Record of the Cancer Treatments Subcommittee of PTAC Meeting held on 4 and 5 November 2021

Cancer Treatments Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

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

The Cancer Treatments Subcommittee 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.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

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

PTAC Subcommittees 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 PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.

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1. Attendance

Present

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

Observer from Te Aho o Te Kahu
Simon Pointer

2. The role of PTAC Subcommittees and records of meetings

2.1. This meeting record of the Cancer Treatments Subcommittee of PTAC (CaTSoP) is published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016, available on the Pharmac website at https://www.pharmac.govt.nz/assets/ptac-terms-of-reference.pdf.

2.2. The Terms of Reference describe, *inter alia*, the establishment, activities, considerations, advice, and the publication of such advice of PTAC Subcommittees and PTAC.

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

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

Pharmac considers the recommendations provided by both the Cancer Treatments Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for Cancer Treatments.

3. Record of Cancer Treatments Subcommittee meeting held Friday, July 9, 2021

3.1. The Subcommittee reviewed the minutes of the Cancer Treatments Subcommittee meeting held on Friday July 9, 2021 and agreed that the minutes be accepted.

4. Correspondence and Matters Arising

4.1. Widened access to peginterferon alfa-2a for the first-line treatment of myeloproliferative disorders

4.1.1. The Subcommittee reviewed correspondence from the applicant regarding its April 2021 review of the application for widened access to peginterferon alfa-2a for the first-line treatment of myeloproliferative disorders.

4.1.2. The Subcommittee noted that the correspondence did not include any new evidence since its review of this application in April 2021.

4.1.3. The Subcommittee noted the growing consensus acknowledging the value of treatment with interferon as a class of agents (including peginterferon alfa-2a and ropeginterferon) for this patient group and the anecdotal evidence from consumers, which has highlighted the value and benefit of interferons compared to hydroxyurea.

4.1.4. The Subcommittee considered that the use of interferons for the first-line treatment of myeloproliferative disorders would be primarily driven by alignment with international jurisdictions and opinion. The Subcommittee noted that intolerance to hydroxyurea, is likely the primary driver to the switching of patients to peginterferon alfa-2a.

4.1.5. The Subcommittee considered that there was evidence supporting the short-term safety and efficacy of peginterferon alfa-2a. However, the Subcommittee

noted that the evidence supporting a longer-term benefit was still being evaluated.

4.1.6. The Subcommittee noted that the role of peginterferon alfa-2a will be further defined following publication of the final results of the randomised, open label Phase III MPN-RC112 trial comparing hydroxyurea to peginterferon alfa-2a as initial treatment of high-risk polycythaemia vera (PV) and high-risk essential thrombocythemia (ET). The Subcommittee noted that preliminary results showed similar overall response rate for hydroxyurea and peginterferon alfa-2a after 12 months of treatment (Mascarenhas J et al. Blood 2018; 132 (Supplement 1): 577). However, the Subcommittee noted that at 24 months, among 106 patients eligible to receive treatment at 24 months, peginterferon alfa-2a response rates were similar to hydroxyurea but peginterferon alfa-2a was associated with higher rates of grade 3/4 toxicity, with no clear advantage in quality of life (Mesa R et al. Blood 2018; 132(Supplement 1): 3032–3032).

4.1.7. The Subcommittee noted a systematic review and meta-analysis which included evidence regarding the use of interferon in patients with ET and PV (Bewersdorf J et al. Leukemia. 2021. 35, 1643–1660.). The Subcommittee considered that peginterferon alfa-2a had similar efficacy with respect to both molecular response and haematological response. The Subcommittee considered that there may be a rationale for superiority upon longer exposure and considered that it would be useful to obtain longer-term data for the use of peginterferon alfa-2a in this setting to inform on its long-term efficacy and safety.

4.1.8. The Subcommittee considered that peginterferon alfa-2a would likely initially result in an increase in adverse events, and that the pattern of these would differ compared to hydroxyurea. The Subcommittee considered that peginterferon alfa-2a is widely considered an acceptable alternative to hydroxyurea in patients with the following: low-risk disease requiring frequent phlebotomy, pruritis, symptomatic splenomegaly, persistent microvascular symptoms, intolerance to hydroxyurea, and in young women of reproductive age.

4.1.9. The Subcommittee noted that the treatment of polycythaemia vera (PV) in New Zealand was largely aligned to that described in a recent review (Tefferi A et al. Leukemia. 2021. https://doi.org/10.1038/s41375-021-01401-3). The Subcommittee noted that in patients less than 60 years of age there would be very few that would require additional treatment beyond phlebotomy and low-dose aspirin. However, the Subcommittee noted that for those that do require additional treatment, peginterferon alfa-2a could be used. The Subcommittee considered that it is important for women of reproductive age to receive peginterferon alfa-2a as opposed to hydroxyurea. The Subcommittee noted that this group of patients could already access peginterferon alfa-2a via the current Special Authority criteria. The Subcommittee considered that the additional patient populations for whom peginterferon alfa-2a provides a benefit in the treatment of myeloproliferative disorders can also already access it via the Special Authority criteria, which were widened when interferon-alfa was discontinued in June 2020.

4.1.10. The Subcommittee noted that there is increasing concern regarding the longer-term safety (eg. tumorigenicity) of hydroxyurea in young patients who are likely to be exposed to this treatment for a long period of time, however considered that the risk of this remained uncertain and that the evidence supporting this was largely circumstantial. In particular, the Subcommittee considered that the risk of development of acute myeloid leukaemia from prolonged exposure to

hydroxyurea was unknown and the evidence supporting the tumorgenicity of hydroxyurea in the setting of leukaemia was limited. The Subcommittee noted that interferons can reduce tumour mutational burden and considered that this could be considered beneficial for younger patients as they would likely be exposed to treatment for many years. However, the Subcommittee considered that predisposition for tumorigenicity was more likely to be related to other background factors associated with the disease such as clonal instability, mutational landscape and risk status of the myeloproliferative disorder.

4.1.11. The Subcommittee noted that there would be a small proportion of younger patients that would present with myeloproliferative disorders and therefore, there would be a small group of patients that would be treated with peginterferon alfa-2a if funded for this group. The Subcommittee noted that there would be a greater cost to the Combined Pharmaceutical Budget if peginterferon alfa-2a were funded for the universal first-line treatment of myeloproliferative disorders. However, the Subcommittee considered that most haematologists would likely use hydroxyurea even if peginterferon alfa-2a were made available, according to the guidelines regarding the treatment of PV.

4.1.12. The Subcommittee considered that the incidence of adverse events that would be experienced with peginterferon alfa-2a would be greater than that of both hydroxyurea and anagrelide. The Subcommittee noted that very few patients receive anagrelide in New Zealand and considered that this was primarily due to cardiac adverse events, which is of particular concern for this patient group. The Subcommittee noted that the use of busulfan was favoured in elderly, or frail, patients as it is well tolerated and very effective. The Subcommittee further noted that peginterferon alfa-2a has been previously associated with mood alterations (eg. depression, a common adverse event for patients receiving peginterferon alfa-2a) in patients receiving this agent for treatment of hepatitis C.

4.1.13. The Subcommittee considered that if funded, the use of peginterferon alfa-2a would be similar to other refrigerated products that are administered subcutaneously. The Subcommittee considered that the pegylation made this product more suitable than interferon alfa-2a, but that ropeginterferon alfa-2b had suitability advantages as it is administered once every two weeks.

4.1.14. The Subcommittee noted that ropeginterferon alfa-2b appears to be superior to peginterferon alfa-2a and hydroxyurea with respect to both efficacy and safety (Kiladjian J-J et al. Blood 2019; 134 (Supplement_1): 553; Gisslinger H et al. Blood 2018; 132 (Supplement 1): 579; h Heinz Gisslinger H et al. Blood 2017; 130 (Supplement 1): 320; Huang C et al. J Formosan Med Ass. 2021. 120:863-73). The Subcommittee also noted that ropeginterferon alfa-2b also seems to have lower reported rates of mood alterations than peginterferon alfa-2a.

