Record of the Cancer Treatments Advisory Committee Meeting held on 8 April 2022

Cancer Treatments Advisory Committee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) Specialist Advisory Committees 2021.

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

The Cancer Treatments Advisory Committee may:

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

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

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

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.

TABLE OF CONTENTS

1. Attendance

Marius Rademaker (Chair)
Scott Babington
Christopher Frampton
Peter Ganly
Richard Isaacs
Allanah Kilfoyle
Vidya Mathavan
Stephen Munn
Anne O'Donnell
Matthew Strother
Lochie Teague
Michelle Wilson

2. Summary of recommendations

The following recommendation summary is in order of the discussions held at the meeting.

Pharmaceutical and Indication	Recommendation
• Pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with a Combined Positive Score (CPS) ≥1	Low Priority
• Generic abiraterone acetate (Yonsa) for high-risk metastatic hormone-naïve prostate cancer (mHNPC) patients and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC)	High priority
• Acalabrutinib as an alternative option to venetoclax regimens in previously untreated CLL patients, for whom acalabrutinib is a more appropriate option due to venetoclax monotherapy being unsuitable	Medium Priority
• Acalabrutinib as an alternative option to venetoclax regimens in previously untreated CLL patients, for whom acalabrutinib is a more appropriate option due to intolerance of venetoclax	High Priority
• Acalabrutinib as a subsequent line of therapy to venetoclax regimens in relapsed or refractory CLL patients who have relapsed within 36 months	Medium priority
• Atezolizumab for the first-line treatment of patients with ES-SCLC in combination with chemotherapy	High priority

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

3.1. This meeting record of the Cancer Treatments Advisory Committee is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and Specialist Advisory Committees 2021, available on the Pharmac website at https://pharmac.govt.nz/assets/2021-Specialist-Advisory-

Committee-Terms-of-Reference.pdf. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of Specialist Advisory Committees and PTAC.

3.2. Conflicts of Interest are described and managed in accordance with section 7.2 of the PTAC Terms of Reference.

3.3. The Cancer Treatments Advisory Committee is a Specialist Advisory Committee. The Cancer Treatments Advisory Committee and PTAC and other Specialist Advisory Committees have complementary roles, expertise, experience, and perspectives. The Cancer Treatments Advisory Committee and other Specialist Advisory Committees may therefore, at times, make recommendations for treatments for Cancer 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'.

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

4. Record of PTAC meeting held in November 2021

4.1. The Advisory Committee reviewed the Record of the PTAC meeting held in November 2021 and noted the considerations at that meeting.

5. Correspondence and Matters Arising

Palbociclib in second-line combination treatment of unresectable locally advanced metastatic breast cancer

Recommendation

5.1. The Advisory Committee **recommended** that the Special Authority renewal criteria for palbociclib be amended to clarify that palbociclib treatment is to be ceased upon disease progression (additions in bold):

> Palbociclib
> Renewal application - only from a medical oncologist or any other 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. No evidence of progressive disease **since initiation of palbociclib therapy**; and
> 3. The treatment remains appropriate and the patient is benefitting from treatment.

Discussion

5.2. The Committee reviewed correspondence from a consumer regarding current access to palbociclib therapy noting patients are not eligible for ongoing palbociclib once they have experienced disease progression. The Committee noted that funding is currently subject to Special Authority criteria which enable use in either first-line or second-line with renewal criteria requiring treatment to cease upon identification of progressive disease. The Committee noted that this correspondence considered that funding of palbociclib should continue for patients following progression from a first line endocrine

agent, to enable continuation of palbociclib in combination with fulvestrant as a second line combination therapy.

5.3. The Committee noted that given the available evidence, the combination of a CDK4/6 inhibitor with an endocrine partner is current standard of care, with palbociclib and an aromatase inhibitor used in New Zealand, unless the patient had received prior prolonged endocrine aromatase inhibitor therapy in the adjuvant setting in which case, fulvestrant in combination with palbociclib may be preferred.

5.4. The Committee noted that, following use of palbociclib, over time patients are likely to develop resistance to CDK4/6 inhibitors, the endocrine partners, or both. The Committee noted the correspondent indicated the belief that sensitivity to the CDK4/6 inhibitor persists beyond disease progression related to resistance to the endocrine partner, and therefore patients should be able to switch the endocrine partner on progression whilst maintaining access to palbociclib, prolonging chemotherapy free survival and by implication, overall survival.

5.5. The Committee considered there is currently little evidence to support this approach to CDK4/6 treatment:

5.5.1. The Committee noted a prospective database cohort report (with no control group) of 30 patients (Eziokwu et al. Clin Breast Cancer. 2021; 21(3):205-2019.) which reported a median PFS of 11.8 months who switched to a second endocrine partner on identification of progressive disease.

5.6. The Committee noted the most appropriate available evidence to inform this approach will come from the PADA-1 study (Clinicaltrials.govt.Identifier: NCT03079011), a French multi-centre study conducted in patients receiving an aromatase inhibitor and palbociclib as first-line therapy for ER+ve, HER2 negative metastatic breast cancer which is focused on the development of mutations in ESR1, This study has noted that a cohort of patients display increased numbers of mutations as their malignancy matures and progresses, where mutations may be unusual in de novo disease but increase in prevalence as the disease metastasises. The Committee noted the study aims to determine if arising mutations of ESR1 can be detected in circulating tumour DNA before clinical progression, whether switching to a new endocrine partner in patients with these mutations improves overall survival.

5.6.1. The Committee noted the study recruited over 1,000 participants and all patients were screened for ESR1 mutations at regular intervals while treated with palbociclib and an aromatase inhibitor (letrozole, anastrozole or exemestane). Upon identification of a rising circulating ESR1 mutations, patients were randomised (1:1) to either change aromatase inhibitor in combination with fulvestrant, no change until confirmation of tumour progression, or cross-over following identification of tumour progression (to enable fulvestrant + palbociclib treatment).

5.6.1.1. The Committee noted preliminary results presented at SABCS 2021 indicated 170 patients demonstrated increased prevalence of ESR1 mutations ahead of visceral progression, with a median PFS of those switched to fulvestrant/palbociclib of 11.9 months (05% CI, 9.1-13.6) vs. 5.7 months (95% CI, 3.9-7.5) for those who continued on an aromatase inhibitor/palbociclib (HR, 0.63, 95% CI, 0.45-0.99 P=0.007). The Committee noted that for patients with identified disease progression who had been randomised to continue on aromatase inhibitor/palbociclib, and then crossed over to fulvestrant + palbociclib treatment the median PFS was 3.5 months (95% CI, 2.7-5.1) after 14.7 months of follow up.

5.6.2. The Committee considered these results indicated ongoing evaluation is needed to understand whether addition of fulvestrant to palbociclib therapy, after identification of disease progression, alters outcomes in a clinically meaningful way.

5.7. The Committee noted one randomised study currently recruiting (ClinicalTrials.govt Identifier: NCT02738866), investigating the use of palbociclib with fulvestrant for metastatic breast cancer after treatment with palbociclib and an aromatase inhibitor.

5.7.1. The Committee noted other available trials are evaluating a switch to the CDK4/6 component to another available CDK4/6 agent such as ribociclib; however, these trials are ongoing and have not yet reported any outcomes.

5.8. The Committee noted there was anecdotal information which indicated some clinicians may be extending the use of palbociclib for patients who experience disease progression during the 12-month renewal period by changing aromatase inhibitor to fulvestrant to regain disease control prior to the re-assessment period required for a further Special Authority renewal. The Committee considered this was not within the intent of the Special Authority criteria and that this was done in hope of therapeutic benefit, but at present there is insufficient evidence to support funding palbociclib use in this way.

5.9. The Committee noted palbociclib is a high-cost medicine and supported amendment to the current Special Authority criteria to signal the intent of the renewal criteria which requires cessation of treatment upon identification of any disease progression.

5.10. The Committee considered further review of the evidence for switching CDK4/6 inhibitors/aromatase inhibitors in metastatic breast cancer would be warranted and welcomed an application from the relevant Special Interest Groups once new evidence is published.

Continuity of supply for daunorubicin

5.11. The Committee reviewed correspondence from the supplier of daunorubicin regarding its intention to discontinue supply of daunorubicin in late 2023. The Committee noted this was the only Medsafe approved daunorubicin product currently available in New Zealand.

5.12. The Committee noted that daunorubicin is an anthracycline, of which there are several others currently listed on the Pharmaceutical Schedule (doxorubicin, epirubicin and idarubicin). The Committee considered daunorubicin to be an essential medicine (on the WHO model list of essential medicines).

5.13. The Committee noted that there are approximately 150 patients per year that require treatment with daunorubicin. The Committee noted that it is primarily used as part of treatment protocols for acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). The Committee considered that the majority of daunorubicin use occurs in AML. The Committee noted that it was used in both adult and paediatric treatment protocols.

5.14. The Committee noted that there may be alternative supply options available for continuity of access for daunorubicin, but that this was uncertain at this time. The Committee noted that the other anthracyclines such as idarubicin and mitoxantrone are used in certain protocols (FLAG-Ida, AIDA, MidAC) for particular subtypes of AML. The Committee noted that doxorubicin is used in some ALL treatment protocols (HyperCVAD and children's oncology group [COG]).

5.15. The Committee noted a meta-analysis, which included results from 29 randomised controlled trials, which compared various dosing regimens of anthracyclines in younger adults with AML (Teuffel O et al. Br J Haematol. 2013; 161: 192-203). The Committee noted that higher doses of daunorubicin were equivalent to idarubicin in patients with AML and that there was no difference in outcome observed for several of the anthracyclines. The Committee considered that this was the reason for the higher doses of daunorubicin as standard first line therapy, and that protocols using idarubicin were reserved for salvage treatment and treatment of high-risk patients.

5.16. The Committee noted that there was limited evidence comparing differing anthracycline treatment in patients with ALL. The Committee noted however, that two studies of patients with ALL had been undertaken during a supply shortage of daunorubicin. From these studies, similar outcomes were observed following the substitution of daunorubicin with mitoxantrone (Nickel R et al. Pediatr Blood Cancer. 2014;61(5):810-814); doxorubicin was associated with similar remission rates, but increased toxicity (Patel S. Leukemia & Lymphoma. 2013.54:10, 2231-2235).

5.17. The Committee noted its previous recommendations for funding for gemtuzumab ozogamicin. The Committee considered that the AML19 trial has reported reduced relapse rates in those treated with gemtuzumab ozogamicin added to either daunorubicin or idarubicin containing treatment protocols. The Committee however noted the increased toxicity associated with FLAG-Ida (fludarabine cytarabine idarubicin and filgrastim) and considered that further international trials would continue to use daunorubicin.

5.18. The Committee considered that in AML, alternatives such as idarubicin would be appropriate as a substitute anthracycline, but that lack of access to daunorubicin would limit involvement in international clinical trials and the benefits that arise from participation in such clinical trials. The Committee considered that involvement in these trials was important and that it would be important to align with contingency plans for Australia, as they similarly use daunorubicin from the supplier. The Committee considered that there was limited data to support alternatives to daunorubicin for patients with ALL.

5.19. The Committee considered that should long term supply of daunorubicin be at risk, it would be important to liaise with the Australasian Leukaemia & Lymphoma Group (ALLG) to help identify alternative daunorubicin or anthracyclines and engagement with Te Aho o Te Kahu would also be important, noting the work underway on the ACT-NOW project. The Committee also considered that there are peripheral benefits from access to paediatric oncology trials, which could be at risk should there be limited availability of daunorubicin.

Correspondence relating to the record of apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer (nmCRPC)

5.20. The Committee reviewed correspondence from Janssen-Cilag Pty Ltd (Janssen) regarding its November 2021 review of the application for apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer (nmCRPC). The correspondence was regarding the use of abiraterone following apalutamide treatment and outlined that funding of apalutamide should not have any impact on the Special Authority criteria for access to abiraterone acetate.

5.21. The Committee noted that Janssen highlighted the results of the SPARTAN trial (Smith et al. N Engl J Med. 2018:378;1408-18) where over 1,000 patients were randomised to apalutamide or a placebo, with a primary end point analysing metastasis

free survival (MFS) and an exploratory end point analysing progression free survival (PFS). Janssen noted that of the 806 men treated in the apalutamide arm of the trial, almost half (n=386, 48%) received a first subsequent systemic therapy for prostate cancer after study treatment discontinuation (ie following apalutamide treatment). The majority of this group (78%) received abiraterone acetate following apalutamide. A similar percentage (72%) of the placebo group also received abiraterone acetate as first subsequent treatment.

5.22. The final analysis of SPARTAN reported that apalutamide extended median PFS with first subsequent anti-cancer therapy (PFS2) by 14.4 months (apalutamide, 55.6 months; placebo, 41.2 months) and Janssen considered this data supported extended PFS from treatment with abiraterone acetate post apalutamide treatment. Janssen considered that the evidence from SPARTAN supports subsequent treatment with abiraterone and therefore a change to the special authority criteria for abiraterone is not appropriate.

