 18-month progression-free survival was reported to be 85% zanubrutinib and 84% ibrutinib and 18-month survival rate was 97% zanubrutinib and 93% ibrutinib.

10.20.3. The Committee noted the results of the toxicity and safety analysis of the ASPEN trial and noted that the incidence of adverse events involving atrial fibrillation/flutter, diarrhoea, contusion, muscle spasms, peripheral oedema and pneumonia occurred at ≥10% higher rates in individuals receiving ibrutinib compared with zanubrutinib and the incidence of neutropenia was ≥10% higher in individuals receiving zanubrutinib. The Committee noted that the higher incidence of neutropenia did not translate into a higher infection rate.

10.20.4. The Committee noted the long-term follow-up study of the ASPEN trial and noted that ibrutinib was associated with 19.4% of individuals experiencing an adverse event leading to discontinuation compared to 14.3% of individuals receiving zanubrutinib. The Committee noted the following proportions of individuals receiving either zanubrutinib or ibrutinib who experienced atrial fibrillation (7.9% zanubrutinib; 23.5% ibrutinib), diarrhoea (21.8% zanubrutinib; 34.7% ibrutinib), haemorrhage (55.4% zanubrutinib; 62.2% ibrutinib), major bleeding (7.9% zanubrutinib; 12.2% ibrutinib), hypertension (14.9% zanubrutinib; 25.5% ibrutinib), muscle spasm (10.9% zanubrutinib; 28.6% ibrutinib), localised infection (1.0% zanubrutinib; 11.2% ibrutinib), neutropenia (33.7% zanubrutinib; 19.4% ibrutinib), pneumonia (5% zanubrutinib; 18.4% ibrutinib), infection (grade ≥3) (78.2% zanubrutinib; 79.6% ibrutinib) (Dimopoulos et al. Hemasphere. 2922;6:1048-9).

10.20.5. The Committee noted the results of the non-randomised arm of the ASPEN trial, and noted that 27% individuals with *MYD88* wild-type were reported to have experienced a very good partial response when receiving zanubrutinib (Dimopoulos et al. Blood Adv. 2020:4 6009-18). The Committee noted that compared to *MYD88* mutant WM individuals with *MYD88* wild type WM experienced lower rates of very good partial response. The Committee noted that Phase II study treating individuals with *MYD88* wild type WM with ibrutinib, and noted that individuals received less health benefit compared to individuals with *MYD88* mutant WM (Treon et al. J Clin Oncol. 2021;39:565-575). The Committee noted that the evidence was limited due to the small number of individuals with *MYD88* wild type WM, however considered that overall individuals with *MYD88* wild type WM receive less health benefit when receiving an BTKi therapy.

10.21. The Committee considered that there is high-quality evidence for what is a rare disease supporting the efficacy of zanubrutinib in the R/R setting. The Committee considered the evidence supporting the efficacy of zanubrutinib in the first line setting to be of lower quality due to the smaller number of participants in the ASPEN trial. The Committee considered that there was no evidence to suggest that zanubrutinib is inefficacious in the treatment naïve setting.

10.22. The Committee noted that BTKis have better safety profiles when compared to immunochemotherapy for the treatment of WM, however the Committee noted zanubrutinib has lower incidence of adverse events, highlighting the lower risk of atrial fibrillation/flutter in comparison to ibrutinib to be of particular importance as individuals with WM are usually older and more likely to be predisposed to atrial fibrillation/flutter.

10.23. The Committee noted the clinician-lead supporting submission requesting BTKi funding for individuals who are younger than 55 years old who relapse within five years of first-line immunochemotherapy and noted that requiring a second-line of treatment before the age of 55 years old is a rare situation. The Committee considered there to be a high probably that the disease course in this setting is more aggressive and considered the proposed SA criteria for individuals with R/R WM would be inclusive and appropriate for this situation.