4.1.15. The Subcommittee considered that it would welcome an application for ropeginterferon alfa-2b for this patient group as this may be where the evidence of benefit is clearer. The Subcommittee considered that it would be important to include review literature regarding its long-term efficacy, safety and risk of development of malignancy.

4.1.16. The Subcommittee noted the desire for wider access to peginterferon alfa-2a from some clinicians and patient groups and that consensus guidelines acknowledge a growing enthusiasm for the use of interferons in general in this setting, particularly ropeginterferon alfa-2b, for the treatment of PV. However,

the Subcommittee considered that there was no new evidence presented that would alter or impact its previous recommendation at this time. The Subcommittee considered that the current levels of evidence supporting longer term outcomes in relation to tumorigenicity of hydroxyurea compared to peginterferon alfa-2a remain insufficient, that there is no survival benefit for peginterferon alfa-2a compared to hydroxyurea, and that decreasing mutational burden does not change a patients risk profile. The Subcommittee therefore did not change its previous recommendation to decline this funding application for widened access to peginterferon alfa-2a for the first-line treatment of myeloproliferative disorders.

4.2. Obinutuzumab for the treatment of chronic lymphocytic leukaemia (CLL)

4.2.1. The Subcommittee noted that in March 2015 it recommended that obinutuzumab for patients with previously untreated chronic lymphocytic leukaemia (CLL) be funded with a medium priority, primarily for patients who have comorbidities and could not be treated with standard treatments (fludarabine, cyclophosphamide and rituximab). The Subcommittee noted that obinutuzumab was funded in January 2017 for patients with CLL ineligible for full dose chemotherapy, subject to eligibility criteria.

4.2.2. The Subcommittee noted information provided by Pharmac indicating the supplier of obinutuzumab (Roche New Zealand) would be increasing the price of obinutuzumab, given the unintended and increased usage of this product due to suspected usage in patients with relapsed or refractory CLL.

4.2.3. The Subcommittee noted that obinutuzumab is primarily used in combination with chlorambucil in patients with previously untreated CLL. The Subcommittee noted however that under the current Special Authority criteria it can be used in later lines, as long as the patient is obinutuzumab naïve and has not previously received this as a treatment.

4.2.4. The Subcommittee noted that obinutuzumab is a different antibody to rituximab, with a subtly different mechanism of action. The Subcommittee considered that the evidence supporting the use of obinutuzumab in later lines of therapy was less established and that use in these settings was expected to be less efficacious (Leblond et al. Haematologica. 2018;103:1889-98). The Subcommittee considered that single agent obinutuzumab can be effective in reducing CLL cells in heavily pre-treated patients, but that the duration of effect is uncertain and the current treatment algorithms in New Zealand do not include treatment with obinutuzumab for these patients.

4.2.5. The Subcommittee noted that while the evidence of benefit for the use of obinutuzumab is less established in patients with relapsed or refractory CLL compared to previously untreated CLL, it is currently being used in these later lines of therapy in New Zealand. The Subcommittee considered that the use of obinutuzumab in the relapsed or refractory setting was primarily due to the limited access to other agents that would be effective for this patient group. The Subcommittee considered that access to obinutuzumab for patients with relapsed or refractory CLL does provide a benefit for patients.

4.2.6. The Subcommittee noted that since the funding of venetoclax in combination with rituximab in the 2nd line setting, the use of obinutuzumab in this setting has reduced substantially and it is likely that its use will be pushed to the 3rd line setting over time, likely further reducing its expected efficacy.

4.2.7. The Subcommittee considered there was clear reasoning to limit the use of obinutuzumab to those patients with CLL who are treatment-naïve (as per the pivotal trial Goede et al. New Engl J Med. 2014; 370:1101-10), and that the Subcommittee would rather funds be targeted to more efficacious treatments in later lines of CLL. However, the Subcommittee considered that further restrictions of the access criteria would likely be poorly received in the absence of additional treatment options available for patients with relapsed or refractory CLL.

4.3. Multiple Myeloma

4.3.1. The Subcommittee noted that in August 2021, PTAC had requested that the Cancer Treatments Subcommittee of PTAC (CaTSoP) provide advice regarding the preference for the various agents that have received positive funding recommendations from CaTSoP in the first, second and third-line treatment of patients with multiple myeloma (April 2021).

4.3.2. The Subcommittee reviewed correspondence from the New Zealand Myeloma Interest Group (NZMIG) that indicated its preference for Pharmac funding the previously considered agents for the first, second and third-line treatment of patients with multiple myeloma.

4.3.3. The Subcommittee noted that at previous meetings it had recommended:

4.3.3.1. Lenalidomide as first line treatment in combination with bortezomib and dexamethasone for both transplant eligible and transplant ineligible patients with a **low** priority.

4.3.3.2. Lenalidomide in combination with dexamethasone for transplant ineligible patients with a **medium** priority

4.3.3.3. Daratumumab (intravenous and subcutaneous) in combination with bortezomib and dexamethasone, pomalidomide in combination with bortezomib and dexamethasone and carfilzomib in combination with dexamethasone for the second line treatment of multiple myeloma, with a **high** priority

4.3.3.4. Pomalidomide in combination with bortezomib and dexamethasone and carfilzomib in combination with dexamethasone for the third line treatment of multiple myeloma, with a **high** and **medium** priority, respectively

4.3.3.5. Pomalidomide in combination with dexamethasone only for the treatment of second and third-line multiple myeloma with a **low** priority

4.3.4. The Subcommittee noted the primary priority for the NZMIG was for improved access to novel treatments in lenalidomide refractory patients. Specifically, the NZMIG indicated its preference for daratumumab, noting that current standard of care for patients eligible for autologous stem cell transplant (ASCT) who then relapse is inadequate, since the funding of lenalidomide as maintenance therapy for patients with multiple myeloma post autologous stem cell transplant (ASCT), which provides more effective first-line treatment but reduces the treatment options for patients who relapse. The Subcommittee noted that the discussion regarding priority by the NZMIG occurred prior to publishing of the record of the July 2021 meeting. The Subcommittee noted that in its review of daratumumab (IV and SC) in July 2021 it highlighted a preference for daratumumab in this setting, noting its novel mechanism of action and that most of its evidence supports its use in the

second line setting. The Subcommittee noted that it is preferable to use these agents earlier in the disease course, while patients are more likely to respond and are less refractory.

4.3.5. The Subcommittee noted the second priority of the NZMIG, for improved access to lenalidomide in first line, noting that lenalidomide in combination with bortezomib and dexamethasone (LenBorD) would be preferable compared to status quo (cyclophosphamide, bortezomib and dexamethasone (CyBorD)). The Subcommittee considered that this preference was likely an acknowledgement of its use in international jurisdictions. The Subcommittee noted that LenBorD is an effective induction regimen for transplant eligible patients. The Subcommittee considered that there is unlikely to ever be any new evidence comparing it to the standard of care in New Zealand (CyBorD). The Subcommittee noted that treatment with LenBorD for transplant eligible patients would be limited to four cycles, limiting the financial impact, as lenalidomide is already funded as maintenance therapy post autologous haematopoeitic stem cell transplant (HSCT). The Subcommittee noted that lenalidomide is not available, and would be less effective in later lines of therapy in patients who receive lenalidomide maintenance and therefore LenBorD is preferred as induction by treaters to ensure patients receive full dose treatment with lenalidomide as part of their therapy.

4.3.6. The Subcommittee considered that conversely, there would be a significant increase in the use of lenalidomide for patients who were not eligible for transplant if it were funded in the first line setting for these patients. The Subcommittee noted that clinicians would likely want to add bortezomib to lenalidomide in the majority of this patient group given the evidence of efficacy of less intensive regimens (O'Donnell E et al. Blood 2019; 134 (Supplement_1): 3178). The Subcommittee noted that bortezomib can be self-administered so would not necessarily impact heavily on infusion resource, however that there would be a small proportion (less than 20%) of patients for whom self-administration would not be possible (eg. due to frailty).

4.3.7. The Subcommittee noted the third priority of the NZMIG, which was for improved access to novel agents in later lines of therapy (eg. pomalidomide and carfilzomib). The Subcommittee noted that the previous recommendations provided by the Subcommittee indicates the preference for pomalidomide in the later line setting compared to carfilzomib.