5.23. The Committee noted that the correspondence did not include any new evidence since its review of this application in November 2021. The Committee considered that whilst the patients treated with apalutamide had a PFS-2 of 14.4 months longer than those in the placebo arm, the majority of those 14.4 months were accounted for in the first PFS. Therefore, the Committee consider that there is no specific data to support using PFS-2 as a measure of benefit for use of abiraterone following treatment with apalutamide. The Committee considered further evidence would be required to definitively state that patients derived additional benefit from second line treatment with abiraterone following use of apalutamide. The Committee considered that 78% of patients using abiraterone following apalutamide treatment demonstrates that abiraterone is used following apalutamide treatment but does not provide evidence showing additional benefit with respect to PFS or MFS to support the use.

5.24. The Committee noted a lack of data showing response rates of sequence treatments for apalutamide and abiraterone; however, the Committee considered that apalutamide and enzalutamide have a similar mechanism of action and considered the response rates from enzalutamide could be indicative of expected response rates from apalutamide.

5.24.1. The Committee noted a randomised, open-label phase 2 crossover trial (Khalaf et al. Lancet Oncol. 2019;20:1730-9) comparing time to second prostate-specific antigen (PSA) progression between abiraterone and enzalutamide. The Committee noted that the time to second PSA progression for patients treated first-line with abiraterone and second-line with enzalutamide was 19.3 months, compared to the reverse showing 15.2 months.

5.24.2. The Committee also noted the AFFIRM trial (Scher et al. NEJM 2012;367:1187-97), a retrospective case series of 38 patients who received abiraterone following identification of disease progression following treatment with enzalutamide. The Committee noted three patients (8%) attained a PSA response and out of the 12 patients assessed radiologically, only one patient (8%) attained a confirmed partial response. The Committee acknowledged this data is limited due to the small patient population; however, considered it indicated low levels of response following sequential abiraterone use and aligned with their previous statement that there may be an approximate 10% response rate to subsequent therapies.

5.25. The Committee considered that this evidence suggests patients are more likely to benefit when first treated with abiraterone and then enzalutamide, rather than the reverse and while there is evidence of use, there is no evidence supporting use of subsequent therapy with abiraterone acetate.

5.26. The Committee considered its previous statement in the November 2021 record stating that funding apalutamide for nmCRPC would change the subsequent use of abiraterone acetate for metastatic CRPC (mCRPC) remained appropriate based on the available evidence to support the use of sequential abiraterone therapy. This included that the Special Authority criteria for abiraterone acetate for mCRPC may require amendment to restrict use of abiraterone to apalutamide-naïve patients with mCRPC, given the likely 10% response rate to subsequent therapy The Committee would welcome further evaluation of this should new data become available.

6. Pembrolizumab for the first-line monotherapy of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with a Combined Positive Score (CPS) ≥1

Application

6.1. The Advisory Committee considered correspondence from Merck Sharpe and Dohme (NZ) Ltd (MSD) regarding the Committee's November 2021 recommendation to list pembrolizumab in combination with chemotherapy for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with a Combined Positive Score (CPS) ≥1.

Recommendation

6.2. The Advisory Committee **recommended** that pembrolizumab as monotherapy for the first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with a Combined Positive Score (CPS) ≥1 be listed with a **low priority** within the context of treatment of malignancy, subject to the following Special Authority criteria noting these criteria would be similarly used for use of pembrolizumab as combination with chemotherapy for the first line treatment of patients with HNSCC with a CPS ≥1:

PEMBROLIZUMAB

Initiation – (head and neck squamous cell carcinoma)

Applications only from a medical oncologist. Approvals valid for four months

All of the following

1. Patient has recurrent or metastatic head and neck squamous cell carcinoma that is incurable by local therapies; and
2. Patient has not received prior systemic therapy in the recurrent or metastatic setting; and
3. The patient has a positive PD-L1 combined positive score (CPS) of ≥1; and
4. The patient has ECOG performance score of 0-1; and
5. Patient has measurable disease as defined by RECIST version 1.1; and
6. Baseline measurement of overall tumour burden is documented; and
7. Either:
    - 7.1 Pembrolizumab to be used in combination with platinum-based chemotherapy; or
    - 7.2 Pembrolizumab to be used as monotherapy; and

Continuation

Applications only from a medical oncologist. Approvals valid for four months.

All of the following

1. One of the following:
    - 1.1 Patient's disease has had a complete response to treatment according to RECIST criteria; or
    - 1.2 Patient's disease has had a partial response to treatment according to RECIST criteria; or
    - 1.3 Patient has stable disease according to RECIST criteria; and
2. No evidence of disease recurrence; and

3. Patients disease has not progressed clinically and disease response to treatment has been clearly documented in patient notes; and
4. No evidence of disease progression according to RECIST criteria; and
5. The total treatment received must not exceed 24 months.

6.3. In making this recommendation, the Committee considered the unmet health need and lack of viable treatment options for patients with recurrent or metastatic HNSCC, the association between HNSCC incidence and populations experiencing socioeconomic deprivation, uncertainty due to the trial design, and uncertain magnitude of benefit in a New Zealand context.

Discussion

6.4. The Committee noted that the application for pembrolizumab for the first line treatment of head and neck squamous cell carcinoma (HNSCC) had first been considered in October 2020, where it was recommended for decline. The Committee noted this was re-reviewed in November 2021 following receipt of additional information from the supplier which included updated data, clarification of the epidemiology, applicability of the data to the New Zealand population, and clinical input from New Zealand clinicians regarding the applicability of the evidence supporting pembrolizumab use in this setting as well as the relevance of outcomes to the New Zealand context.

6.4.1. The Committee noted that the positive recommendation made in November 2021 was for pembrolizumab in combination with chemotherapy in patients with a positive PD-L1 combined positive score (CPS) >1 and noted this should in fact include patients with a CPS equal to 1 (CPS ≥1).

6.5. The Committee noted the new correspondence from the supplier queried whether the recommendation made in November 2021 should be extended to enable access to pembrolizumab as monotherapy therapy for patients with a CPS ≥1, noting while response rates were slightly lower for monotherapy, clinically significant results were observed in the monotherapy group, and access to this would provide clinician choice based on patient circumstances.

6.6. The Committee noted it had reviewed the primary evidence (KEYNOTE-048) and accepted that that the CPS ≥1 patient populations met statistical significance end points and noted that this study extended to statistical end points being met in the monotherapy group in the final analysis; acknowledging that this final analysis occurred in the second interim analysis which may have impacted overall evaluation of the statistical significance.

6.7. The Committee noted that prior review of MSD's correspondence focused on the extrapolation of the KEYNOTE-048 patient population to the NZ patient population and considered that, based on its prior review, it was reasonable to assume that that there would be a statistical benefit in both treatment regimens (combination and monotherapy), in patients with CPS ≥1. The Committee noted evidence regarding overall survival from the 2020 ESMO presentation (R Geril KN048 ESMO 2020) showing four-year OS of 16.7% vs. 5.9% in monotherapy (pembrolizumab vs. cetuximab + chemotherapy), compared to 21.8% and 4.1% in combination therapy (pembrolizumab + chemotherapy vs. cetuximab + chemotherapy). The Committee noted that response rate and OS is lower in both initial and long-term analysis in monotherapy compared to combination therapy with pembrolizumab; however, there is no evidence that one is a preferred treatment regimen due to the multi-way randomisation process which ensured no difference in base population.

6.8. The Committee noted a recently published meta-analysis (Chen. Am J of Oto. 2022) regarding the use of PD-1/PD-L1 inhibitors as monotherapy, evaluating existing checkpoint inhibitors (nivolumab, pembrolizumab and durvalumab) and noted all provided consistent OS benefits associated with a HR of approximately 0.7-0.8 in an analogous population, but with no effect in patients with low PD-1 expression. The Committee considered this new evidence supports the use of pembrolizumab in monotherapy for HNSCC in patients with CPS≥1 and considered that this evidence supports a possible class effect across this class of agents.

6.9. The Committee noted new analysis of KEYNOTE-048 released to JCO 2022 (Burtness, B et al. J Clin Oncol. 2022) which appeared to indicate that patients with CPS <1 had worse outcomes compared to the chemotherapy arm of treatment, noting this was part of an unplanned secondary analysis.

6.10. The Committee considered further amendments should be made to the proposed Special Authority criteria including inclusion of RECIST criteria to align with other Special Authority criteria to ensure there is a defined measurement of benefit required for ongoing access to treatment for both monotherapy and combination therapy. The Committee noted that access to KEYNOTE-048 excluded patients with ECOG ≥2 and noted the Special Authority criteria should align with this patient population, noting that real world data indicates that patients with poor performance status typically have lower response rates to treatment with corresponding reduced benefit (Chalker, C et al. Cancer Med. 2022, Iwasa, YI et al. Oncology. 2022).

6.11. The Committee considered that enabling access to pembrolizumab as monotherapy may result in a greater number of patients accessing treatment as it may result in access for patients with larger comorbidity who would otherwise be unable to access treatment due to being unsuitable for chemotherapy.

6.12. The Committee considered combination immunotherapy with chemotherapy offered the best chance of response and overall survival, with no evidence to indicate whether patients with comorbidities experienced differential outcomes when treated with combination therapy; however, the Committee considered that enabling access to monotherapy for patients with ECOG 0-1 would provide clinicians the option for both (monotherapy or combination therapy) depending on a patient's individual circumstances.

6.13. Committee considered relapsed or refractory HNSCC is a disease that disproportionately impacts Māori with lower relative survival compared with non-Māori and is a condition that also has increased prevalence in lower-socioeconomic populations with an increased prevalence of comorbidities.

7. Trastuzumab commercial and implementation options

Application

7.1. The Advisory Committee reviewed a paper from Pharmac staff on the commercial and implementation options associated with the funding of trastuzumab in New Zealand.

Recommendation

7.2. The Committee supported a competitive process for the supply of trastuzumab and considered a transition period of six months would be appropriate to enable transition of existing patients to any incoming agent should there be a change to a trastuzumab biosimilar as a result of any competitive procurement process.

7.3. The Committee considered further assessment of the use of trastuzumab in other indications, particularly its use in gastric cancer, was warranted and sought further information to enable consideration of this.

Discussion

7.4. The Committee noted that trastuzumab is currently listed in the Pharmaceutical Schedule (brand, Herceptin) and considered this was one of the most used, and most expensive biologic oncology agents. The Committee noted the availability of biosimilar forms of trastuzumab, noting these are highly similar agents identified to provide the same level of efficacy and disease activity, at a reduced cost.

7.5. The Committee noted the regulatory requirements supporting and approving biosimilars for use is very stringent and demonstrates that there are no clinically meaningful differences in quality, safety or efficacy from the original biologic. The Committee noted that, when seeking regulatory approval for a specific indication, if the total evidence of a biosimilar application (to the regulator) supports the demonstration of biosimilarity for at least one of the reference products indications, then the biosimilar manufacturer may utilise the available data to scientifically justify approval for other indications.

7.6. The Committee noted trastuzumab biosimilars are used extensively internationally including in Europe, the United States of America and Australia. The Committee noted there are four trastuzumab biosimilar agents which are Medsafe approved in New Zealand, with one other under review and noted that all five are currently available in Australia. The Committee noted the reference biologic, Herceptin is no longer available in Australia having been withdrawn following the introduction of biosimilars, with patients successfully transitioning to the biosimilar; this aligned with the international experience.

7.7. The Committee noted the availability of biosimilars was expected to significantly improve the cost-effectiveness of trastuzumab, whilst maintaining clinical efficacy and tolerability. The Committee considered there to be increasing acceptance and interest from treating clinicians regarding the introduction of biosimilars and increasing use in the private sector based on the improved cost-effectiveness.

7.8. The Committee noted a biosimilar trastuzumab had been reviewed by both CaTSoP in October 2019 and PTAC in August 2019 where it was noted that there were no concerns regarding clinical efficacy or safety. The Committee noted there was limited data specifically on the interaction of trastuzumab with other antibody agents (such as pertuzumab) but noted that biosimilars were used in combination with pertuzumab in international markets without reported issues; the Committee considered there was no rationale to consider differences in outcomes associated with biosimilar trastuzumab, but that further real world data on the ongoing use of this may become available as use of biosimilars increases.

7.9. The Committee noted that several biosimilars have been introduced in New Zealand, including a rituximab biosimilar introduced in 2020 which was well accepted by clinicians. The Committee noted the transition period available for rituximab was nine months; however, noted the majority of DHB's had introduced the biosimilar within the first three months and considered this reflected the improved cost-effectiveness of the new agent and confidence in the evidence supporting its use.

7.10. The Committee noted that in its 2019 review, it considered a six-month transition period would be clinically acceptable noting this would enable patients to change to any incoming trastuzumab product with more than six months Herceptin treatment remaining. The Committee confirmed that six months remained an appropriate transition

period noting this effectively balanced the time for clinicians to manage and discuss any change with patients, with the importance of conveying confidence in the evidence supporting comparable efficacy and tolerability of biosimilars.