10.24. The Committee noted that zanubrutinib would provide a health benefit to family, whānau and wider society, by allowing an individual to receive zanubrutinib at home, the lower toxicity profile, reducing the need to travel for individuals in rural areas, more time with family and whānau, and reduced chair time in chemotherapy units or hospital admission.

Suitability

10.25. The Committee noted that zanubrutinib is an oral medication that is administered twice daily. The Committee noted that funding zanubrutinib could reduce the need for individuals to travel to receive therapy at infusion facilities, as the funding alternatives to zanubrutinib are administered as infusions.

Cost and savings

10.26. The Committee noted that, based on the supplier-provided analysis of Manatū Hauora-New Zealand Cancer Registry data, there were an estimated 20 to 50 cases of newly diagnosed cases of WM per year in New Zealand and that the average annual growth in new cases over the period 2010 to 2020 was roughly 7% per annum.

10.27. The Committee noted that the median time from diagnosis of WM to needing treatment is 5 to 10 years (Kyle et al. Blood. 2012;119:4462-6). The Committee noted that, due to the long natural history of the disease, and the population with WM being predominantly older adults, some individuals are dying from other causes.

10.28. The Committee considered the supplier's estimate that 87% of newly diagnosed cases of WM would require treatment and noted this was based on a Spanish observational study of cases of WM who had IgM paraprotein concentrations of >30g/L and percentage of clonal lymphocytes of >20% in the marrow (García-Sanz. Br J Haematol. 2001;115:575-82). The Committee noted that a diagnosis of WM requires the proportion of clonal lymphocytes in the bone marrow to be >10%, and there were no diagnostic criteria related to IgM paraprotein concentration. As such, the Committee considered that this cohort study was unlikely to be representative of the population with WM in New Zealand.

10.29. The Committee noted a previous CTAC discussion in October 2022, in the context of bortezomib for WM, that between 40 to 70 individuals with newly diagnosed or relapsed refractory WM could be eligible for treatment per year. The Committee considered those estimates could be appropriately applied to zanubrutinib for WM, noting these funding applications targeted the same population.

10.30. The Committee noted that zanubrutinib was unlikely to be used in combination with rituximab, as there was a lack of evidence that a zanubrutinib-rituximab combination would be any more efficacious than zanubrutinib alone.

10.31. The Committee considered a cost-utility analysis submitted by the supplier which used rituximab monotherapy (R) as the comparator treatment for zanubrutinib in the first line setting and BR as the comparator in the relapsed/refractory setting. The Committee considered that the supplier-modelled comparators were not representative of the currently funded alternatives to zanubrutinib in either setting.

10.32. The Committee considered that, in a first line setting, zanubrutinib would most likely be considered for people with WM where BR chemotherapy is not suitable. The Committee considered that BR would not be suitable in approximately 40% of people requiring first-line treatment for WM. The Committee noted that currently either RCVP or CDR is the preferred treatment for those in which first-line BR is not suitable, with a roughly equal proportion of individuals between the two regimens.

10.33. The Committee considered that BR re-treatment would be suitable for less than 10% of people with relapsed/refractory WM, and that zanubrutinib would likely be considered for this group (regardless of performance status). The Committee noted that currently R, RCVP, or CDR are the preferred treatments for those in which second-line BR is not suitable, with a roughly equal proportion of individuals between the three regimens.

10.34. The Committee noted that there was a modelled overall survival benefit in the supplier-provided cost-utility analyses for zanubrutinib. The Committee considered that there was limited overall survival data from ASPEN and relevant trials of comparators, and the available data did not indicate an apparent overall survival benefit associated with zanubrutinib.

Summary for assessment

10.35. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for zanubrutinib if it were to be funded in New Zealand for WM. 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.

Table 4: PICO for zanubrutinib if it were to be funded in New Zealand for WM.