4.3.8. The Subcommittee considered that preference for treatment, as in earlier lines, would be driven primarily by the mechanism of action of the unfunded agent(s) and that the funding of any treatment in a given line may change the preference for subsequent treatments in later lines. The Subcommittee considered that it was difficult to provide recommendations based on the multiple permutations that are possible for addressing the unmet need that exists in each line of treatment for patients with multiple myeloma. The Subcommittee therefore considered that should there be a change in the funded treatments in earlier lines of treatment, then the preference for different agents in later lines would need to be revisited.

4.3.9. The Subcommittee considered that there would be a preference for daratumumab over pomalidomide or carfilzomib in the second line setting and a preference for pomalidomide in combination with bortezomib and dexamethasone (PVd) in the third line setting over carfilzomib in combination with dexamethasone.

4.3.10. The Subcommittee considered that it may be appropriate to consider including a maximum duration for daratumumab, pomalidomide and carfilzomib in the Special

Authority criteria for these agents. In addition, the Subcommittee considered that it would be appropriate to ensure that the initial and renewal approval durations would be the same for all agents that could be used in the relapsed or refractory multiple myeloma setting.

4.3.11. Overall, the Subcommittee considered that the greatest unmet need in multiple myeloma was for those patients who relapse after first line treatment, and that the funding of lenalidomide as maintenance therapy post ASCT has increased the need for patients who do progress, due to the limited treatment options for patient who do progress. The Subcommittee considered that its previous recommendations reflected this.

Daratumumab for the third line treatment of multiple myeloma

4.3.12. The Subcommittee noted that it had not previously considered the funding of daratumumab for patients with multiple myeloma in the third line setting. The Subcommittee considered that the data for the use of daratumumab after two prior lines comes from the CASTOR trial which compared the use of daratumumab in combination with bortezomib and dexamethasone (DBorD) versus bortezomib and dexamethasone (BorD) (Palumbo A et al. N Engl J Med. 2016;375:754-66). The Subcommittee noted that the efficacy (progression free survival) as demonstrated in the CASTOR trial of daratumumab beyond one prior line of treatment reduced from median time not reached at 30 months of follow up for patients with one prior line of treatment to approximately 9.8 months for patients with 2-3 prior lines of treatment (Spencer et al. Haematologica.2018;103:2079-87; Mateos et al. Clin Lymphoma Myeloma Leuk. 2020. 20:509-518). The Subcommittee noted that this indicates that daratumumab would be an efficacious treatment in this setting, although acknowledged that this efficacy is reduced compared to its use in earlier lines. The Subcommittee also noted that while carfilzomib would not be an option for all patients due to its toxicity profile, daratumumab would likely to be able meet the unmet need for this entire population.

4.3.13. The Subcommittee noted that the use of daratumumab would be preferred in second line as it is more effective in this setting, represents a generally well tolerated regimen and that this is consistent with its use internationally. However, as daratumumab would be expected to provide similar benefit to other agents (pomalidomide and carfilzomib) that have been recommended for funding in later lines of therapy, the Subcommittee considered that its use in later lines could also address the health need for patients, if they were to progress on earlier lines of treatment.

4.3.14. The Subcommittee **recommended** that daratumumab for the third-line treatment of relapsed or refractory multiple myeloma be listed with a **medium priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

DARATUMUMAB
Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
2. Patient has received two prior lines of treatment; and
3. Either
    3.1. Both:
        3.1.1. In patients who received first-line bortezomib, patient's disease was not refractory to bortezomib (ie received >6 months response to first-line bortezomib), nor were they intolerant to bortezomib; and

3.1.2. Daratumumab to be administered in combination with bortezomib and dexamethasone for weeks 1 through 24 and as a monotherapy from week 25 until disease progression; or

3.2. Both:

3.2.1. In patients who received first-line bortezomib, patient's disease was refractory to bortezomib in first line or they were intolerant to bortezomib; and

3.2.2. Daratumumab to be administered in combination with dexamethasone

Renewal - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:

Both:

1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

4.3.15. The Subcommittee requested that its preferences for treatment of patients with multiple myeloma be reviewed should there be a change in the funding landscape regarding the first and/or second line treatment of multiple myeloma.

4.4. Durvalumab for unresectable non-small cell lung cancer (NSCLC)

4.4.1. The Subcommittee reviewed correspondence received from the New Zealand Lung Oncology Special Interest Group (LOSIG) regarding the review of the application for funding of durvalumab for stage III, locally advanced, unresectable NSCLC.

4.4.2. The Subcommittee noted durvalumab for locally advanced, unresectable NSCLC irrespective of PD-L1 status was first reviewed and recommended for funding with a **medium priority** by PTAC in August 2020. The Subcommittee noted this application was subsequently reviewed by CaTSoP and recommended for funding irrespective of PD-L1 status with a **high priority** in October 2020, with a recommendation that durvalumab be funded for locally advanced, unresectable NSCLC which is PD-L1 positive (>1%) with a **high priority.**

4.4.3. The Subcommittee noted LOSIG did not endorse the requirement for patients to have PD-L1 testing in order to access durvalumab. In response, the Subcommittee noted the post-hoc PD-L1 analysis (Faivre-Finn et al. 2020) used a PD-L1 threshold that identified less PFS and OS benefit in patients with PD-L1 status of <1%; and considered that benefit in this population was uncertain however acknowledged that benefit could not be completely excluded. The Subcommittee considered that treatment with durvalumab in this patient population could expose patients to potential toxicity with little opportunity for benefit.

4.4.3.1. The Subcommittee considered that the recommendation to target funding of treatment to PD-L1 >1% was proposed as an option to control pharmaceutical expenditure and ensure treatment access in the patient population most likely to benefit. The Subcommittee considered that the benefit associated in each recommended patient group would inform later cost-utility analysis based on the proportion of PD-L1 >1% patients within the overall patient population. The Subcommittee noted a recommendation for access irrespective of PD-L1 status potentially reflected the lack of access to validated PD-L1 testing throughout New Zealand and the risk that mandating testing could result in inequities for patients either unable to access testing, or unable to achieve samples conducive to testing. However, it considered that if such a recommendation was made these barriers were likely to be overcome as they had been for other molecularly targeted agents

4.4.3.2. The Subcommittee noted that patients with stage III NSCLC are likely to have previously undergone biopsies for tissue samples due to the nature of disease, and availability of targeted tyrosine kinase treatments (targeting EGFR and ALK) and considered PD-L1 expression was likely to be tested in a hierarchical manner if required for access to durvalumab. The Subcommittee considered some patients are likely to require additional biopsies to evaluate PD-L1 status depending on the size and quality of prior samples and considered this could further add to possible barriers for access to treatment.

4.4.3.3. The Subcommittee considered the number of patients expressing PD-L1 would likely align with Faivre-Finn et al. 2020 where 63% of the cohort had available tissue for testing, and 77% of patients expressed a PD-L1 level >1%, and noted that there is an association between higher levels of PD-L1 expression and patients with later stage disease. The Subcommittee noted this trial was conducted across numerous countries and there was no reason to suspect the proportion of PD-L1 expression in New Zealand patients would differ from these estimates.

4.4.4. The Subcommittee noted the request from LOSIG that the proposed Special Authority criteria restricting access to patients who have completed their last dose of radiation within six weeks of starting durvalumab be extended to eight weeks.

4.4.4.1. The Subcommittee noted its recommendation to enable access to treatment within six weeks of radiation was clinically appropriate and based on the clinical trial and ensured that patients proceeding to durvalumab therapy had a high-performance status; however, considered that some patients may benefit from a longer period to recover from radiation without this recovery time impacting on their overall performance status.

4.4.4.2. The Subcommittee noted the PACIFIC trial initially randomised patients at two weeks post radiation; however, the protocol was amended to enable inclusion for patients up to six weeks post radiation which was the basis of the Special Authority. The Subcommittee considered that extension of the Special Authority to enable access for patients up to eight weeks post radiation is unlikely to change access but is clinically pragmatic to enable access to patients likely to benefit from treatment.