7.10.1. The Committee considered a six month transition would also limit the risk of multiple trastuzumab products being available in the market at one time and considered that many DHBs may choose when to introduce an incoming biosimilar within this transition period to enable change to a single agent for all patients simultaneously to reduce the risk of inadvertent switching and the administrative burden associated with managing multiple brands. The Committee considered there was rationale for a shorter transition period (three months) based on evidence supporting the use of biosimilars; however, noted that additional time to enable appropriate education of clinicians and patients would be of benefit and would be supported by the proposed six-month transition.

7.11. The Committee considered education of clinicians and engagement with patient advocacy groups was critical to support any change, noting the evidence supporting comparable benefits from treatment would assist in acceptance of any change. The Committee suggested this engagement and education should occur as early as possible following any potential decision to introduce a biosimilar.

7.12. The Committee noted there were no clinical concerns or specific clinical risks associated with changing existing patients to a biosimilar trastuzumab and considered there to be no evidence to support a clinical need for patients to return to Herceptin should disease progression occur whilst on a biosimilar trastuzumab. The Committee considered adverse reactions to a biosimilar trastuzumab, eg. allergic reaction for patients previously managed on Herceptin, would similarly be likely to occur on any return to the reference biologic. The Committee considered that, based on evidence and international experience, there were no clinical scenarios that were identifiable that may warrant return to the reference biologic from the biosimilar; however, the Committee considered a process should be available for exceptional circumstances for patients previously managed on Herceptin noting that all new patients would be started on the incoming biosimilar.

7.13. The Committee considered increased access to trastuzumab across other indications would be an advantage, particularly to Māori and Pacific patients who are often disproportionately affected by indications treated by trastuzumab and considered widened access to new indications would also likely make any change more palatable.

7.13.1. The Committee noted that whilst funded exclusively for breast cancer, trastuzumab is also Medsafe approved for treatment of advanced gastric cancer, which has previously been considered by Pharmac (link to Application Tracker). The Committee recommended reassessment of the evidence for the use of trastuzumab in this indication noting: trastuzumab is used extensively for this indication internationally; the high health need of patients with locally advanced, or metastatic HER2 positive gastric cancer; including the health need for Māori with gastric cancer, and the likely improved cost-effectiveness following the introduction of a biosimilar.

7.13.2. The Committee noted there are also a number of other uses for trastuzumab (eg. use beyond disease progression, and for treatment of uterine serous carcinoma), and welcomed applications from the relevant Special Interest Groups to support consideration of funding in these settings as well.

8. Generic abiraterone acetate (Yonsa) for prostate cancer for selected indications Interests

Application

8.1. The Advisory Committee reviewed an application for the use of a generic abiraterone acetate (Yonsa) for use in multiple indications

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 considered that generic abiraterone acetate (Yonsa) could be listed for high-risk metastatic hormone-naïve prostate cancer (mHNPC) patients and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) patients, with a **high priority**, consistent with previous consideration of funding for these indications, subject to the following Special Authority criteria:

> **Special Authority for Subsidy**
> **Initial application** – (hormone-naïve or hormone sensitive) only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has metastatic prostate cancer documented by a positive bone scan or metastatic lesions on CT or MRI; and
> 2. Patient was diagnosed with metastatic prostate cancer within the last three months; and
> 3. Patient does not have neuroendocrine differentiation or small-cell histologic features; and
> 4. Patient has an ECOG performance score of 0-2; and
> 5. At least two of the following:
>   5.1. Patient has measurable visceral metastases on CT or MRI (excluding nodes); or
>   5.2. Patient has three or more lesions by bone scan, CT or MRI; or
>   5.3. Patient has a Gleason score of eight or more (International Society of Urological Pathologists [ISUP] Grade 4 or 5); and
> 6. Any of the following
>   6.1. Patient has not previously received treatment for metastatic prostate cancer; or
>   6.2. Patient has received only one course of palliative radiation or surgical therapy to treat symptoms associated with metastatic disease; or
>   6.3. Patient has received up to three months of androgen deprivation therapy and their disease is continuing to respond to treatment; and
> 7. Abiraterone not to be given with taxane chemotherapy.
>
> **Renewal** – (hormone-naïve or hormone sensitive) only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of clinical disease progression; and
> 2. No initiation of taxane chemotherapy with abiraterone; and
> 3. The treatment remains appropriate and the patient is benefitting from treatment.

Discussion

8.4. The Committee noted it had previously considered the health need of people with prostate cancer, specifically, the high health need of patients with hormone naïve or hormone sensitive high-risk, metastatic, castration-resistant prostate cancer. The Committee noted that Māori and Pacific peoples experience worse outcomes from

prostate cancer than non-Māori and non-Pacific peoples and would receive benefit from increased access to suitable treatments in earlier lines of therapy.

8.5. The previous high recommendation from the Committee of abiraterone acetate for mHNPC/mHSPC was based on an unmet need for an alternative treatment option for individuals with newly diagnosed metastatic prostate cancer who are not candidates for chemotherapy or who would not consider chemotherapy because its tolerability and impact on daily life.

8.6. The Committee noted a retrospective study that determined time to progression to castration resistant prostate cancer (CRPC) in prostate cancer patients who undergo androgen deprivation therapy (ADT) (Tamada et al, Oncotarget 9(97): 36966 – 36974, 2018).

8.7. The Committee noted that the median time to the development of castration resistance was 26.6 months longer for patients with no metastasis at initial diagnosis compared to those with metastasis.

8.8. The Committee considered that in this context, the terms mHNPC and mHSPC might be used interchangeably. The Committee noted that the definition of hormone sensitive includes patients who are hormone naïve and that equal outcomes are likely to be obtained in both groups.

8.9. The Committee noted a post-hoc analysis of the phase II-III STAMPEDE trial (Hoyle et al, Eur. Urol. 76(6): 719-728, 2019), which assessed the 3-year survival in prostate cancer patients that were treated with abiraterone acetate with prednisolone and ADT, compared with ADT-alone. This post-hoc analysis indicated that low risk mHNPC/mHSPC patients would also receive an OS benefit from abiraterone acetate but that the number needed to treat (NNT) would be considerably higher (4-fold) than that for high risk mHNPC/mHSPC. Nonetheless, the Committee consider that this could represent a future unmet health need.

Comparison to originator abiraterone acetate

8.10. The Committee note that Yonsa is Medsafe approved for prostate cancer, with the recommended dosage of 500 mg (4 x 125 mg) single dose in combination with methylprednisolone 4 mg orally twice daily. The Committee noted that development of Yonsa uses a fine particle technology that improves bioavailability, requiring less dependence on postprandial status, improving the ease of use and suitability for the patient. The improved bioavailability resulted in a lower dose required; half that of Zytiga.

8.11. The Committee noted the STAAR trial (Stein CA et al. Urol Oncol. 2018 36:81.e9-81.e16), a randomised phase II controlled trial to investigate therapeutic equivalence between the originator abiraterone acetate (Zytiga) and the comparator abiraterone acetate (Yonsa). Fifty-three mCRPC patients were enrolled, with the primary endpoint being a comparison of average serum testosterone levels on treatment days 9 and 10. The Committee considered that the suppression of testosterone levels were similar for Zytiga and Yonsa, with suppression of serum testosterone levels on days 9 and 10 being 1.05 ng/dL and 1.02 ng/dL for patients treated with Yonsa and Zytiga, respectively.

8.12. The Committee noted the one-year extension study of the STAAR trial (Chapas-Reed et al. Clin Med Insights: Urol 2020), a non-randomised open-label, safety and efficacy study that enrolled 20 patients, and evaluated the long-term safety and efficacy

of Yonsa and Zytiga. Both prior treatment groups maintained a significant decrease in serum testosterone from run-in baseline at all timepoints.

8.13. The Committee noted that the STAAR trial used surrogate measures of bioequivalence and that there is a lack of direct head-to-head clinical trials to determine the efficacy of Zytiga and Yonsa. The Committee noted that similar efficacy and safety would be expected from a change to a generic abiraterone acetate, with potential for improvements in ease of use. The Committee noted that any generic abiraterone entering the market needs to demonstrate equivalency to the originator. The Committee considered that given the bioequivalence data to support regulatory approval, there is no reason to consider that a generic abiraterone acetate (Yonsa) would provide differing health benefits or risks to the originator.

Corticosteroid partner

8.14. The Committee noted that Yonsa would be co-prescribed with methylprednisolone, which is listed on the Pharmaceutical Schedule. The Committee commented that, were a combination pack containing Yonsa and methylprednisolone to become available, it would be well-received and likely help adherence.

8.15. The Committee noted that Zytiga is usually co-administered with prednisone (5 mg) whilst Yonsa is co-administered with methylprednisolone (4 mg); these are considered to be dose equivalent. The Committee note that Zytiga is currently under patent for the use of abiraterone when it is co-administered with prednisone for the treatment of prostate cancer.

8.16. The Committee noted that it was unaware of any head-to-head trials comparing the use of abiraterone acetate with methylprednislone vs prednisone. The Committee considered that it was unlikely that data comparing efficacy of abiraterone acetate in combination with all available steroids would exist and that strong head-to-head data is unlikely to be produced in the future.

8.17. The Committee noted that the corticosteroid co-administered with abiraterone acetate is primarily used to mitigate the side effect profile associated with the hormone therapy. The Committee considered that prednisone and methylprednisolone at the prescribed doses can be used interchangeably and are expected to have equivalent effect on the inflammatory process. The Committee considered however, that there remained uncertainty how different corticosteroids relate to individual hormone therapy response.

Potential competitive process

8.18. The Committee noted that abiraterone acetate is a high-cost medicine and considered that introduction of generics with evidence of equivalent benefit would improve the cost-effectiveness and were supportive of a competitive process for the supply of abiraterone acetate. The Committee considered that equivalent benefit would be expected for patients commencing treatment with this generic abiraterone (Yonsa) compared to Zytiga.

8.19. The Committee considered that new patients could be initiated on a generic abiraterone acetate and expect the same level of benefit and risks compared to originator abiraterone acetate.

8.20. The Committee considered that further evaluation would be required to understand the impact of existing patients changing the steroid component of their hormone duplet

therapy. The Committee considered that there was uncertainty regarding how a change in patients' corticosteroid partner could result in changes to overall benefit from treatment for patients currently receiving Zytiga in combination with prednisone. The Committee considered that there was therefore uncertainty as to how changing the steroid component of their therapy could impact existing patients. The Committee considered that further consideration of this may be necessary depending on the nature of any potential future competitive process in this area.

8.21. The Committee considered that implementation would play a key role in any change in the market and that many health care professionals, such as pharmacists and nurse practitioners would require engagement and education in order to support their patients for such a change. The Committee noted the importance of clear and supported communication.

9. Acalabrutinib for the treatment of patients with CLL

Application

9.1. The Advisory Committee reviewed the application acalabrutinib for the treatment of previously untreated CLL with 17p deletion or TP53 mutation who are ineligible for venetoclax, and relapsed or refractory CLL who are ineligible for venetoclax with rituximab.

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

Recommendation

9.3. The Advisory Committee **recommended** that acalabrutinib as an alternative option to venetoclax regimens in previously untreated CLL patients, for whom acalabrutinib is a more appropriate option due to venetoclax monotherapy being unsuitable, be listed with a **medium** priority, subject to the following Special Authority criteria:

> ACALABRUTINIB
> Initial application (previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has treatment-naïve CLL requiring therapy; and
> 2. There is documentation confirming that patient has 17p deletion or TP53 mutation; and
> 3. Patient has an ECOG performance status of 0-2; and
> 4. Treatment with venetoclax monotherapy is considered unsuitable for the patient.
>
> Renewal application (previously untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation*) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment.
>
> ACALABRUTINIB
> Initial application (relapsed/refractory chronic lymphocytic leukaemia (CLL)) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:

1. Patient has received at least one prior immunochemotherapy for CLL; and
2. Patient has not previously received funded acalabrutinib; and
3. The patient's disease has relapsed within 36 months of previous treatment; and
4. Treatment with venetoclax in combination with rituximab is considered unsuitable for the patient.

Renewal application (relapsed/refractory CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

9.4. The Advisory Committee **recommended** that acalabrutinib as an alternative option to venetoclax regimens in previously untreated CLL patients, for whom acalabrutinib is a more appropriate option due to intolerable side effects with venetoclax be listed with a **high priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

ACALABRUTINIB
Initial application (previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has CLL requiring therapy; and
2. There is documentation confirming that patient has 17p deletion or TP53 mutation; and
3. Patient has an ECOG performance status of 0-2; and
4. Patient had experienced intolerable side effects with previously funded venetoclax monotherapy.