Population	People with WM, requiring first-line treatment (mostly individuals for whom bendamustine-rituximab [BR] is not suitable)	People with relapsed/refractory (R/R) WM
Intervention	Zanubrutinib capsules, 160mg, twice daily (eviQ - Lymphoma zanubrutinib)	
Comparator(s) (NZ context)	*Roughly equal split of people on comparator treatment regimens* Dexamethasone, rituximab and cyclophosphamide (DCR) every 3 week for 6 cycles. OR Rituximab combined with vincristine and prednisone (RCVP) every 3 weeks for 6 cycles.	*Roughly equal split of people on comparator treatment regimens* Dexamethasone, rituximab and cyclophosphamide (DRC) every 3 week for 6 cycles. OR Rituximab combined with vincristine and prednisone (RCVP) every 3 weeks for 6 cycles. OR Rituximab monotherapy with 6 cycles of rituximab as currently funded or: *8-week course (two four-weekly cycles split 3 months apart) of rituximab 375mg/m^2.*

Outcome(s)	Increased progression free survival Increased overall response rate Potential overall survival benefit

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.

11. Zanubrutinib for treatment of relapsed/refractory mantle cell lymphoma

Application

11.1. The Advisory Committee reviewed the application for zanubrutinib in the treatment of relapsed/refractory mantle cell lymphoma (MCL).

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

Recommendation

11.3. The Advisory Committee **recommended** that zanubrutinib for relapsed/refractory mantle cell lymphoma (MCL) be listed with a **high priority,** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **ZANUBRUTINIB**
> **Initial application – relapsed or refractory relapsed/refractory mantle cell lymphoma (MCL)**
> Applications from any relevant practitioner. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory MCL confirmed by a haematologist; and
> 2. Patient has good performance status; and
> 3. Zanubrutinib is to be given with curative intent
>
> Renewal application (relapsed or refractory MCL) – from any relevant practitioner
> Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Treatment remains clinically appropriate, and the patient is benefitting from treatment.

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

- people with relapsed/refractory MCL experience high unmet health need in New Zealand due to current funded therapies being often ineffective and/or intolerable, and the high mortality rate of the disease.
- a funded BTK inhibitor for relapsed/refractory MCL could provide substantial additional health benefit to currently funded treatments, including a large improvement in progression-free survival.
- Committee members were not aware of any apparent suitability issues relating to the use of zanubrutinib that the Committee had not previously discussed in other considerations of BTK inhibitors.

11.5. The Committee **recommended** the same Special Authority criteria apply to ibrutinib, thus replacing the Special Authority criteria previously recommended for ibrutinib in May 2016.

Discussion

Māori impact

11.6. The Committee discussed the impact of funding zanubrutinib for the treatment of MCL on Māori health areas of focus and Māori health outcomes. The Committee noted that MCL is not specifically a Pharmac Hauora Arotahi Māori health area of focus. The Committee was not aware of any direct evidence to suggest that incidence and/or severity or disease burden of MCL in Māori is any greater than that of other New Zealand populations.

Background

11.7. The Committee noted that zanubrutinib is a Bruton tyrosine kinase (BTK) inhibitor. The Committee noted that funding of treatments for MCL had previously been considered by Pharmac in the context of ibrutinib, a different BTK inhibitor. The Committee noted that a funding application had been previously assessed for ibrutinib for relapsed/refractory MCL. In November 2015, with PTAC in May 2016 recommending ibrutinib be listed in the Pharmaceutical Schedule for MCL with a **low priority**, CaTSoP (now CTAC) in August 2016 recommending ibrutinib be funded for the indication with a **medium priority**, PTAC in November 2016 reviewing CaTSoP's recommendations and recommending ibrutinib be funded with a **low priority**, and Pharmac completing relative ranking of the application in June 2020.