4.4.5. The Subcommittee noted comments that indicated there is insufficient data to inform on the later use of immunotherapy for patients who have received treatment with durvalumab for NSCLC. The Subcommittee noted this aligned with its previous consideration, noting the lack of outcome data on the use of immunotherapy following durvalumab treatment.

4.4.5.1. The Subcommittee noted that restricting access to immunotherapy for NSCLC to once per patient lifetime may reduce the number of patients accessing immunotherapy at later stages of disease (eg stage IV / metastatic). The Subcommittee considered it would be clinically advantageous to treat in the maintenance setting due to the possibility of durable control or remission.

4.4.5.2. The Subcommittee noted there was an updated report of a small cohort of patients from the PACIFIC trial proceeding to later immunotherapy treatment but as second time to progression is the only outcome published, the evidence was of low strength and quality. The Subcommittee noted the

retrospective data analysis by Gobbini, E et al. Clin Lung Cancer. 2020; 21(5):497-510 which considered patients who ceased immunotherapy treatment due to toxicity or clinical decision – and reported that those who maintained a durable treatment free period and those with good performance status may be potential candidates for rechallenge. Again, this evidence was considered of very limited strength and quality.

4.4.5.3. The Subcommittee considered that that there was currently insufficient evidence supporting retreatment with immunotherapy in a later stage of NSCLC and favoured restricting immunotherapy treatments to immunotherapy naïve patients. The Subcommittee considered the access criteria for use of immunotherapy in Stage IV NSCLC should be updated to reflect this; however, considered it would be appropriate to reassess this as evidence evolves in this setting.

4.4.6. The Subcommittee noted the information provided from LOSIG supporting four weekly dosing of durvalumab of a fixed 1500 mg dose.

4.4.6.1. The Subcommittee noted it had not reviewed any evidence supporting four weekly dosing during its October 2020 review and dosing was based on the dosing included in the PACIFIC trial. The Subcommittee noted the November 2020 FDA approval to enable flat dosing of 1,500 mg per dose as compared to weight-based dosing, based on the flat dosing used in the CASPIAN trial. The Subcommittee noted this was provided as an alternative to the 10 mg/kg two weekly weight-based dosing for patients greater than 30 kg.

4.4.6.2. The Subcommittee noted it had previously considered that fortnightly treatment may be challenging for rural patients and those in high deprivation areas and considered that enabling dosing four weekly would reduce the burden on patients and significantly free up resourcing across most centres. The Subcommittee noted similar flat dosing regimens were standard of care across other immunotherapy agents and the pharmacokinetic modelling for these agents supported the transition to longer dosing intervals.

4.4.7. The Subcommittee considered the following changes to the Special Authority for durvalumab for treatment of stage III, locally advanced, unresectable NSCLC would be appropriate (proposed changes in **bold** and ~~strikethrough~~ as follows):

DURVALUMAB

Initial application – only from a medical oncologist or on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1 Patient has histologically or cytologically documented stage III, locally advanced, unresectable Non-Small Cell Lung Cancer (NSCLC); and
2 Patient has received two or more cycles of platinum-based chemotherapy concurrently with definitive radiation therapy; and
3 Patient has no disease progression following the second or subsequent cycle of platinum-based chemotherapy with definitive radiation therapy treatment; and
4 Patient has a ECOG performance status of 0 or 1; and
5 Patient has completed last radiation dose within ~~6~~ **8** weeks of starting treatment with durvalumab; and
6 Patient must not have received prior PD-1 or PD-L1 inhibitor therapy for this condition; and
7 Either:
7.1. Durvalumab is to be used at a maximum dose of no greater than 10 mg/kg every 2 weeks; **or**
7.2. **Durvalumab is to be used at a maximum dose of no greater than 1500 mg every 4 weeks**; and
8 Treatment with durvalumab to cease upon signs of disease progression.

Renewal – only from a medical oncologist or on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1. The treatment remains clinically appropriate and the patient is benefitting from treatment; and
2. Either:
2.1 Durvalumab is to be used at a maximum dose of no greater than 10 mg/kg every 2 weeks; **or**
2.2 **Durvalumab is to be used at a maximum dose of no greater than 1500 mg every 4 weeks**; and
3. Treatment with durvalumab to cease upon signs of disease progression; and
4. Total continuous treatment duration must not exceed 12 months.

4.5. Lenvatinib for unresectable hepatocellular carcinoma (HCC)

4.5.1. The Subcommittee reviewed correspondence received from the supplier of lenvatinib (Eisai) regarding the review of the application for funding of lenvatinib as a first-line treatment for hepatocellular carcinoma (HCC).

4.5.2. The Subcommittee noted the supplementary updated evidence provided to support the use of lenvatinib in this setting:

4.5.2.1. Briggs et al, British Journal of Cancer. Covariate adjusted analysis of Phase 3 REFLECT study of lenvatinib versus sorafenib in the treatment of unresectable hepatocellular carcinoma.

4.5.2.2. Singal AG et al, ASCO-GU. Real-world effectiveness of lenvatinib monotherapy among unresectable hepatocellular carcinoma patients treated in United States clinical practises.

4.5.3. The Subcommittee noted the Briggs et al paper detailed the methodology, results and analysis of lenvatinib compared to sorafenib in the treatment of HCC and considered that whilst there appeared to be some benefit associated with lenvatinib treatment, noting the alpha-fetoprotein levels indicated positive outcomes associated with treatment and were identified as the most influential variable across groups; however, there remained uncertainty of the impact of treatment on overall survival within each cohort.

4.5.4. The Subcommittee noted its previous consideration that this patient population had a high health need, with an unmet need for effective treatment options, and a disproportionately high incidence of this disease in Māori and Pacific. The

Subcommittee noted it had assessed another application for the use of atezolizumab in combination with bevacizumab for use in this patient population in July 2021.

4.5.5. The Subcommittee considered that, despite the unmet health need of this patient population, the quality and strength of evidence of benefit from lenvatinib is currently such, that its October 2020 recommendation to fund with a low priority remained appropriate.

4.6. Treatment breaks for trastuzumab and pertuzumab for metastatic breast cancer

4.6.1. The Subcommittee noted that it previously reviewed treatment breaks for pertuzumab and trastuzumab for patients with metastatic breast cancer in October 2020. The Subcommittee noted this prior review was in response to correspondence received by Pharmac from a clinician regarding the Special Authority criteria for trastuzumab and pertuzumab, and whether access would be permitted for patients who experienced disease progression following a period of deliberate cessation off treatment for reasons other than disease progression. The Subcommittee noted that following this review it was considered that the Special Authority criteria do not permit treatment breaks and, should a patient stop treatment without experiencing disease progression, they would not be considered eligible to recommence treatment upon disease progression.

4.6.1.1. The Subcommittee noted its previous consideration of a possible fiscal rationale for enabling treatment breaks, the lack of clear, high quality supporting evidence to support treatment breaks for trastuzumab (and pertuzumab), uncertainty regarding the risk of patients resuming treatment beyond treatment progression, and the associated implications of enabling treatment breaks for other treatments of malignancy.

6.6.2 The Subcommittee noted patients with metastatic HER2-positive breast cancer are currently treated with trastuzumab or trastuzumab/pertuzumab combination and considered approximately 10% of treated patients experience complete response, and experience long periods of disease control on treatment. The Subcommittee noted that following relapse, patients have access to trastuzumab emtansine and further chemotherapy, but would be unable to restart trastuzumab and pertuzumab, in combination with chemotherapy once they experience progression.

6.6.3 The Subcommittee considered that treatment breaks would reduce the need for patients to have prolonged maintenance therapy with trastuzumab alone or in combination with pertuzumab if they were responding to treatment. The Subcommittee noted that ongoing trastuzumab treatment in the setting of disease progression had previously been considered in November 2010 by CaTSoP, in which it recommended further use at the time of disease progression be declined. The Subcommittee considered that enabling access to further HER2 antibody treatment following identification of disease progression whilst off treatment could be considered differently to treatment in the setting of disease progression whilst on treatment.