Renewal application (previously untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation*) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

ACALABRUTINIB
Initial application (relapsed/refractory chronic lymphocytic leukaemia (CLL)) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has received at least one prior immunochemotherapy for CLL; and
2. Patient has not previously received funded acalabrutinib; and
3. The patient's disease has relapsed within 36 months of previous treatment; and
4. Patient had experienced intolerable side effects with previously funded venetoclax in combination with rituximab regimen.

Renewal application (relapsed/refractory CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

9.5. The Advisory Committee **recommended** that acalabrutinib as a subsequent line of therapy to venetoclax regimens in relapsed or refractory CLL patients who have

relapsed within 36 months be listed with a **medium** priority, subject to the following Special Authority criteria:

> ACALABRUTINIB
> Initial application (relapsed/refractory chronic lymphocytic leukaemia (CLL)) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has not previously received funded acalabrutinib; and
> 2. Acalabrutinib is to be used as monotherapy; and
> 3. Either
>   3.1. Patient's CLL is refractory while on treatment with a venetoclax containing regimen; or
>   3.2. Patient's CLL has relapsed within 36 months of previous treatment with a venetoclax containing regimen.
>
> Renewal application (relapsed/refractory CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment.

9.6. The Advisory Committee considered that those patients refractory to, or intolerant of venetoclax had the highest unmet health need and therefore the greatest priority for treatment with acalabrutinib.

9.7. The Committee considered there to be a class type effect for these Bruton's tyrosine kinase (BTK) inhibitors and that the same priority recommendations should be reflected for ibrutinib in the relevant patient populations.

9.8. The Committee considered there to be a broader need for access to BTK inhibitors across other patient groups of patients with CLL.

Discussion

9.9. The Committee noted that Chronic Lymphocytic Leukaemia (CLL) is a malignancy of B cells that predominantly affects the older population who often also have comorbidities and is characterised by the proliferation and accumulation of B lymphocytes in peripheral blood, bone marrow, and lymphoid organs. The Committee noted that the incidence of CLL in New Zealand is reported to be around 267 people per year (Leukaemia & Blood Cancer New Zealand, 2015).

9.10. The Committee noted that there is no evidence of a higher incidence of CLL in Māori or Pacific patient populations.

Current treatment options

9.11. The Committee noted that current treatment options are largely dictated by patient fitness and 17p del and TP53 mutational status. The Committee considered that approximately 10% of CLL patients will have 17p deletion or TP53 mutation at diagnosis, and that nearly all of these patients would be offered venetoclax as first-line treatment. The Committee noted that the remaining 90% of patients would be treated with FCR (fludarabine, cyclophosphamide, rituximab), bendamustine with rituximab, or obinutuzumab with chlorambucil, depending on patient fitness.

9.12. The Committee noted that patients with a 17pdel/TP53 mutation who relapse following venetoclax monotherapy in the first line have limited options and considered this to be an area of unmet need. The Committee considered for patients without a 17pdel/TP53 mutation, approximately 40% of patients would be estimated to relapse within 36 months and nearly all would receive venetoclax in combination with rituximab, and that less than 20% of these patients would be retreated with FCR, and approximately 20% would have the option of obinutuzumab with chlorambucil.

9.13. The Committee noted that some patients may be able to progress to allogenic stem cell transplantation, though the Committee noted that few patients would be fit enough to be eligible for transplant.

9.14. The Committee considered that duration of response mainly depends on the intensity of the front-line regimen with FCR resulting in the longest progression free survival (PFS) (average 77 months versus 34 and 27 months for rituximab with bendamustine and obinutuzumab with chlorambucil, respectively).

9.15. The Committee noted that there is a large gap in treatment options when comparing options in New Zealand to CLL treatment overseas. The Committee noted that ESMO guidelines recommend BTK inhibitor or venetoclax containing regimens for all patients who are immunoglobulin heavy chain unmutated and that FCR was reserved for only those with an immunoglobulin heavy chain gene (IGHV) mutation and deemed fit for intensive chemotherapy. The Committee noted that treatment options in New Zealand are limited for both treatment naïve patients, and those who have relapsed.

Acalabrutinib discussion

9.16. The Advisory Committee noted that acalabrutinb is a small-molecule inhibitor of BTK. The Committee noted that the submission for acalabrutinib requested funding for previously untreated CLL patients with 17p deletion or TP53 mutation for whom acalabrutinib is a more appropriate option, relapsed or refractory CLL patients for whom acalabrutinib is a more appropriate option, and as a subsequent line for patients relapsed or refractory to venetoclax containing regimens within 36 months of prior treatment. The Committee noted that acalabrutinib is taken orally twice daily.

9.17. The Committee noted that it had previously considered another BTK inhibitor (ibrutinib) for the same population groups and recommended that ibrutinib be funded with a high priority for relapsed/refractory patients who progress during or relapse after venetoclax treatment (within 36 months) or who are intolerant to venetoclax, and with a medium priority for the wider population of previously untreated patients with 17p deletion/TP53 mutation and for relapsed/refractory patients with CLL for whom ibrutinib is a more appropriate option. The Committee also noted that it previously recommended ibrutinib for previously untreated CLL patients, for whom fludarabine-based chemoimmunotherapy is inappropriate, with or without immunoglobulin heavy chain (IGHV) mutation, be listed with a low priority. The Committee noted that at the time of consideration of ibrutinib, it considered that the highest area of unmet need was for those who were refractory or intolerant to venetoclax and reiterated this consideration.

9.18. The Committee noted that there are three pivotal trials relating to the use of acalabrutinib in the first and subsequent lines of treatment for 17p deletion/TP35 mutated CLL:

9.18.1. ELEVATE-TN (Sharman et al. Lancet. 2020. 395:1278-91): a phase 3, randomised, open-label, three-arm, multicentre study of acalabrutinib monotherapy (until progression) versus acalabrutinib (until progression) with obinutuzumab (6 cycles)

versus obinutuzumab with chlorambucil (6 cycles) for the treatment of previously untreated CLL patients 65 years or over (or younger with comorbidities). The Committee noted that the median PFS was not reached for acalabrutinib treatment arms versus 17.5 months for obinutuzumab with chlorambucil for patients with 17p deletion/TP53 mutation. The Committee noted that the addition of obinutuzumab to acalabrutinib treatment did not seem to impact the PFS for this group. The Committee noted that at a median follow-up of 46.9 months, overall survival was not significantly different between treatment groups (not reached in any treatment group) but noted that 39% of patients were able to cross over from the obinutuzumab with chlorambucil treatment arm to the acalabrutinib monotherapy arm.

9.18.2. The Committee noted that the acalabrutinib monotherapy arm had a higher incidence of atrial fibrillation than the obinutuzumab containing regimens, as well as an increased rate of infection and secondary skin related malignancies.

9.18.3. ELEVATE-RR (Byrd et al. J Clin Ocol. 2021;39:3441-52): a randomised, multicentre, open-label Phase III non-inferiority trial of acalabrutinib versus ibrutinib (until progression) in relapsed/refractory patients 17p deletion/TP53 mutation or 11q deletion. The Committee noted that the majority of patients had received two prior lines of therapy, but than none appeared to have been treated with venetoclax. The Committee noted that at a median follow-up of 40.9 months, the PFS for both treatment arms was 38.4 months, and that overall survival was not reached in either treatment arm. The Committee also noted that there were no differences in PFS between subgroups.

9.18.4. The Committee noted that ibrutinib carries a higher risk of cardiac toxicity than acalabrutinib (22.8% and 15.6% versus 8.6% and 9% for hypertension and atrial fibrillation for ibrutinib and acalabrutinib, respectively). The Committee noted that treatment discontinuation due to adverse events occurred in 21.3% of the ibrutinib group versus 14.7% of the acalabrutinib group.

9.18.5. Ascend (Ghia et al. J Clin Oncol. 2020;38:2849-61): an ongoing phase 3, randomised, open-label study of acalabrutinib (until disease progression) versus bendamustine with rituximab (6 cycles) or idelalisib with rituximab (IdR; Id until progression and rituximab for 8 cycles) in patients with relapsed/refractory CLL. The Committee noted that no patients seemed to have received venetoclax as a prior line of therapy. The Committee noted that the 18 months PFS was 82% for acalabrutinib versus 48% for IdR/bendamustine with rituximab group. The Committee also noted that the median duration of response was not reached in the acalabrutinib arm, versus 18 months for the other agents.

9.18.6. The Committee noted that patients with 17p deletion or TP53 mutation did significantly worse than those without the deletion/mutation when treated with comparator treatments. The Committee noted that this trend was not present for patients treated with acalabrutinib and that outcomes were irrespective of mutational status. The Committee noted that all subgroup analyses (age group, ECOG status, disease bulk, number of prior therapies) indicated favourable outcomes for acalabrutinib compared to other agents used in this study (age group, ECOG status, disease bulk, number of prior therapies).

9.19. The Committee noted that patients with reduced renal function (creatine clearance less than 80 mL/min) may require more intensive prophylaxis and monitoring to reduce the risk of tumour lysis syndrome (TLS) when initiating treatment with venetoclax, but that this is not a contraindication for venetoclax treatment. The Committee noted that there is limited information regarding appropriate dosing of venetoclax for those with severe renal impairment (creatine clearance less than 30 mL/min). The Committee

noted that there is also limited information regarding the pharmacokinetics and safety of acalabrutinib in CLL patients with severe renal impairment (eGFR <29 mL/min/1.73 m2) or end-stage renal disease. The Committee considered that patients with severe renal impairment, for which venetoclax is unsuitable, acalabrutinib would also not be considered suitable.

9.20. The Committee noted that patients with bulky disease are also considered to be at a higher risk of TLS upon initiation of venetoclax treatment and would require prophylaxis and monitoring at initiation of treatment, with hospital admission on day 1 and day 8 of treatment. The Committee noted that low-risk patients still require blood tests 6-8 hours and 24-hours post treatment on days one and eight. The Committee noted that there are some logistical difficulties for managing rural patients during this venetoclax dose titration stage, due to limited access to timely blood tests. The Committee considered that about 50% of patients would require the low-risk blood testing protocol during venetoclax dose titration. The Committee considered that a BTK inhibitor without the TLS risk associated with venetoclax and not requiring TLS prophylaxis would be more convenient, as patients would be able to start treatment at home, without the need for blood testing or hospital admission.

9.21. The Committee considered that for both treatment naïve patients and patients with relapsed disease, venetoclax would be intolerable for approximately 20% of patients, and that a further 20% of patients would experience an inadequate response to venetoclax containing regimens upfront (Stilgenbauer et al. Lancet Oncol. 2016;17:768-78; Mato et al. Haematologica. 2018;103:1151-17).

Considerations of class effect

9.22. The Committee noted that it was not aware of any evidence to support efficacy of acalabrutinib following treatment with venetoclax, as none of the patients with relapsed/refractory disease in the trials had received prior treatment with venetoclax containing regimens.

9.23. The Committee considered that the evidence indicated that acalabrutinb is an effective therapy and is as effective as ibrutinib for the patient populations requested in the application, including patients experiencing multiple relapses of disease. The Committee noted that the increased incidence of atrial fibrillation and secondary skin malignancies is a known risk across all BTK inhibitors and is slightly less for acalabrutinib compared to ibrutinib.

9.24. The Committee considered that based on the available evidence, there appears to be a class effect with BTK inhibitors and considered that either ibrutinib or acalabrutinib would effectively address the current unmet health need for these patient populations, regardless of small variation in toxicity profile between the agents.

9.25. The Committee noted that although there isn't evidence for treatment with acalabrutinib subsequent to venetoclax containing regimens, there is evidence to suggest that BTK inhibitor treatment is effective for CLL patients post-venetoclax. The Committee noted a retrospective review on the efficacy of BTK inhibitors following treatment with venetoclax in which the majority of patients were treated with ibrutinib (Lin et al. Blood. 2020;135:2266-70). The Committee also noted that the majority of patients had received more than four prior lines of therapy. The Committee noted that 91% of patients treated with a BTK inhibitor achieved an objective response, and that those who had achieved remission on venetoclax for greater than 24 months were more likely to achieve a response with the BTK inhibitor treatment.

9.26. The Committee also noted an international study that identified a cohort of patients who discontinued venetoclax and were subsequently treated with a BTK inhibitor (acalabrutinib or ibrutinib), PI3K inhibitor, or cellular therapy (Mato et al. Clin Cancer Res. 2020;26:3589-96) The Committee noted that the most common reasons for discontinuation of venetoclax included progression of CLL and adverse events/toxicity. The Committee also noted that the estimated PFS to a post-venetoclax BTK inhibitor was 32 months.

9.27. The Committee noted that the evidence suggests that a BTK inhibitor can be used effectively following progression on venetoclax treatment but considered that the magnitude of benefit may differ depending on the duration of remission with venetoclax treatment. The Committee considered that any evidence relating to acalabrutinib efficacy post treatment with venetoclax is unlikely to be forthcoming as BTK inhibitors are already used widely internationally, usually before treatment with venetoclax. The Committee considered that although it is not aware of any direct evidence relating to the efficacy of acalabrutinib following treatment with a venetoclax containing regimen, given the class effect of these BTK inhibitors, it would be reasonable to assume similar efficacy in later lines of therapy between ibrutinib and acalabrutinib.