Health need

11.8. The Committee noted that MCL is a distinct subtype of non-Hodgkin lymphoma accounting for less than 10% of all lymphoid malignancies. (Sant et al. Blood. 2010;116:3724-3734). The Committee noted studies indicate MCL accounts for approximately 6% of all B-cell malignancies and the ratio of males to females affected is about 4:1 (Bradstock & Browett. Leukaemia & Blood Foundation New Zealand. 2010; Goy et al. Crit Rev Oncol Hematol. 2011;80:69-86; McKay et al. Br J Haematol. 2012;159:405-26; Skarbnik et al. Clin Adv Hematol Oncol. 2015;13:44-55).

11.9. The Committee noted that with a median age at diagnosis of between 60-70 years, MCL disproportionately affects the elderly, who may have comorbidities and limited mobility, and for whom chemotherapy (and any associated adverse events) may be less well tolerated (Chandran et al. Leuk Lymphoma. 2012;53:1488-93, Skarbnik et al. Discov Med. 2013;15:177-87).

11.10. The Committee noted that MCL is not curable, with most people with the disease experiencing a relapse. MCL has relatively short median overall survival (OS) (an estimated 4-5 years), and a median progression free survival (PFS) of 20 months (Goy et al. Crit Rev Oncol Hematol. 2011;80:69-86). The Committee noted the 5-year OS for MCL is around 50% (Chandran et al. 2012). The Committee noted that among people who experience relapse, the median life expectancy is only 1-2 years following salvage therapies, which are often associated with significant toxicities, and can make treatment difficult in more fragile and/or older people (Goy et al. 2011; McKay et al. 2012).

11.11. The Committee noted that the current treatment paradigm for relapsed/refractory MCL in New Zealand is chemoimmunotherapy. The Committee considered that various other countries including England and Wales, Australia, and Canada currently fund ibrutinib for this indication, but access to ibrutinib for MCL in New Zealand requires self-funding as it is not currently funded.

11.12. The Committee noted the results of a phase 2 study reporting observational outcomes for chemotherapy treatment for relapsed/refractory MCL (Czuczman et al. Ann Haematol. 2015;94:2025-32). Bendamustine with rituximab (BendR) was used for 45 people with relapsed/refractory MCL with a median of 2 different prior lines of

treatment. The Committee noted that overall response rate (ORR) was 82%, PFS was 17.2 months and OS at three years was 55%. The Committee also noted that Grade 3 or higher toxicities occurred in 90% of participants. The Committee noted that in New Zealand people often received BendR upfront for MCL, so it was unable to be used in the relapsed/refractory setting.

11.13. The Committee noted the results of a Phase 2 study reporting observational outcomes for ibrutinib for relapsed/refractory MCL (Wang et al. Blood. 2015;126:739-45). Ibrutinib was used for 116 people who had previously 1-6 previous lines of treatment. The Committee noted that ORR was 67%, PFS at 24 months was 31%, and OS at 24 months was 47%.

11.14. The Committee considered that adverse events of BTK inhibitors are generally manageable, but noted that Wang et al. 2015 showed that atrial fibrillation occurs in around 10% of people who use ibrutinib, and grade 3 bleeding occurs in approximately 6%.

11.15. The Committee considered that people with relapsed/refractory MCL experience high unmet health need in New Zealand due to currently funded therapies being often ineffective and/or intolerable and the low overall survival with the disease.

Health benefit

11.16. The Committee noted that zanubrutinib is a second generation BTK inhibitor, and noted the efficacy of zanubrutinib for MCL in the following clinical trials:

- BGB-3111-AU-003 and BGB-3111-206 (Zhou et al. J Haematol Oncol. 2021;14:167)
- NCT02343120 (Tam et al. Blood Adv. 2021;5:2577-85)
- NCT03206970 (Song et al. Clin Cancer Res. 2020;26:4216-24, Song et al. Blood. 2022;139:3148-58)
- NCT04116437(Shadman et al. Lancet Haematol. 2023;10:e35-e45)