6.6.4 The Subcommittee noted that access to pembrolizumab / nivolumab for metastatic melanoma was widened in 2019 to enable recommencing of treatment following a period off treatment, following consideration of this by CaTSoP in September 2016. This review noted that patients stable on treatment may wish to cease treatment for

reasons other than toxicity or disease progression, such as travel, or good response to treatment. At this review it was considered that whilst there was no data to support patients with signs of relapsed disease having the same level of response when recommencing treatment, it was reasonable for patients who planned stopping treatment (for reasons other than disease progression or toxicity) to recommence treatment upon signs of relapse, noting this would facilitate clinical management of patients on long-term treatment.

6.6.5 The Subcommittee noted data from the phase III CLEOPATRA randomised control trial of patients with metastatic breast cancer (Swain, MD et al. N Engl J Med. 2015; 372:724-734) comparing the combination of pertuzumab, trastuzumab and docetaxel compared with placebo, trastuzumab and docetaxel. The Subcommittee noted a median progression free survival of 18.7 months in the pertuzumab patient population and 12.4 months in the control arm (HR 0.69 95% CI, 0.58-0.08) and considered that this indicated that the majority of relapse in metastatic breast cancer occurred within the first two years of therapy, with rates of relapse then slowing following this time period.

6.6.6 The Subcommittee noted evidence supporting the association between complete remission and overall survival in 717 patients with HER2-positive metastatic breast cancer noting radiological complete remission (rCR) was associated with better long-term survival, compared to patients who achieved a partial response to treatment (HR 0.27 95% CR 0.8-0.40), noting a 10-year OS estimate of 52% in patients with a rCR compared to patients without rCRC (Steenbruggen, TG et al. Breast Cancer Res Treat. 2019; 178(3):597-605). The Subcommittee noted this historic analysis evaluated 72 patients to assess the effect of stopping trastuzumab treatment in the setting of rCR, with approximately 2/3 of patients (20/30) maintaining complete remission for a long period following treatment cessation with a medium follow up of 78 months.

6.6.7 The Subcommittee considered approximately 100 patients per year relapse following adjuvant trastuzumab treatment, with 10 of these likely to be long-term responders (considered those demonstrating response to treatment for >5 years) and the majority experiencing relapse within the first two years of treatment. The Subcommittee noted this was supported by the estimated average time on trastuzumab treatment based on Pharmac data, which indicated the majority of patients are on treatment for under two years, with treatment in excess of four years accessed by approximately 90 patients (out of approximately 5,000 patients).

6.6.8 The Subcommittee noted the real-world studies (listed below) reporting outcomes in long term responders:

6.6.8.1 Battisti NML et al. Breast Cancer Res Treat. 2019; 178(2):401-408 reporting long term outcomes with targeted therapy in advanced/metastatic HER2-positive breast cancer. Seven patients stopped trastuzumab in complete response after 17-87 months of active treatment with all remaining in complete remission after 79-171 months.

6.6.8.2 Daniels B et al. Breast Cancer Res Treat. 2018; 171(1):151-159 reporting long term survival in trastuzumab-treated patients with HER2-positive metastatic breast cancer in an Australian patient cohort. 4,177 patients were assessed over 15 years with 1,082 (26%) classified as long-term responders (response > 5 years) and 85% of these patients' experienced periods of time off treatment, lasting a median of 30.4 months (9.2-NR) off treatment. The Subcommittee noted no follow up data of response rates for patients that were retreated.

6.6.8.3 Niikura N et al. Breast Cancer Res Treat. 2018; 167(1):81-86 retrospectively reporting 108 patients with HER2 positive metastatic breast cancer, of which 57 achieved complete response. Trastuzumab therapy was interrupted for 27 (47.4%) based on clinician recommendation. Disease progression occurred in 4 patients following interruption of therapy with a median duration of therapy of 5.1 years (0.9-9.3 years).

6.6.8.4 Gullo G et al. Annals of oncology. 2012; 23:2204-2208 reporting durable complete response following treatment for metastatic HER2-positive breast cancer. Of 120 patients, 11 experienced complete response beyond 3 years with maintenance therapy ceased in 7 patients at a median of 5 years since initiation, 4 of which remain in durable complete response.

6.6.9 The Subcommittee considered that that there remains a lack of data supporting response to retreatment following a treatment break and that the likelihood of response was unknown.. The Subcommittee noted that for patients who experience progression after re-challenge of HER2-directed therapy, further lines of treatment would need to be considered based on published evidence-based guidelines.

6.6.10 The Subcommittee considered that based on available evidence, treatment breaks are likely to be most appropriate for patients who have been maintained on treatment for at least two years, where either, complete response has been observed or partial response is maintained for >2 years and thus considered to be representative of metabolic complete response. The Subcommittee considered that patients who had experienced long periods of complete response on treatment may subsequently remain in remission for long periods.

6.6.11 The Subcommittee considered that, if enabled under the Special Authority, the choice to take a treatment break would be one agreed to between clinician and patient. The Subcommittee considered that the number of patients who may choose this option are likely to be small and could be approximately 10 per year but noted this would depend on both clinician and patient comfort with this approach.

6.6.12 The Subcommittee considered that by enabling treatment breaks in settings of disease response, patients could avoid or reduce drug toxicities and render cost savings (both those associated with reduced pharmaceutical usage as well as reduced use of health resources associated with the need for less infusions, with the standard monitoring required). The Subcommittee considered that renewal criteria confirming no disease progression whilst on treatment would remain appropriate.

6.6.13 The Subcommittee considered there to be a range of possible factors for consideration of a treatment break for patients including low levels of intolerance to treatment, increasing difficulty with venous access associated with prolonged requirements for IV administration, length of time on treatment, clinician experience and personal preference. The Subcommittee noted there were likely to be some health benefits associated with this for patients who subsequently experienced long periods of remission off treatment, including possible quality of life improvements for patients associated with reduced treatment burden but acknowledged this was difficult to quantify.

6.6.14 The Subcommittee considered that whilst it was supportive of enabling treatment breaks for trastuzumab and pertuzumab, further consideration of this for other

oncologic treatments should be individually reviewed to ensure this approach is appropriate based on the individual treatment paradigm, likely prognosis, durable response rates, and available evidence.

6.6.15 The Subcommittee recommended that the Special Authority criteria for trastuzumab and pertuzumab be amended to include new renewal criteria for patients who are stable on long term treatment as follows (changes in bold):

Trastuzumab
Renewal – metastatic breast cancer:
Either:
1. All of the following:
   1.1 The patient has metastatic breast cancer expressing HER-2 IHC3+ or ISH+ (including FISH or other current technology) ; and
   1.2 The cancer has not progressed at any point during the previous 12 months whilst on trastuzumab; and
   1.3 Trastuzumab not to be given with lapatinib; and
   1.4 Trastuzumab to be discontinued at disease progression; or
2. **All of the following:**
   2.1 Patient has previously discontinued treatment with trastuzumab for reasons other than severe toxicity or disease progression; and
   2.2 Patient has signs of disease progression; and
   2.3 Disease has not progressed during previous treatment with trastuzumab.

Pertuzumab
Renewal – metastatic breast cancer:
Either:
1. All of the following:
   1.1 The patient has metastatic breast cancer expressing HER-2 IHC3+ or ISH+ (including FISH or other current technology) ; and
   1.2 The cancer has not progressed at any point during the previous 12 months whilst on pertuzumab and trastuzumab; or
2. **All of the following:**
   2.1 Patient has previously discontinued treatment with pertuzumab and trastuzumab for reasons other than severe toxicity or disease progression; and
   2.2 Patient has signs of disease progression; and
   2.3 Disease has not progressed during previous treatment with pertuzumab and trastuzumab.

4.7. Update from Te Aho o Te Kahu regarding molecular testing and diagnostics

6.7.1 The Subcommittee noted a presentation from Te Aho o Te Kahu, which outlined the role, scope and organisational makeup of the agency, and the work that it is scoping in the area of molecular testing and diagnostics.

6.7.2 The Subcommittee noted that access to molecular testing across New Zealand is currently inconsistent, with difficulties in linking pharmaceutical funding to the companion diagnostics, and difficulty obtaining alignment between different centres across New Zealand. The Subcommittee considered that Pharmac, due to its role in the collation of a Hospital Medical Devices List, may have a role in the equitable access to molecular testing and diagnostics in New Zealand moving forward.