Remaining unmet need

9.28. The Committee considered that there remains an unmet need for those patients whose disease progresses after 36 months of previous treatment. The Committee noted that fit patients with good performance status without 17p deletion or TP53 mutation who are treated with FCR and relapse after three years or more following treatment have limited treatment options. The Committee noted that FCR is not usually considered for patients who have reduced performance status (eg. older than 70-75 years), meaning that few patients would be fit enough to be re-treated with FCR at relapse. Fit patients who relapse after treatment with bendamustine in combination with rituximab or after treatment with obinutuzumab in combination with chlorambucil also have limited further options. The Committee considered that retreatment with venetoclax/rituximab may be an option for those patients whose disease progresses after greater than 36 months of prior venetoclax treatment. The Committee considered that restricting access to acalabrutinib to only those patients whose disease had relapsed within 36 months would mean that those whose disease responded better to treatment with venetoclax with rituximab would be without effective treatment options in later lines of therapy.

Other considerations

9.29. The Committee considered that whilst the patient populations considered for acalabrutinib have unmet health needs, there is a broader need for a BTK inhibitor or expanded access to venetoclax treatment for CLL patients.

9.30. The Committee considered that whilst the oral administration of BTK inhibitors is a more practical option especially for those living rurally, treatment with acalabrutinib or ibrutinib is until progression, as opposed to a fixed duration of treatment with some venetoclax containing regimens. Therefore, the Committee considered that ongoing treatment with a BTK inhibitor would require continued adherence, frequent prescription pick-ups, and increased outpatient clinic visits compared with fixed duration therapy. The Committee also noted that acalabrutinb dosing is twice daily whilst ibrutinib dosing is once daily. The Committee considered it important to consider the ease of oral therapy as well as the duration of treatment. The Committee noted that there is also an increased risk of development of secondary malignancies for patients treated with BTK inhibitors, including non-melanoma skin cancers (Bond et al. Leukemia. 2020;34:3197-205).

9.31. The Committee considered that whilst Māori and Pacific patient populations generally have higher rates of cardiac and renal morbidity, this would not necessarily mean that treatment with venetoclax or ibrutinib would be unsuitable for them. The Committee considered that risks associated with moderate renal impairment, TLS risk and atrial fibrillation can be managed. The Committee considered that when selecting the appropriate treatment for individual patients, a number of factors are taken into consideration including but not limited to the patient's response to prior treatment, toxicities associated with treatments, patient preference and fitness.

9.32. The Committee considered that the patient population that would benefit the most from treatment with acalabrutinib, in order of unmet need and evidence of benefit, includes those who experience intolerable side effects with venetoclax, those whose disease is refractory to venetoclax, those whose disease progresses on venetoclax, those whose disease progresses on chemo immunotherapies, those who live at a distance from a hospital, those with TLS risk, and first line patients without IGHV mutations. The Committee considered that these patient populations have limited options available currently or would be better treated with extended access to a BTK inhibitor.

9.33. The Committee considered that the most appropriate average treatment duration for patients on venetoclax monotherapy or BTKi monotherapy could be in the order of years. The Committee considered that the efficacy of upfront treatment with acalabrutinib for patients with 17p deletion/TP53 mutation would likely be similar to that of venetoclax monotherapy in the absence of any head-to-head trial data to inform this. For patients with relapsed/refractory disease, the Committee noted that fixed duration of venetoclax containing regimens (2 years) would be replaced by continuous acalabrutinib treatment until progression which could mean BTK inhibitor treatment for longer than 5 years. The Committee noted that in the Resonate II trial for ibrutinib, 30% of patients were still receiving ibrutinib treatment at 5-6 years (Burger et al. Leukaemia. 2020;34:787-798).

9.34. The Committee considered that if acalabrutinib were to be funded, and the Special Authority criteria specified that patients must have experienced intolerable side effects with venetoclax, that this would include up to 20% of patients. The Committee also considered that if acalabrutinib was funded for those patients where venetoclax treatment was considered unsuitable, then a significantly higher number of patients would access acalabrutinib due to clinician preference for BTK inhibitors resulting from ease of treatment initiation. The Committee considered that this would include at least 50% of patients.

9.35. The Committee considered that should a BTK inhibitor not be funded in a subsequent line to venetoclax and be only accessible for those patients where venetoclax is considered unsuitable, it would be appropriate to limit access to venetoclax post treatment with a BTK inhibitor for those patients where venetoclax had been considered unsuitable previously.

9.36. The Committee considered that if acalabrutinib were funded in a subsequent line to venetoclax containing regimens, that those with 17p deletion/TP53 mutation whose disease progressed while receiving treatment with venetoclax would all be progressed directly to acalabrutinib treatment without delay. The Committee considered that patients who complete the full two-year treatment with venetoclax and subsequently experience relapse within 36 months (about 50% of patients with relapsed/refractory disease) would also all move to acalabrutinib treatment.

9.37. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for acalabrutinib if it were to be funded in New Zealand as an alternative to or subsequent to venetoclax containing regimens. 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	Alternate line for patients unsuitable for venetoclax	Alternate line for patient's intolerant to venetoclax	Subsequent line for patients relapsed/refractory to venetoclax within 36 months.
	• Previously untreated CLL patients with 17pDel or TP53 mutation who are unsuitable for venetoclax monotherapy.	• CLL patients with 17pDel or TP53 mutation intolerant to venetoclax in first line.	• CLL patients with 17pDel or TP53 mutation relapsed/refractory to venetoclax in first line
	• Relapsed or refractory CLL who are unsuitable for treatment with venetoclax in combination with rituximab.	• CLL patients with refractory or relapse within 36 months of first line therapy who are intolerant to venetoclax as second line	• CLL patients relapsed/refractory to venetoclax in 2nd line
Intervention	Acalabrutinib – 100mg Twice daily		
Comparator(s) (NZ context)	Previously untreated 17pdel/TP53– • Obinutuzumab + chlorambucil • Bendamustine • FC	17pDel or TP53 mutation • Obinutuzumab + chlorambucil • FC • Bendamustine	17pDel or TP53 mutation • Obinutuzumab + chlorambucil
	Relapsed/refractory (second line) – • Obinutuzumab + chlorambucil • FCR retreatment • Chlorambucil monotherapy	Relapsed/refractory (third line) • Obinutuzumab + chlorambucil • FCR retreatment • Chlorambucil monotherapy	Relapsed/refractory (third line) • Obinutuzumab + chlorambucil • Chlorambucil monotherapy
Outcome(s)	Health related quality of life Progression free survival Overall survival		

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

10. Atezolizumab - First line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with chemotherapy [P-001649]

Application

10.1. The Committee reviewed the application for atezolizumab for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC) in combination with chemotherapy.

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

Recommendation

10.3. The Committee **recommended** that atezolizumab for the first-line treatment of patients with ES-SCLC in combination with chemotherapy be funded with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **ATEZOLIZUMAB**
> **Initial approval – (extensive-stage small cell lung cancer)** only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months.
> Both
> 1. Patient has extensive-stage small cell lung cancer; and
> 2. Either:
>
> 2.1. The patient has ECOG performance status of 0-1 before chemotherapy commences for previously untreated disease; or
> 2.2. The patient has received one cycle of chemotherapy and has achieved an ECOG performance status of 0-1 prior to the initiation of chemotherapy cycle 2.
>
> **Renewal** only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 4 months for applications where there was no evidence of disease progression.

10.4. In making this recommendation, the Committee considered:

- the high clinical need of people with ES-SCLC due to the burden of this rapidly progressive disease which is associated with a poor prognosis, high hospitalisation rates and a high symptom burden
- the unmet need for improvements in treatment given that chemotherapy does not provide durable long-term responses for people with ES-SCLC
- the high impact on Māori who are disproportionately affected by SCLC and are more likely to die from lung cancer than non-Māori.

Discussion

Māori impact

10.5. The Committee noted that lung cancer is one of Pharmac's Hauora Arotahi (Māori health areas of focus) and that the registration rate for lung cancer for Māori in 2019 was about three times the rate for non-Māori. The Committee noted evidence that Māori patients with lung cancer were 30% more likely to die from the disease than non-Māori with lung cancer. The Committee noted that SCLC is strongly associated with smoking; however, even when adjusted for smoking status, Māori patients were still 1.5 times more likely to have SCLC than non-Māori. The Committee considered that lung cancer has a high and disproportionate impact on Māori who are more likely to experience a greater disease impact, may have a longer delay before presentation and diagnosis, and may have more advanced disease at presentation compared with non-Māori. The Committee considered that, if atezolizumab were to be funded for patients with ES-SCLC whose performance status improved to zero or one following one cycle of chemotherapy, it may improve the equity of access to this treatment for Māori who may present with more advanced disease and worse performance status than non-Māori.

Discussion

10.6. The Committee noted that small-cell lung cancer (SCLC) is an aggressive and highly invasive lung cancer that is strongly associated with smoking. The Committee noted that SCLC accounts for 11% of lung cancers in New Zealand (Te Aho o Te Kahu. 2021. Lung Cancer Quality Improvement Monitoring Report 2021. Wellington: Cancer Control Agency). The Committee noted that the disease can be described as either limited stage (LS-SCLC) where there is primary or nodal disease only in one hemithorax, or extensive stage (ES-SCLC) where the cancer has spread beyond one lung to the opposite lung or elsewhere in the body. The Committee noted that ES-SCLC is a rapidly progressive disease associated with a poor prognosis, high hospitalisation rates and a high symptom burden. The Committee considered that ES-SCLC has a large impact on family/whānau, and friends of the patient because the patient experiences substantial illness over a short period of time due to the rapid progression and high mortality rate in this disease.

10.7. The Committee noted that 65% of people with SCLC present with extensive stage disease and considered that a majority present via admission to hospital with poor performance status (ECOG PS). The Committee considered that for those admitted to hospital, biopsies are performed promptly with a view to commencing treatment quickly if ES-SCLC is confirmed and noted that treatment may start based on high suspicion of ES-SCLC in instances where treatment cannot be further delayed. The Committee noted that other tumour tissue testing is not often used for treatment decisions in this disease and that programmed death-ligand 1 (PD-L1) testing would not be routinely done upfront. The Committee noted that timelines for testing (eg PD-L1) may take 7-10 days in some centres which would be too long to guide treatment.

10.8. The Committee noted that between 2015 and 2018, 71.3% of New Zealand patients with SCLC received systemic anti-cancer therapy, although rates varied by District Health Board (Te Aho o Te Kahu. 2021). The Committee considered that two-year survival for patients with ES-SCLC is approximately 10% (Wang et al. Mayo Clin Proc. 2019;94:1599-622, Carter et al. Radiographics. 2014;34:1707-21), that median survival with first-line chemotherapy is in the range of eight to ten months (Allen and Jahanzeb. Clin Lung Cancer. 2008;9:262-70, Carter et al. 2014), and that the prognosis at relapse is weeks to months (Oronsky et al. Neoplasia. 2017;19:842-7).

10.9. The Committee noted that people with ES-SCLC would be offered first-line chemotherapy with a platinum agent (eg carboplatin) and etoposide. The Committee noted that intravenous (IV) administration of etoposide is considered the gold standard, however, noted it is generally given IV on day one and then orally on days two and three at most New Zealand centres, as some centres that previously exclusively used IV have opted to use oral instead on days two and three in response to the impacts of the COVID-19 pandemic. The Committee considered that etoposide may continue to be administered in this manner even after the COVID-19 response. The Committee considered that there are high response rates to chemotherapy in ES-SCLC of about 70-80% which is evidenced by symptom control and patient improvement, however, considered that obtaining a durable response remains a challenge in ES-SCLC. The Committee considered that patients with ES-SCLC have a high clinical need and an unmet need for improvements in treatment, given that chemotherapy does not provide durable long-term responses.

10.10. The Committee noted that the supplier's treatment paradigm did not show second-line treatment, but considered that approximately 50-60% of patients with ES-SCLC might receive second-line therapy despite there being limited efficacy from current treatments in the second line setting. The Committee considered that the remaining proportion of patients may not receive treatment and instead receive best supportive care.

10.11. The Committee noted that patients diagnosed with ES-SCLC predominantly have ECOG performance status (PS) of two to three, and that patients with ECOG PS of zero to one would account for about 10-15% of cases. The Committee considered that patients with ECOG PS of two to three would be candidates for chemotherapy despite having poor performance status since chemotherapy results in a rapid oncologic response and dramatic improvement in this disease within a matter of weeks for most patients. The Committee considered that approximately 80% of patients with ES-SCLC would have improved to ECOG PS zero to one by cycle two, however, the remaining 20% would be expected to have poor prognosis with rapid deterioration and death due to the disease.