11.17. The Committee also noted the efficacy of ibrutinib in MCL in the following clinical trials:

- PCYC-1104-CA (Wang et al. N Engl J Med. 2013;369:507-16), Wang et al. Blood. 2015;126:739-5)
- NCT01646021 (Dreyling et al. Lancet. 2016;387:770-8, Rule et al. Leukemia. 2018;32:1799-803)
- RAY trial; MCL3001 (Hess et al. Leuk Lymphoma. 2017;58:2824-32)

11.18. The Committee considered from the above evidence for both therapies, that there was a class effect of efficacy across BTK inhibitors, with zanubrutinib and ibrutinib reporting comparable PFS and OS. The Committee considered that zanubrutinib had superior safety than ibrutinib, as zanubrutinib is associated with less cardiac adverse events.

Suitability

11.19. The Committee was not aware of any suitability issues relating to the use of zanubrutinib that the Committee had not previously discussed in other considerations of BTK inhibitors, specifically the consideration of ibrutinib for relapsed/refractory MCL.

Cost and savings

11.20. The Committee considered that uptake would likely be very high for a BTK inhibitor in this setting, due to its likely benefits relative to currently funded treatment options.

11.21. The Committee considered that the appropriate comparator for a BTK inhibitor in this setting would be rituximab-based regimens, including R-CHOP and R-CVP. The Committee considered that rituximab with bendamustine is most commonly used in a first-line setting and so would not often be used in a relapsed setting. The Committee considered that rituximab monotherapy was not often used in this setting.

11.22. The Committee considered that single-agent chemotherapies such as gemcitabine (as in the Hess et al. J Clin Oncol 2009;27:3822-9 trial) are not generally used in this setting and so would not be appropriate comparators. The Committee further considered that some people cannot tolerate treatment with the currently funded agents, and so the comparator for these people would be no chemoimmunotherapy.

11.23. The Committee considered that while a BTK inhibitor was likely to offer substantial improvements in PFS and OS compared to funded treatments, the magnitude of benefit was uncertain, given the data available. The Committee considered that some evidence suggests BTK-inhibitors may be associated with PFS duration more than twice that of temsirolimus, based on the Dreyling et al. 2016 study and a crude comparison between BTK inhibitor results with other trial results in MCL.

11.24. The Committee considered that using evidence relating to temsirolimus to model comparator PFS and OS was subject to a high degree of uncertainty, given the lack of evidence comparing temsirolimus with funded comparators and the lack of temsirolimus use in New Zealand.

Funding criteria

11.25. The Advisory Committee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for [the pharmaceutical] if it were to be funded in New Zealand for [the indication]. 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.

11.26. The Advisory Committee noted that elements of 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 relapsed/refractory MCL
Intervention	Zanubrutinib, at a dose of 320mg per day until disease progression or unacceptable toxicity
Comparator(s) (NZ context)	Likely to be a combination of: - R-CHOP - R-CVP - Potentially other chemo-immunotherapies Some people may currently receive no systemic treatment due to intolerance to current treatments (likely to be a low proportion, less than 20%) - Outcomes for these individuals are uncertain, given absence of evidence, however are likely to be poor Appropriate evidence to model the outcomes on the comparator is uncertain, with no evidence identified on R-CHOP or R-CVP in a second-line setting for MCL
Outcome(s)	Similar PFS and OS compared to other BTK inhibitors Magnitude of benefit vs comparator uncertain, given the lack of published evidence against funded comparators - Likely to be a significant PFS and OS benefit

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.

12. Other Business

Goserelin injections

12.1. The Committee noted goserelin injection had been included in Pharmac's 2022/23 Annual Tender and the tender had not been unresolved. The Committee noted Pharmac had received a number of complaints from clinicians and people receiving goserelin about the currently funded goserelin product.

12.2. The Committee considered there were suitability issues with the currently funded product. The Committee also noted individuals receiving goserelin had reported more pain when the currently funded product is administered compared to the previous brand of goserelin.

12.3. The Committee considered it would be appropriate to change the funded brand of goserelin injections to manage these concerns.