6.7.3 The Subcommittee considered that the competition between different providers may present difficulties when seeking a collaborative solution to the equitable provision of diagnostic testing. The Subcommittee considered that the relative

priority of test validation for different pharmaceuticals would need to be well aligned and carefully considered. The Subcommittee considered that it would be useful for Pharmac to provide sufficient notice of a pharmaceutical funding decision to relevant laboratories across New Zealand, should there be an associated requirement for diagnostic testing to access to the funded pharmaceutical, to allow sufficient time to prioritise and validate the relevant test should this be required.

6.7.4 The Subcommittee considered that it could be useful for an Anatomical Pathologist to join the Subcommittee to help align the provision of companion diagnostics and molecular testing to pharmaceutical funding. The Subcommittee considered that it would be useful to be kept informed of developments as this work is undertaken by Te Aho o Te Kahu.

5. Inotuzumab - Adults with relapsed/refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (ALL)

Application

7.2 The Subcommittee noted an application from Auckland City Hospital, and a supporting application from Pfizer, for the use of inotuzumab ozogamicin (Besponsa) monotherapy for the treatment of adults with relapsed or refractory CD22-positive B cell precursor acute lymphoblastic leukaemia (R/R ALL).

Recommendation

7.3 The Subcommittee **recommended** that inotuzumab ozogamicin as a bridge to hematopoietic stem cell transplant for adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia be listed with a **high priority** within the context of treatments for malignancies subject to the following Special Authority criteria:

Initial application – relapsed/refractory CD22-positive B-cell acute lymphoblastic leukaemia/lymphoma
Only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for patients meeting the following criteria:
All of the following:

1. Patient has relapsed or refractory CD22-positive B-cell acute lymphoblastic leukaemia/lymphoma, including minimal residual disease; and
2. Patient will undergo a consolidative hematopoietic stem cell transplant if an adequate response to inotuzumab ozogamicin occurs; and
3. Patient has an ECOG performance status of 2 or less; and
4. Either:
   - 4.1. Both:
     - 4.1.1. Patient has Philadelphia chromosome positive B-Cell ALL; and
     - 4.1.2. Patient has previously received a tyrosine kinase inhibitor; or
   - 4.2. Patient has received one prior line of treatment involving intensive chemotherapy
5. Treatment is to be administered for a maximum of 3 cycles.

7.4 The In making this recommendation, the Subcommittee noted the:

7.4.1 Increased likelihood of patients with relapsed or refractory B-Cell acute lymphoblastic leukaemia/lymphoma progressing to allogenic haematopoeitic stem cell transplant (HSCT), which may be curative, after treatment with inotuzumab ozogamicin

7.4.2 Improvements in overall survival and progression free survival compared to current standard of care that would be expected with inotuzumab ozogamicin

7.4.3 High health need and lack of alternative satisfactory therapies for patients

7.4.4 Expected reduction in hospital stay duration and reduced adverse events compared to currently funded alternatives.

7.5 The Subcommittee **recommended** that inotuzumab ozogamicin for adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia ineligible for allogenic hematopoietic stem cell transplant be listed with a **low priority** within the context of treatments for malignancies subject to the following Special Authority criteria:

Initial application – relapsed/refractory CD22-positive B-cell acute lymphoblastic leukaemia/lymphoma

Only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for patients meeting the following criteria:

All of the following:

1. Patient has relapsed or refractory CD22-positive B-cell acute lymphoblastic leukaemia/lymphoma, including minimal residual disease; and
2. Patient has an ECOG performance status of 2 or less; and
3. Either:
   - 3.1. Both:
     - 3.1.1. Patient has Philadelphia chromosome positive B-Cell ALL; and
     - 3.1.2. Patient has previously received a tyrosine kinase inhibitor; or
   - 3.2. Patient has received one prior line of treatment involving intensive chemotherapy
4. Treatment is to be administered for a maximum of 3 cycles.

Renewal - relapsed/refractory CD22-positive B-cell acute lymphoblastic leukaemia/lymphoma

Only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for patients meeting the following criteria:

All of the following:

1. Patient is not proceeding to a stem cell transplant; and
2. Either:
   - 2.1. Patient has achieved a complete response; or
   - 2.2. Patient has achieved complete remission with incomplete haematological recovery; and
3. Treatment is to be administered for a maximum of 3 cycles

7.6 In making this recommendation, the Subcommittee noted the:

7.6.1 high health need and lack of alternative satisfactory therapies for patients with relapsed or refractory B-cell acute lymphoblastic leukaemia/lymphoma

7.6.2 improvements in overall survival, although more evident in the transplant eligible population, and also in progression free survival compared to what would be expected from current standard of care without inotuzumab ozogamicin

7.6.3 reduced likelihood of benefit for patients who are not eligible for potentially curative allogenic HSCT, and the increase in number of doses required for this patient group.

7.6.4 expected reduction in hospital stay duration and reduced adverse events compared to currently funded alternatives

Discussion

7.7 The Subcommittee noted that acute lymphoblastic leukaemia (ALL) is a cancer of the white blood cells characterised by the overproduction and accumulation of immature white blood cells (lymphoblasts) and inhibition of normal cells in the bone marrow.

The Subcommittee noted that ALL can also spread to other organs such as the liver, spleen, lymph nodes, and central nervous system. The Subcommittee noted that patients with B-Cell ALL typically present with symptoms related to anaemia, thrombocytopenia, and neutropenia due to replacement of the bone marrow with tumour cells and that symptoms can include fatigue, easy or spontaneous bruising/bleeding, and infections. The Subcommittee noted that there are approximately 17 incident patients with relapsed or refractory B-cell ALL per year in New Zealand. The Subcommittee considered that equity as it pertains to socioeconomic status and ethnicity is not a relevant consideration for patients with B-cell ALL.

7.8 The Subcommittee noted that approximately 45% of adult patients with ALL experience disease relapse, with a further 4-11% demonstrated to be treatment refractory (Fielding et al. Blood. 2007;109:944-50, Oriol et al. Haematologica. 2010;95:589-96). The Subcommittee noted that the primary goal from treatment of patients with relapsed or refractory B-cell ALL is complete remission (CR) or complete remission with incomplete haematological recovery (CRi). The Subcommittee noted that patients who achieve a CR/CRi may be eligible for allogenic HSCT, which may potentially be curative.

7.9 The Subcommittee noted that current standard first-line salvage treatment for relapsed or refractory B-cell ALL is reintroduction of intensive chemotherapy treatment as part of an overall plan for long-term disease control to allow for an allografting procedure if eligible. The Subcommittee noted the intensive chemotherapy treatment includes the use of FLAG (Fludarabine, cytarabine [Ara-C] and granulocyte-colony stimulating factor) with anthracycline (idarubicin), mitoxantrone with cytarabine, high-dose cytarabine (HiDAC) based chemotherapy, and high-dose methotrexate in combination with pegylated-asparginase, vinca alkaloids, steroids, etoposide or alkylating agents. All of which require extended hospital stays for patients. The Subcommittee noted that currently available treatments for adult patients with relapsed or refractory B-Cell ALL are also limited by toxicity, associated with extended hospital stays and are associated with adverse events including haematotoxicity, infection, hepatotoxicity, nephrotoxicity, mucositis and neurotoxicity which can limit further treatment and dose intensity, and which may compromise patient outcomes.

7.10 The Subcommittee noted that multiple studies have reported 5-year survival rates of less than 10% in adults with R/R ALL (Fielding et al. Blood. 2007;109:944-50, Oriol et al. Haematologica. 2010;95:589-96). The Subcommittee considered that only 5-30% of patients with relapsed or refractory B-cell ALL will be able to proceed to allogenic HSCT with currently funded treatments.

7.11 The Subcommittee noted that there are other treatments which are currently not funded in New Zealand that have been shown to be effective for this patient group, including blinatumomab, a bispecific T-cell engager, and Chimeric antigen receptor (CAR) - T cell therapy, though the latter (eg. tisagenlecleucel) is currently restricted to the treatment of patients under 24 years of age.