10.12. The Committee noted that lung cancer is one of Pharmac's Hauora Arotahi (Māori health areas of focus) and that the registration rate for lung cancer for Māori in 2019 was three times the rate for non-Māori (68.8 for Māori per 100,000 population, age standardised to the WHO World Standard Population, vs 23.3 for non-Māori; Ministry of Health, December 2021). The Committee noted that a review of New Zealand cancer registry data from 2007 to 2016 reported that Māori patients with lung cancer were 30% more likely to die from the disease than non-Māori with lung cancer and were more likely than non-Māori to die across all levels of comorbidity (Gurney et al. JCO Glob Oncol. 2020;6:766-74). The Committee noted that SCLC is strongly associated with smoking, however, even when adjusted for smoking status, Māori patients were still 1.55 times more likely to have SCLC than non-Māori (adjusted odds ratio 1.55; 95% CI, 1.17 to 2.05) (Lawrenson et al. 2018). The Committee considered that lung cancer has a high and disproportionate impact on Māori who are more likely to experience a greater disease impact, may have a longer delay before presentation and diagnosis, and may have more advanced disease at presentation compared with non-Māori.

10.13. The Committee noted that there is limited data for the impact of ES-SCLC on Pacific peoples and on other groups experiencing health disparities relative to the wider New Zealand population.

10.14. The Committee noted that atezolizumab in combination with carboplatin and etoposide is Medsafe approved for the first-line treatment of patients with extensive-stage small cell lung cancer (ES-SCLC). Atezolizumab is also Medsafe approved for the treatment of several non-small cell lung cancer (NSCLC) indications, urothelial carcinoma, hepatocellular carcinoma, and triple-negative breast cancer.

10.15. The Committee noted that atezolizumab (1200 mg), carboplatin and etoposide are administered by intravenous (IV) infusion for induction on day one (etoposide is also administered on days two and three) for four 21-day cycles, then atezolizumab monotherapy maintenance is given at a dose of either 840 mg every two weeks, 1200 mg every three weeks, or 1680 mg every four weeks from cycle five onwards until disease progression. The Committee was made aware of pooled data for atezolizumab in lung and urothelial cancers which suggests the two-weekly, three-weekly and four-weekly dosing schedules are all comparable in terms of exposure and response (Morrissey et al. Cancer Chemother Pharmacol. 2019;84:1257-67). Members considered that the three-weekly regimen would be preferred for most patients to align with the chemotherapy cycle length, that four-weekly may be preferred during maintenance for some patients (eg those who live in rural areas), and that very few would opt to receive treatment every two weeks.

10.16. The Committee noted the key evidence for atezolizumab in this setting comes from IMpower133; a double-blind, placebo-controlled, randomised (1:1) phase III study of 403 patients with untreated ES-SCLC (staged according to the Veterans

Administration Lung Study Group Staging System) with measurable disease per RECIST v1.1 and an ECOG performance status of zero to one (Horn et al. N Engl J Med. 2018;379:2220-9). The Committee noted that IMpower133 patients received either atezolizumab 1200 mg every 21 days plus carboplatin and etoposide chemotherapy for four 21-day cycles followed by atezolizumab maintenance until progression ("atezolizumab"), or they received placebo plus carboplatin and etoposide chemotherapy for four 21-day cycles followed by placebo maintenance until progression ("placebo").

10.17. The Committee noted that the Asia Pacific region contributed about 20% of patients to the IMpower133 study although there were no New Zealand study sites, and considered that New Zealand-specific data wouldn't be expected to become available. The Committee considered that IMpower133 patients were staged in a similar manner to that used for New Zealand patients. The Committee noted that an ECOG PS of zero to one was required for eligibility, that about two-thirds of patients had ECOG of one and that patients with treated asymptomatic central nervous system metastasis were eligible. The Committee considered that a large proportion of New Zealand patients with ES-SCLC (~70%) are diagnosed with an ECOG of two or more and would not have been eligible for the trial at diagnosis. On balance, the Committee considered that the IMpower133 trial evidence was applicable to the New Zealand population with ES-SCLC.

10.18. The Committee noted that the primary outcomes of IMpower133 were progression-free survival (PFS) and overall survival (OS), and that objective response rate (ORR) was a secondary outcome. The Committee noted that the median PFS was not that different between groups [5.2 months (95% CI 4.4 to 5.6) atezolizumab vs 4.3 months (95% CI 4.2 to 4.5) placebo], however, there was a difference of 7.2 months between groups in the rate of PFS at 12 months [12.6% with atezolizumab vs 5.4% with placebo (stratified HR for disease progression or death 0.77; 95% CI: 0.62 to 0.96; *P*=0.02)] (Horn et al. N Engl J Med. 2018;379:2220-9). The Committee noted that, after median follow-up of 13.9 months, median OS was 12.3 months (95% CI 10.8 to 15.9) with atezolizumab vs 10.3 months (95% CI 9.3 to 11.3) with placebo and the rate of OS at 12 months was 51.7% and 38.2% for atezolizumab and placebo, respectively (stratified hazard ratio [HR] for death 0.70; 95% CI: 0.54 to 0.91; *P*=0.007). The Committee noted that the objective confirmed response rate was similar between groups and considered this was likely driven by the high response rate to chemotherapy in ES-SCLC.

10.19. The Committee noted that patients received a median of seven doses of atezolizumab vs median six doses of placebo, and that 5% of patients receiving atezolizumab discontinued treatment due to an adverse event (AE) compared with 1% of placebo patients. The Committee considered that the safety profile of atezolizumab in terms of immune-related AEs was similar to that in other published evidence for atezolizumab.

10.20. The Committee noted the updated IMpower133 results after a longer follow up (median follow-up of 22.9 months), which reported median OS of 12.3 (95% CI: 10.8 to 15.8) months with atezolizumab vs 10.3 (95% CI: 9.3 to 11.3) months with placebo (Reck et al. Ann Oncol. 2019; 30 (suppl_5):v710-7; Liu et al. J Clin Oncol. 2021;39:619-30). The Committee noted there was a significant difference in the rate of OS at 12 months (51.9% atezolizumab vs 39.0% placebo) which persisted at 18 months (34.0% vs 21.1%, respectively) (HR, 0.76; 95% CI, 0.60 to 0.95; descriptive *P*=0.0154). The Committee noted that there appeared to be no significant difference in OS across subgroups.

10.21. The Committee noted that 110 (54.7%) atezolizumab patients and 125 (61.9%) placebo patients in Impower133 went on to receive a second-line therapy, although crossover to immunotherapy in the placebo group was low (<10%). Members considered that a similar proportion of patients (ie 50-60%) with ES-SCLC would receive second-line treatment in New Zealand.

10.22. The Committee noted that Impower133 assessed patient-reported outcomes (PROs) using the EORTC-QLQ-C30 and QLQ-LC13 questionnaires every three weeks during treatment and at three and six months after treatment discontinuation. The Committee considered there was evidence of maintained quality of life up to at least 45 weeks with atezolizumab compared with placebo, although there were small numbers of patients remaining on study at those timepoints (Mansfield et al. Ann Oncol. 2020;31:310-7).

10.23. The Committee noted that the Impower133 subgroup analyses reported by Horn et al. suggested that all subgroups appeared to receive similar benefit and that no biomarkers (eg tumour mutational burden - TMB) appeared to offer a means to differentiate. However, members considered that there was some evidence to suggest an improvement in survival for patients with PD-L1 expression of >5% compared with the overall population, although this analysis included small patient numbers as only one third of patients provided tissue for PD-L1 testing (Reck et al.; Liu et al.). Overall, the Committee considered there was insufficient evidence for a difference in outcomes according to PD-L1 status or any other biomarker and therefore not enough data to currently support a biomarker threshold for access to atezolizumab treatment in this setting.

10.24. The Committee noted evidence from Impower133 reporting characteristics of long-term survivors (Liu et al. Ann Oncol. 2020; 31 (suppl_4): S974-S987. Presented at 2020 ESMO Congress) and was made aware of evidence from an Impower133 subgroup analysis of Japanese patients (Nishio et al. Clin Lung Cancer. 2019;20:469-76.e1). The Committee also noted the following systematic reviews and meta-analyses regarding immunotherapy with platinum-etoposide chemotherapy vs platinum-etoposide alone in first-line treatment of SCLC:

- Chen et al. Cancers (Basel). 2020;12:3629
- Zhou et al. JAMA Netw Open. 2020;3:e2015748
- Zhang et al. Ann Palliat Med. 2020;9:4081-8)
- Wang et al. J Oncol. 2020;2020:2368164

10.25. The Committee was made aware of evidence from studies investigating other immunotherapies with a chemotherapy backbone in ES-SCLC [Pacheco et al. J Thorac Dis. 2020;12:6212-24; Reck et al. 2019. Presented at the European Society for Medical Oncology (ESMO) Immuno-Oncology Congress] and noted a meta-analysis of overall survival with immunotherapy and chemotherapy vs chemotherapy alone (Arriola et al. Oncol Ther. 2022;10(1):167-1842). The Committee considered this evidence suggested the PD-L1 agents in those studies (ie atezolizumab, durvalumab, and pembrolizumab) in combination with chemotherapy provide durable benefits and a favourable median survival compared with placebo and considered there could be a class effect of PD-L1 agents in this setting.

10.26. Overall, the Committee considered that Impower133 provided evidence of an improvement in long-term disease control at 18 months for a proportion of patients

with ES-SCLC. The Committee considered that the benefit of atezolizumab in ES-SCLC appears different to that in other cancers (eg melanoma) and noted that ES-SCLC is a disease that typically has a very poor prognosis. The Committee considered that the Impower133 trial evidence was applicable to the New Zealand population with ES-SCLC despite the trial selecting for patients with better ECOG performance status. The Committee considered that, whilst atezolizumab would be expected to provide only modest benefit including an improvement in quality of life for patients with ES-SCLC, these minor gains would be highly valued by patients and clinicians. The Committee considered that atezolizumab in combination with chemotherapy would enable more patients with ES-SCLC to live longer and maintain their quality of life, providing benefits for family and whānau.

10.27. The Committee considered that the application as proposed (for patients with ECOG PS of zero to one) was too narrow to capture the relevant patient population in New Zealand and that it could lead to slippage to patients with ECOG PS of two based on clinician judgement. The Committee considered that there is substantial uncertainty at cycle one regarding which patients will respond well, as 20% will not benefit from chemotherapy. The Committee considered a pragmatic approach to enable access for those expected to benefit whilst controlling the risk of non-response could be accomplished by reassessing ECOG PS after chemotherapy cycle one, given the dramatic and rapid improvement with chemotherapy expected in 80% of cases of ES-SCLC. The Committee acknowledged that this advice deviated from the clinical trial evidence, however, considered it reasonable to assume that patients receiving atezolizumab from cycle one and patients receiving atezolizumab from cycle two with improved ECOG PS would receive the same benefit from atezolizumab combination therapy and monotherapy maintenance. The Committee therefore considered that the Special Authority criteria for atezolizumab should enable access for patients whose ECOG PS improved to zero or one following a first cycle of chemotherapy, allowing for combination treatment with atezolizumab to commence at cycle two. The Committee considered that, if atezolizumab were to be funded for patients with ES-SCLC whose performance status improved to zero or one following one cycle of chemotherapy, it may improve the equity of access to this treatment for Māori who may present with more advanced disease and worse performance status than non-Māori, but who may meet the required ECOG PS within one cycle of chemotherapy.

10.28. The Committee considered that Pharmac's estimate of 153 cases of ES-SCLC per year, of which 109 might be eligible for atezolizumab as proposed, was likely reasonable and noted this estimate was informed by data from Te Aho o Te Kahu. The Committee considered that uptake would be almost 100% from the time of funding among all those eligible for platinum/etoposide chemotherapy (ie the 71.3% with ES-SCLC who would receive systemic treatment), given the high health need in ES-SCLC. The Committee considered that the suitability of chemotherapy is a key factor and that very few patients with ES-SCLC would have a contraindication to immunotherapy. The Committee considered that, if atezolizumab were funded for patients whose ECOG PS improved to zero or one at cycle two, an additional 65-70% may be eligible.

10.29. The Committee considered that the majority of patients who completed cycle two of chemotherapy would be expected to complete all four cycles and considered it unlikely that patients would start combined treatment with atezolizumab only to stop chemotherapy in favour of atezolizumab monotherapy after one cycle (due to the atezolizumab response taking about three months, by which time the patient's disease would have progressed). The Committee considered that about 50-60% of patients with ES-SCLC would receive further second line chemotherapy following treatment with atezolizumab.

10.30. The Committee considered that funding atezolizumab for ES-SCLC was unlikely to lead to any substantial differences in the rates of adverse events and hospitalisations, although members considered that an improvement in quality of life during treatment with atezolizumab for patients with ES-SCLC could lead to health resource savings due to fewer hospitalisations and reduced healthcare resource required for disease-related symptoms and effects until disease progression.