7.12 The Subcommittee noted that inotuzumab ozogamicin is a humanised anti-CD22 monoclonal antibody conjugated to calicheamicin, which is a cytotoxic antibody agent. The Subcommittee noted that CD22 testing for the percentage of blasts with CD22 expression is currently routine for ALL patients, and that funding of inotuzumab ozogamicin would not create additional requirements for diagnostic testing. The Subcommittee noted that although CD22-positivity testing is widely used, receptor density of CD22 expression is not available in routine clinical practice and considered

that this would not be necessary as response to inotuzumab ozogamicin was observed irrespective of receptor density of CD22 expression in the pivotal trial.

7.13 The Subcommittee noted the results from the phase III multicentre, global, open-label, randomised INOVATE trial in which patients ≥18 years old with relapsed or refractory CD22-positive B-cell -positive ALL and scheduled to receive first or second salvage treatment received either inotuzumab ozogamicin for up to six cycles (n=164) or standard of care (n=162) (Kantarjian et al. Cancer. 2019;125:2474-87). The Subcommittee noted that patients with Philadelphia positive ALL would be eligible for treatment with an alternate tyrosine kinase inhibitor. The Subcommittee noted that median follow-up duration for patients who completed the study or were censored for overall survival (OS) was 29.6 months (range, 1.7-49.7 months). The Subcommittee noted that the most common standard of care received was FLAG chemotherapy (n=102) and that this was representative of what the New Zealand patient population with relapsed or refractory B-cell ALL would receive.

7.14 The Subcommittee noted that the proportion of all patients with CR/CRi was higher for patients that received inotuzumab ozogamicin compared to standard of care (121 of 164 [73.8%] vs 50 of 143 [35.0%]), and that for patients achieving CR/CRi, the duration of remission was significantly longer in the inotuzumab ozogamicin treatment arm (HR, 0.62 [95% CI, 0.42-0.91]; 1-sided P = 0.0071; median, 5.4 months [95% CI, 4.2-7.0 months] versus 4.2 months standard of care arm [95% CI, 2.7-5.7 months]). The Subcommittee also noted that the median progression free survival in the inotuzumab ozogamicin treatment arm was 5.0 months (95% CI, 3.9-5.8 months) compared to 1.7 months (95% CI, 1.4-2.1 months) in the standard of care treatment arm (HR, 0.45 [97.5% CI, 0.34-0.60]; 1-sided P < .0001).

7.15 The Subcommittee noted that the median overall survival for the inotuzumab ozogamicin treatment arm was 7.7 months (95% CI, 6.0-9.2 months) compared to 6.2 months in the standard of care arm (95% CI, 4.7-8.3 months; HR 0.75; 95% CI 0.57 to 0.99; 1-sided P = 0.0105). The Subcommittee also noted that the 2-year survival was 22.8% in the inotuzumab ozogamicin treatment arm (95% CI 16.7 to 29.6), compared to 10.0% in the standard of care arm (95% CI 5.7 to 15.5; P = 0.0004). The Subcommittee noted that three-year survival was 20.3% in the inotuzumab ozogamicin treatment arm (95% CI 14.4 to 27.0) compared to 6.5% in the standard of care arm (95% CI 2.9 to 12.3; P = 0.0093).

7.16 The Subcommittee noted that no difference in overall survival was observed in the Philadelphia-positive group, but when only Philadelphia-negative patients were considered, the HR for overall survival was 0.68 (97.5% CI, 0.51-0.92). The Subcommittee also noted that patients in the inotuzumab ozogamicin treatment arm had a lower rate of subsequent therapies (34.1%) than the standard of care arm (56.8%). The Subcommittee considered that, because subsequent treatments may have affected overall survival, sensitivity analyses which censored patients at the time of their first subsequent salvage therapy (eg blinatumomab, TKIs, CAR-T, or inotuzumab ozogamicin), had been performed, which may have preserved overall survival for the inotuzumab ozogamicin arm versus the standard of care arm.

7.17 The Subcommittee noted that veno-occlusive disease (VOD)/ sinusoidal obstruction syndrome (SOS) during or after treatment (including after post-HSCT follow-up) occurred in 14.0% of the inotuzumab ozogamicin treatment arm and 2.1% in the standard of care arm.

7.18 The Subcommittee noted that more patients proceeded to HSCT at any time after study treatment in the inotuzumab ozogamicin arm than the standard of care arm (79

of 164 vs 36 of 162; 1-sided P < .0001), and that almost 4 times as many patients in the inotuzumab ozogamicin arm proceeded to HSCT after achieving CR/CRi before the start of any follow-up induction therapy (65 of 164 [39.6%; 95% CI, 32.1%-47.6%] vs 17 of 162 [10.5%; 95% CI, 6.2%-16.3%]; 1-sided P < .0001). The Subcommittee also noted that the median 2-year survival for inotuzumab ozogamicin patients who achieved CR/CRi was 12.6 months (95% CI 9.3 to 27.7) for those with follow-up HSCT and 7.1 months (95% CI 5.6 to 10.8) for those without follow-up HCST (HR 0.55; 97.5% CI 0.32 to 0.95; P = 0.0065).

7.19 The Subcommittee noted that factors associated with improved overall survival in the inotuzumab ozogamicin treatment arm of the INO-VATE trial were best minimal residual disease (MRD) status, baseline platelet count, baseline haemoglobin level, duration of first remission, achieving CR/CRi, and whether a patient underwent HSCT during follow-up (all 2-sided P values < .05).

7.20 The Subcommittee noted that subgroup analysis of the INO-VATE trial showed that CR/CRi outcomes were better in the inotuzumab ozogamicin treated group compared to standard of care for all age groups, as was MRD negativity (Jabbour et al. Cancer. 2018;124:1722-32). The Subcommittee also noted that the overall survival was better in patients aged under 55 years in both the inotuzumab ozogamicin treated group and the standard of care group (>55 years old: 8.6 months inotuzumab ozogamicin group (95% CI 7.0-11.1) vs 8.0 months standard of care group (95% CI 4.9-9.5); ≥55 years old: 5.6 months inotuzumab ozogamicin group (95% CI 4.8-8.0) vs 5.3 months standard of care group (95% CI 4.2-7.1).

7.20.1 The Subcommittee noted patient reported outcomes from the INO-VATE trial assessed via self-administered European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30) and the EuroQol Group 5 Dimensions Questionnaire (EQ-5D) (Kantarjian et al. Cancer. 2018;124:2151-60). The Subcommittee noted that Overall health status measurements of global health status/QoL from the QLQ-C30, health state from the EQ-5D VAS, and the EQ-5D index scores all were numerically better among patients in the inotuzumab ozogamicin arm versus the standard of care arm, although without statistical significance. The Subcommittee also noted that individual functioning scores favoured inotuzumab ozogamicin (P<0.05) in physical functioning (LSM difference, 6.9; 95% CI 1.4-12.3), role functioning (Least squares mean difference, 11.4; 95% CI 3.2-19.5) social functioning (LSM difference, 8.4; 95% CI 0.7-16.1). The Subcommittee noted that gastrointestinal symptoms such as appetite loss (LSM difference, -8.7; 95% CI 16.0 to -1.4; P <0.05) were in favour of inotuzumab ozogamicin and exceeded the minimum clinically important difference (MCID) of 5.