10.31. The Committee considered that funding atezolizumab for ES-SCLC would require additional clinic visits approximately three- to six-weekly during maintenance (compared with routine three-monthly visits for follow-up), nursing time for treatment administration and management, extra CT scanning during maintenance (approximately three- or six-monthly, or as clinically indicated, depending on the treating centre), and additional resource to manage a small proportion of immune-related adverse events. The Committee noted that although atezolizumab is given over a short infusion time, it would impact the health system due to the wraparound care provided for treatment.

10.32. The Committee considered that the main logistical challenges with immunotherapies relate to short half-lives and limited fridge stability, in addition to patients who may encounter difficulties with travel from rural locations and poor venous access.

10.33. The Committee considered that improved access to community infusion services would be relevant for this population and considered that Pharmac could highlight this to Te Aho o Te Kahu.

10.34. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for atezolizumab if it were to be funded in New Zealand for the first-line treatment of patients with ES-SCLC in combination with chemotherapy. 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	Patients with extensive-stage small cell lung cancer (ES-SCLC) who either: - Have ECOG performance status (PS) of 0-1 before chemotherapy commences for previously untreated disease or - Received one cycle of chemotherapy and has achieved an ECOG PS of 0-1 prior to the initiation of chemotherapy cycle 2.
Intervention	All of the below: • Atezolizumab 1200mg 3 weekly for induction and maintenance (or 1680mg 4 weekly for maintenance in some patients eg those who live in rural areas) until disease progression. Atezolizumab administered from cycle 1 for patients with ECOG PS of 0-1, and from cycle 2 for patients whose ECOG PS improved to 0-1 after one cycle of chemotherapy and prior to cycle 2. • Carboplatin 5AUC on day 1 of the first 4, 21-day cycles. • Etoposide 100mg/m^2 on days 1-3 of the first 4, 21-day cycles. Cycle 1-4 administration time 3.5 hours initial, 2.5 hours subsequent Cycle 5+ 1 hour Source: EviQ Small cell lung cancer extensive disease cARBOplatin etoposide and atezolizumab
Comparator(s) (NZ context)	All of the below: • Carboplatin 5AUC on day 1 of the first 4, 21-day cycles. • Etoposide 100mg/m^2 on days 1-3 of the first 4, 21-day cycles. Cycle 1-4 administration time 2.5 hours subsequent Source: Small cell lung cancer extensive disease cARBOplatin and etoposide
Outcome(s)	Improved progression-free survival (PFS) from IMpower133 • Stratified hazard ratio for disease progression or death, 0.77 (95% CI, 0.62–0.96) Improved overall survival from IMpower133 • Stratified hazard ratio for disease progression or death, 0.77 (95% CI, 0.62–0.96) Improvement in health-related quality of life as a result of improved time in progression-free survival and increased survival. Limited evidence to support a difference in quality of life while on treatment.
Table definitions: Population, the target population for the pharmaceutical; Intervention, details of the intervention pharmaceutical; Comparator, details the therapy(s) that the patient population would receive currently (status quo – including best supportive care); Outcomes, details the key therapeutic outcome(s) and source of outcome data.	

11. Commercial options for stage IV lung cancer treatments

Application

11.1. The Advisory Committee reviewed a request from Pharmac seeking advice regarding the use of immune checkpoint inhibitors (ICI) for the treatment of metastatic non-small cell lung cancer (mNSCLC).

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

Discussion

11.3. The Advisory Committee reviewed a paper from Pharmac seeking updated clinical input regarding the landscape associated with immune checkpoint inhibitors for the treatment of locally advanced or metastatic non-small cell lung cancer (mNSCLC) in New Zealand. The Committee noted that Pharmac sought advice relating to the use and evidence associated with immune checkpoint inhibitors (ICIs) for the treatment of different stages of NSCLC in light of previous considerations of ICIs for this patient group, preference of agents and treatment regimens for different lines of treatment, and potential budget impacts.

11.4. The Committee noted that the primary evidence for use of ICIs in NSCLC in previous funding applications comes from the following trials:

11.4.1. First-line monotherapy for NSCLC patients

11.4.1.1. KEYNOTE-024 - Reck et al. NEJM 2016;375:1823-33: Pembrolizumab versus platinum-based chemotherapy for previously untreated patients with advanced NSCLC with PD-1 expression of >50% and no EGFR mutation.

11.4.1.2. IMPOWER110 - Conference abstract: Spigel DR, et al. Ann Oncol 2019; 30(Suppl_5):mdz293: Atezolizumab versus platinum based chemotherapy for patients with previously untreated, stage four NSCLC with a PD-L1 expression of greater than 1%. (205 patients with PD-L1 expression > 50%).

11.4.1.3. KEYNOTE-042 - Mok TSK et al, Lancet. 2019;393(10183):1819-1830: pembrolizumab monotherapy versus platinum-based chemotherapy in previously untreated mNSCLC in patients with a PD-L1 ≥1%.

11.4.2. Fist-line combination therapy with chemotherapy, for NSCLC patients

11.4.2.1. KEYNOTE 407 - Paz-Ares et al, N Engl J Med 2018;379:2040-51: pembrolizumab with carboplatin and either paclitaxel or nab-paclitaxel versus placebo with carboplatin and either paclitaxel or nab-paclitaxel in patients with untreated metastatic stage IV, squamous NSCLC.

11.4.2.2. KEYNOTE189 - Gandhi et al, N Engl J Med 2018;378:2078-92: pembrolizumab with pemetrexed in combination with a platinum based aged versus placebo with pemetrexed in combination with a platinum based aged in patients with metastatic non-squamous NSCLC (EGFR or ALK wildtype) who had received no previous treatment for metastatic disease.

11.4.2.3. IMPOWER150 - Socinski et al. N Engl J Med.2018;24:2288-301: atezolizumab + bevacizumab + paclitaxel + carboplatin versus atezolizumab + paclitaxel + carboplatin and bevacizumab + paclitaxel + carboplatin for patients with untreated stage IV or recurrent metastatic non-squamous NSCLC (EGFR/ALK included if prior disease progression / side effects from prior TKI use).

11.4.3. Second-line monotherapy for NSCLC patients

11.4.3.1. KEYNOTE-010 - Herbst et al, Lancet 2016; 387:1540-50: pembrolizumab monotherapy versus docetaxel in patients with previously treated advanced NSCLC with a PD-L1 expression of greater than ≥1%.

11.4.3.2. OAK - Rittmeyer et al, Lancet 2017; 389:255-65: atezolizumab versus docetaxel in patients with non-squamous or squamous NSCLC who have receive one or two previous cytotoxic treatments (one or more containing platinum-based combination therapies for stage IIIb or stage IV NSCLC.

11.4.3.3. CheckMate 017 - Brahmer et al, N Engl J Med 2015;373:123-35: nivolumab versus docetaxel for patients with advanced squamous NSCLC who have progressed following first line chemotherapy.

11.4.3.4. CheckMate 057 - Borghaei et al, N Engl J Med 2015;373:1627-39: nivolumab versus docetaxel in patients with advanced non-squamous NSCLC who had progressed on platinum-based doublet-chemotherapy.

11.5. The Committee noted that immune checkpoint inhibitors for the treatment of metastatic NSCLC had been reviewed on several occasions by the Committee and emphasised that these prior reviews had detailed the unmet health need for NSCLC patients, equity issues relating to stage at diagnosis and disease specific survival for Māori and Pacific patients, the results of the clinical portfolios for the ICI agents, and the uncertainty regarding PD-L1 testing platforms as well as interpretation of PD-L1 testing results.

11.6. The Committee noted that, compared to treatment with docetaxel, the chance of patients being alive at later time points (such as at 18 months) almost doubles with ICI treatment, and that this is a meaningful difference to patients. The Committee noted that the OAK trial reported an 18-month event-free survival rate of 40.04% with atezolizumab compared to 26.9% with docetaxel, while the POPLAR trial (Fehrenbacher et al. Lancet. 2016;387:1837-46) reported 38.1% and 24.5% 18-month event-free survival rates for atezolizumab and docetaxel, respectively. The Committee noted that in Checkmate 017, the 18-month event-free survival rates were 28.0% and 13.0% for nivolumab and docetaxel, respectively. Similarly, the Committee noted that checkmate 057 reported 18-month event-free survival rates of 39% and 23% for nivolumab and docetaxel respectively.

11.7. The Committee noted that there are differences between Stage IV and locally advanced (Stage III) NSCLC that would impact which patients are considered for treatment with ICI's. The Committee noted that Stage IV disease typically included patients with disease that had spread to another area either within the lung, or to another organ outside the lung. In contrast the Committee noted that those with unresectable locally advanced disease could be considered in two groups; those that can be considered for radical treatment (an intensive course of radiotherapy) and those that are being managed palliatively. The Committed noted that patients with locally advanced disease (Stage III) would be considered for radical treatment in the first line, but part of this patient cohort includes patients who, due to comorbidities or performance status, would not be fit for radical treatment and would therefore be managed palliatively.

11.7.1. The Committee considered that this cohort of patients for whom radical treatment is not considered suitable would likely disproportionately include Māori and Pacific patients, and those from other disadvantaged groups. The Committee considered that these patients (unresectable, locally advanced, for whom radical treatment is not considered suitable), as well as those with metastatic disease (ie stage IV), would encompass the patient group for whom treatment with ICIs would be appropriate, noting the former patient population (radical treatment is considered suitable) would likely be offered treatment with durvalumab. The Committee acknowledged however

that this consideration is based on extrapolation of evidence from KEYNOTE-024 and IMPOWER-110, which only included stage IV patients.

11.8. The Committee noted the previous recommendations made for funding of ICIs and considered that these were based on the evidence available at the time of the consideration. The Committee noted that updated progression-free survival and overall survival data has since been made available for many of these studies which has improved the strength of evidence of benefit for these agents over time.

11.8.1. The Committee noted its prior decline recommendation for the use of atezolizumab in combination with bevacizumab/chemotherapy as a first-line combination therapy treatment. The Committee noted decisions made in other international jurisdictions relating to and supporting the use of atezolizumab in this setting and considered its prior decline reflected hesitation around the study design and available data supporting use in this setting rather than specific reservation regarding the likely benefit that atezolizumab could offer as an ICI agent in this context. The Committee considered that it would be willing to reassess the possible benefit offered by atezolizumab if further evidence were to become available, acknowledging that role of bevacizumab (eg atezolizumab with chemotherapy and without bevacizumab) is unclear and has not been proven based on information provided to the Committee to date. The Committee noted that it would also like to review any other ICI agent that could address this unmet need, should a funding application be received.

11.9. The Committee noted the available evidence and considered that it remains appropriate to consider that atezolizumab and pembrolizumab provide the same or similar health benefit for first line NSCLC monotherapy, such that funding of either agent in this line of therapy would be clinically appropriate. The Committee noted updated progression-free survival and overall survival available across the other ICI agents. The Committee considered it reasonable to assume equivalent treatment benefit could be achieved from ICI agents (pembrolizumab, nivolumab and atezolizumab) when funded as second line monotherapy.

11.10. The Committee considered the funding and availability of ICI agents internationally and considered it would be reasonable to consider funding of any ICI that has received a positive recommendation from the Committee for NSCLC in the various treatment lines based on likelihood of clinical benefit. The Committee considered that it was appropriate to assess previously assessed ICI agents as having a class effect for the purpose of enabling listing and noted whilst this may apply to new agents, there would still need to be an assessment undertaken of the adequate strength and quality of evidence for any new agent or agent without a positive funding recommendation.

11.11. The Committee considered that it would be clinically acceptable to have different ICIs funded in different lines of therapy for NSCLC eg first line monotherapy, first line combination therapy, and second line treatment.

11.11.1. The Committee considered that the choice of agent funded in each line was unlikely to change the proportion of which patients access monotherapy versus combination therapy and noted that this would be driven by performance status, prior treatments and PD-L1 testing. The Committee considered that having different agents available in different lines or combinations could easily be managed by clinicians.

11.12. The Committee considered that the estimated incidence of first line patients was reasonable but considered that New Zealand based data should be used to estimate the proportion of patients with EGFR mutations and noted a New Zealand based

study reported rates of EGFR mutations to be approximately 20% (Aye et al. Cancer Epidemiol. 2020;69:101847). The Committee considered that there is no good quality New Zealand data reporting the rate of NSCLC patients with ALK mutations, and that the international rate of 5% is appropriate (Chia et al. Clin Epidemiol. 2014;6:423-32). The Committee considered that, after factoring in the number of patients with stage 1-2 disease that would progress to stage 4, this would result in an annual incident ICI eligible population of approximately 1,021 patients, based on the following assumptions:

- There are 1,506 new NSCLC patients per year in NZ (Te Aho 2021) 83.5% of whom have locally advanced or metastatic disease at diagnosis (Lawrenson et al 2018)
- Of these patients, 20% are expected to have rates of EGFR mutations (Aye et al.) and 5% are expected to have ALK+ mutations (Chia et al.), resulting in 943 patients with neither mutation
- In addition to this number, there are expected to be 248 patients with NSCLC diagnosed with stage 1-2 disease, 186 of whom have neither mutation. 42% of this number will progress to stage 3-4 disease (Sugimura et al 2007), which comes to 78 additional patients
- In total, it is expected that there will be an annual incident 1,021 eligible patients (943 + 78).

11.12.1. The Committee considered that there would be an additional cohort of ICI eligible patients within the first 2-3 years of funding comprised of stage III NSCLC patients who relapse, and who did not receive durvalumab treatment. The Committee considered that this may add an additional 60 patients to the ICI eligible cohort. The Committee noted that stage III patients for whom radical treatment is not considered suitable and who pre-date the listing of durvalumab would have a poor prognosis and would be captured in stage IV data.

11.12.2. The Committee noted that updated data from the 2021 Te Aho Te Kahu Lung Cancer Quality Improvement Monitoring Report reported that 29.7% of people with NSCLC received systemic anti-cancer therapy. The Committee noted that applying this percentage to the above patient number estimate would result in an incident 303 eligible patients per year. The Committee considered that there would be an increase in use of systemic therapy if an ICI was funded, driven by the increased treatment of patients eligible for monotherapy that otherwise would not have received systemic therapy, and the increased uptake for those eligible for chemotherapy given the access to an ICI and the additional benefit that would be anticipated from combination immunotherapy.

11.13. The Committee noted that assessment of patient numbers is dependent on the scenario of funding (ie lines of treatment funded, with testing considerations) but considered it reasonable to assume that if a first line ICI treatment were listed for advanced NSCLC, (as well as providing access to patients needing second-line treatment), all new eligible patients would receive an ICI in the first line setting and the second-line market would be restricted to prevalent patients only, with this patient population diminishing over a relatively short period of time (within the first year of listing). The Committee considered that this second line 'bolus' would likely consist of approximately 800 people and that similar assumptions around uptake could be expected.

11.14. The Committee noted its prior consideration that it would be appropriate to limit the total duration for a course of PD-L1 treatment for locally advanced and metastatic NSCLC to a maximum of two years continuous treatment, unless treatment progression was identified prior to this. The Committee noted that the duration of treatment was variable across the clinical trials, with treatment limited to up to two years in KEYNOTE 024 and KEYNOTE 110, and treatment enabled until progression (or beyond if clinical benefit in IMPower 110, OAK, and Checkmate 057), where the proportion of patients still on active treatment after two years ranged from 23% to 33%. The Committee noted that consideration of duration of treatment is medically complex, and emotionally fraught for patients, however noted that both Australia and the United Kingdom stipulate a maximum treatment duration of up to two years of treatment with ICIs with uncertainty regarding whether this could be challenged upon progression. The Committee considered that alignment with these countries would be appropriate, but that this could be reconsidered if more evidence were to become available regarding optimal treatment duration for these agents.

11.15. The Committee noted that exploratory data from CheckMate 153 (Waterhouse et al. J Clin Oncol. 2020;38:3863-73) compared continuous nivolumab treatment versus 1-year fixed duration in patients without progression. The Committee noted that continuous treatment prolonged progression free survival but had no statistically significant impact on overall survival (HR 0.42 [95% CI 0.25-0.71] and 0.63 [95% CI 0.33-1.20] for progression free survival and overall survival, respectively) noting that this result appeared durable and was regardless of best response achieved by the patient.

11.15.1. The Committee noted that while a prolonged treatment course of over 2-years does not seem to increase the rate of clinical toxicity experienced, it would however, lengthen the timeframe that an individual patient would be at risk of developing such toxicity.

11.16. The Committee noted a cross-trial comparison comparing two years of nivolumab treatment with treatment until progression (Gettinger et al. J Clin Oncol. 2018;36:1675-84). The Committee noted that overall survival was similar for both cohorts as noted by overall survival at two years and at three years (17% vs. 18%). The Committee noted that this was consistent with comparisons of KEYNOTE-001 (two years of treatment with pembrolizumab) and KEYNOTE-010 (treatment with pembrolizumab until progression), where overall survival did not differ significantly between the two groups (21% vs 23%). The Committee noted however, that the numbers of patients who remain on study at these late time points are small.

11.17. The Committee noted that the rate of relapse for patients who stop treatment at two years is roughly similar to those who continue treatment until progression, although those treated with ICI until disease progression usually have a longer overall survival. The Committee considered that there is a clinical concern for patients who relapse following a limited duration for treatment of two years, as the data suggests that around a third of these patients have disease that cannot be ‘rescued’ with re-treatment at disease progression. The Committee noted that 34 patients in Checkmate 153 who stopped treatment after one year were retreated at disease progression, and that a clinical benefit was seen in 59-65% of this patient population. The Committee also noted that in KEYNOTE 010, 79 patients stopped ICI treatment after 2 years, 25 of whom relapsed within the follow-up period. The Committee noted that 14 of these 25 were able to be re-treated, with a clinical benefit seen in 11 patients (79%). The Committee considered that on this basis, it may be clinically reasonable to permit a 3-month rechallenge upon progression, if the initial treatment duration is limited to 2 years. The Committee considered that it would be appropriate

to consider this in more detail should widened access be requested and noted that there was limited evidence to guide how long patients would stay on ICI treatment if rechallenge is effective in eliciting a response.

11.18. The Committee noted that the overall survival curves in the clinical trials KEYNOTE-042 (versus chemotherapy) and KEYNOTE-010 (versus docetaxel) run parallel to each other instead of converging. The Committee considered that the reason for the parallel survival curves was unclear, and that it would suggest a lack of any treatment waning effect, which may be because very late survivors of chemotherapy are surviving because of some intrinsic immune mediated response that has been generated by the chemotherapy they have received.

11.19. The Committee noted that the proportion of patients treated with 3-weekly versus 6-weekly dosing is unknown, and that this would depend on pressures on day-units/infusion services, or if the patients live rurally. The Committee noted that it is likely that clinicians would have a 6-9 month cut-off with dosing 3-weekly to ensure patients will respond and are not experiencing significant toxicities. The Committee considered that then patients may be moved to 6-weekly dosing. The Committee noted, however, that there is no evidence to underpin these assumptions.

11.19.1. The Committee considered that weight-based dosing would be clinically appropriate for pembrolizumab and nivolumab and is consistent with prior listing of these agents in other tumour types. The Committee noted the Medsafe datasheet includes flat dosing regimens for pembrolizumab and for nivolumab. The Committee noted that dosing for atezolizumab is only for flat dosing. The Committee noted that resource constraints in pharmacies preparing these agents are significant, and that flat dosing (with the available vial sizes) may be helpful.

11.20. The Committee considered that the health sector costs presented by Pharmac staff were appropriate and considered the health resource utilisation reported in the PIvOTAL study (Lee et al. BMC Health Services Research. 2018.) to be broadly representative of health care utilisation in New Zealand but noted that this publication predicated the availability of ICI therapies. The Committee considered that funding of ICIs in New Zealand would likely lead to a delay in the intensity of palliative care resource utilised, and that currently most stage IV NSCLC patients are referred to palliative care at diagnosis, based on the evidence that this will improve overall survival.

11.20.1. The Committee considered that it was reasonable not to consider adverse event costs in economic modelling noting the resultant cost compared to the cost of the PD-L1 treatment is considered negligible. The Committee considered that a very small proportion of patients may experience long-term severe side effects that are not seen in the literature, given the limited overall survival in this patient population.

11.21. The Committee considered the following scenarios for PD-L1 testing, noting that currently PD-L1 testing is not funded or accessible to all patients:

11.21.1. If an ICI were funded for first-line monotherapy for patients with PD-L1 expression >50%, the Committee considered that all newly diagnosed locally advanced /stage IV patients who were well enough for treatment would be tested at diagnosis to avoid treatment delays. The Committee considered that this would not be expected to change if there was access to an ICI for all patients in combination with chemotherapy. If an ICI was funded for first line use with no PD-L1 expression specified, the Committee considered it likely that testing may be pursued for patients whose performance status is considered borderline for immunotherapy in order to

justify use without concomitant chemotherapy and considered this could be up to 10-20% of patients.

11.22. The Committee noted that a requirement for PD-L1 testing would have a budgetary impact. The Committee considered that although current standard of care requires biopsies for all patients, there may be an increase in the number of biopsies an individual patient may need to undergo in order to extract enough tissue for testing. The Committee also noted again that the patients who may benefit the most from monotherapy are those with comorbidities, a subgroup likely overrepresented by patients who are Māori or Pacific, or in other populations experiencing disparities. The Committee considered that PD-L1 testing, to identify those likely to benefit from monotherapy, would be of particular benefit to this subgroup of patients.

11.22.1. The Committee noted that in Australia, the PBAC recommended atezolizumab in the first line be funded agnostic of PD-L1 status for both monotherapy and combination therapy (with chemotherapy and bevacizumab). The Committee noted that the PBAC also recommended funding of pembrolizumab in the first line but specified that PD-L1 >50% should be necessary for monotherapy. The Committee also noted that the PBAC recommended nivolumab and atezolizumab (but not pembrolizumab) be funded agnostic of PD-L1 status in the second line.

11.22.2. The Committee noted that the NICE (United Kingdom) recommended funding of atezolizumab monotherapy in first line only for those with a PD-L1 status of >50%, and that atezolizumab combination therapy was recommended those with 0-49% PD-L1 expression. The Committee noted that the NICE recommended that pembrolizumab be funded in the first line for those with a PD-L1 expression over 50%, and PD-L1 agnostic in the second line. The Committee also noted that the NICE recommended funding of nivolumab, pembrolizumab, and atezolizumab in the second line, agnostic of PDL-1 status.

11.22.3. Overall, the Committee considered that PD-L1 testing would likely become reflex at diagnosis over time, to avoid treatment delays. The Committee noted the use of PD-L1 testing in other countries, where most use of ICIs in the treatment of NSCLC utilised PD-L1 testing as a means to limit treatment to PD-L1 >50%, or to inform the use of various agents and target therapy to the group with the highest possibility of benefit.

11.22.4. The Committee considered that if ICIs were funded for first line use with no requirement for PD-L1 testing, that most patients with poor performance status who are considered unfit for chemotherapy would likely receive an ICI as monotherapy. The Committee considered that there would remain a group of patients who would not be offered treatment at all based on presence of very high burden of disease at presentation or with poor performance status. The Committee considered that if an ICI was funded for first line use with no PD-L1 expression specified, the Committee considered it likely that testing would be pursued for most patients in order to justify use without concomitant chemotherapy.

11.22.5. The Committee noted the sub-group analysis of the patient population with PD-L1 1-49% in KEYNOTE 024 indicated minimal benefit from ICI therapy and the benefit seen in the PD-L1 >1% group was skewed by the significant benefit seen from the PD-L1 >50% patient cohort. The Committee considered that access to PD-L1 testing ensures selection of the patient group for first line monotherapy and would be important to enable avoidance of the morbidity of chemotherapy (in combination with immunotherapy). The Committee considered testing should be mandated in this line of therapy in order to access monotherapy. The Committee considered access

without confirmation of PD-L1 expression in this patient population may result in a proportion of patients receiving futile therapy with significant cost to the sector noting the patient group most likely to receive monotherapy are those who are unable to receive combination therapy with chemotherapy.

11.22.6. The Committee considered there is high variability in access to PD-L1 testing, which is partly impacted by the fiscal arrangement within DHB's and how this interacts with national laboratory programmes.

11.22.7. The Committee considered that in any scenario, there are likely to be patients where the amount of tissue obtained from biopsy is insufficient to enable testing, or cannot be undertaken, and considered that a route to ICI therapy should be considered for these patients to avoid the need of multiple biopsies. The Committee considered access to ICI's in 1L combination therapy and 2L therapy without PD-L1 testing would reasonably accommodate for this and reduce the impact on lab testing for PD-L1 testing upon listing of any agent, giving time to develop the systems required to support reflex PD-L1 testing within New Zealand.

11.23. The Committee considered that the proportion of patients accessing ICI therapy as a second-line treatment option over the longer term (in the event that access was enabled in first line also, following uptake of the prevalent patient population) would reduce to a small cohort of patients whose disease has relapsed following treatment with a non-ICI agent in the first line. The Committee considered that these patients are likely to be those with concomitant significant autoimmune conditions, where there could be concern regarding the impact ICI therapy would have on an underlying autoimmune disorder. However, the Committee considered that as use of ICI's increase, confidence regarding their use would likely increase also leading to greater proportion of clinicians recommending use in the first line.

11.24. The Committee considered that funding of ICIs would have a significant impact on infusion service capacity and that the funding of an ICI would require an "all of sector," multi-agency response. The Committee considered that conversations with Health NZ and Te Aho o Te Kahu would be important in facilitating access to testing and treatment to equitably address this significant unmet need in New Zealand.

Chair

Date