7.21 The Subcommittee also noted the following evidence provided by the applicant in relation to inotuzumab ozogamicin treatment for R/R B-cell positive ALL:

- De Angelo et al. Blood Cancer. 2020;10:81
- Kantarjian et al. Clin Cancer Res. 2021;27:2742-54
- Fujishima et al. Int J Hematol. 2019;110:709-22
- Marks et al Bone Marrow Transplantation. Conference: 45th Annual Meeting of the European Society for Blood and Marrow Transplantation. Frankfurt Germany 2019; 54 (pp 149-151)

- Kantarjian et al. Journal of Clinical Oncology. Conference: 2019 Annual Meeting of the American Society of Clinical Oncology, ASCO 2019. Chicago, IL United States. 37 (Supplement 15)
- Jabbour et al. Clinical Lymphoma, Myeloma and Leukemia. Conference: Proceedings of the Society of Hematologic Oncology 2019 Annual Meeting. Hilton Americas, Houston United States. 19 (Supplement 1) (pp S191)
- Cassaday et al. J Clin Oncol. 2018;36:7029
- Kantarjian et al. Lancet Haematol. 2017;4:e387-98
- Advani et al. Blood. 2017;130:2557
- Kantarjian et al. Blood. 2017;130:2574
- Kebriaei et al. Blood. 2017;130:886
- Ruiz-Garcia et al. Ann Oncol. 2017;28 (Supplement 5): 368
- Su et al. J Clin Oncol. 2017;35: no. 15 suppl

7.22 The Subcommittee considered the evidence supporting the benefit of inotuzumab ozogamicin for patients with relapsed or refractory B-cell ALL to be of good strength and quality, with relevance to the New Zealand patient population. The Subcommittee considered that the health benefits that would be experienced if inotuzumab ozogamicin were funded may be expected to be greater in New Zealand due to the current lack of access to alternative salvage therapies. The Subcommittee also considered that the ability to identify and treat toxicities related to inotuzumab ozogamicin treatment according to the INO-VATE trial is possible in current practice.

7.23 The Subcommittee considered that progression free survival is a reasonable measure of expected benefit for patients with relapsed or refractory B-cell positive ALL and is especially relevant to patients who are unable to progress to transplant. The Subcommittee considered that CR/CRi is crucial to the success of subsequent allogenic HSCT, and that the INO-VATE trial clearly showed an advantage in quickly reaching CR/CRi for patients that received inotuzumab ozogamicin.

7.24 The Subcommittee noted the Badar et al trial, which reported real-world outcomes from a multi-centre cohort analysis of patients who received treatment with inotuzumab ozogamicin (Badar et al. Clin Lymphoma Myeloma Leuk. 2020;20:556-60). The Subcommittee noted that this was a relatively small trial (n=84) which reported that the time to progression after induction with inotuzumab ozogamicin within one year was 36% of patients, which was lower than the 57% of patients reported in the INO-VATE trial. The Subcommittee considered that the proportion of patients that were Philadelphia chromosome positive in the Badar et al trial was greater than that of the INO-VATE trial may explain the variation in results between the two trials. The Subcommittee also noted that there were less instances of veno-occlusive disease (VOD) in the Bader et al trial compared to the INO-VATE trial which was likely due to patients receiving prophylactic treatment for VOD in the Bader et al trial rather than treating VOD at onset. The Subcommittee also noted that the Bader et al. trial had relatively high incidence of matched donor transplants which are usually associated with lower rates of

mortality than non-donor matched transplants, compared to both the New Zealand population and the INO-VATE trial population.

7.25 The Subcommittee noted a post-hoc analysis of the INO-VATE trial seeking to assess the relationship between CD22 expression and treatment outcomes for inotuzumab ozogamicin versus standard of care (Kantarjian et al. Clin Cancer Res. 2021;27:2742-54). The Subcommittee noted that in patients with higher (≥90%) CD22 positivity, the rate of CR/CRi was 78.5% (95% CI 69.5% to 85.9%) for inotuzumab ozogamicin versus 35.5% (95% CI 25.8%–46.1%) for standard of care (rate difference 43%; 97.5% CI 28.8%–57.3%; one-sided P < 0.0001). The Subcommittee also noted that in patients with lower (<90%) CD22 positivity, CR/CRi rate of inotuzumab ozogamicin versus standard of care was 65.7% (95% CI 47.8%–80.9%) versus 30.6% (95% CI 16.3%–48.1%; rate difference 35.2%; (97.5% CI, 10.3%–60%; one-sided P = 0.0015). The Subcommittee noted that within the inotuzumab ozogamicin treated group, the rate of CR (indicating a response with better quality of hematopoietic recovery than CRi) was 42.1% and 20% for patients with CD22 positivity ≥90% and <90%, respectively. The Subcommittee considered that the degree of CD22 positivity should not limit access to inotuzumab ozogamicin, as lower CD22-positivity remained sufficient to be able to induce response compared to standard of care.

7.26 The Subcommittee considered that inotuzumab ozogamicin offers significant benefits over currently funded treatments and that these include; high rates of complete response/complete haematological response, higher MRD negativity rates, longer progression free survival, longer overall survival, requires less transfusion support, decreases time spent in hospital, reduced need for second salvage therapy, and an increased likelihood of eligibility for allogenic HSCT.

7.27 The Subcommittee also considered that the largest difference in cost to the health sector if inotuzumab ozogamicin were funded would be in the inpatient setting, as patients would spend considerably less time there compared to current standard of care. The Subcommittee considered that this would be expected to be similar to the differences observed for patients in the INO-VATE trial. The Subcommittee considered, however, that utilization of inotuzumab ozogamicin in this patient population may increase the demand on transplant services due to more patients achieving an adequate response and being able to progress to allogenic HSCT.

7.28 The Subcommittee considered that while all patient subgroups showed benefit with inotuzumab ozogamicin treatment, predictors of increased overall survival with inotuzumab were having the best MRD status, healthy baseline platelet count, high CD22 expression, longer duration of first remission, achieving complete response or complete haematologic response, low disease burden, and receiving follow-up allogenic HSCT. The Subcommittee considered that while treatment with inotuzumab ozogamicin would benefit all patients with relapsed or refractory B-cell ALL, the greatest benefit would be experienced by those patients eligible for potentially curative allogenic HSCT.

7.29 The Subcommittee noted that, if inotuzumab were to be funded for relapsed or refractory B-cell ALL, approximately 15-17 patients per year would be eligible to receive treatment. The Subcommittee considered that if funded for patients as a bridge to allogenic HSCT, approximately 7-8 patients per year may be eligible to receive treatment. The Subcommittee considered that patients would receive, on average, 2-3 cycles of inotuzumab ozogamicin, and that once MRD is achieved, patients would need to proceed to transplant quickly.

7.30 The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for inotuzumab ozogamicin if it were to be funded in New Zealand as a bridge to hematopoietic stem cell transplant for adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia. 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 Subcommittee'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	Adults with relapsed/refractory CD22 positive B-Cell ALL, including Philadelphia chromosome positive diseases, who are likely to be eligible for an HSCT following inotuzumab therapy

Intervention	Intravenous infusion of inotuzumab in 3-4 week cycles.
	• For the first cycle, the dose is 0.8mg/m2 on day 1, and 0.5mg/m2 on days 8 and 15
	• For subsequent cycles, the dose is:
	  ○ 0.5 mg/m2 on days 1, 8 and 15 for patients who achieve CR/Cri
	  ○ 0.8mg/m2 on day 1, and 0.5mg/m2 on days 8 and 15 for patients who do not achieve CR/CRi
	It is recommended that patients receive two treatment cycles (maximum of three if CR/CRi is not achieved after two cycles)

Comparator(s)	Standard chemotherapy regimen for relapsed/refractory CD22 positive B-Cell ALL currently used in New Zealand
Outcome(s)	• Improved CR/Cri rates resulting in more patients proceeding to HSCT • Improved PFS and OS, particularly for patients who receive HSCT, which is a potentially curative treatment • Improved quality of life, particularly for patients who undergo a successful HSCT • Fewer (and shorter) hospitalisations since inotuzumab can be provided in an outpatient setting
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.	

7.31 The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for inotuzumab ozogamicin if it were to be funded in New Zealand for adult patients with relapsed or refractory CD22-positive B-cell precursor acute lymphoblastic leukaemia who are ineligible for allogenic hematopoietic stem cell transplant. 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 Subcommittee'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	Adults with relapsed/refractory CD22 positive B-Cell ALL, including Philadelphia chromosome positive diseases who are not eligible for a HSCT.

Intervention	Intravenous infusion of inotuzumab in 3-4 week cycles.
	• For the first cycle, the dose is 0.8mg/m2 on day 1, and 0.5mg/m2 on days 8 and 15
	• For subsequent cycles, the dose is:
	  ○ 0.5 mg/m2 on days 1, 8 and 15 for patients who achieve CR/Cri
	  ○ 0.8mg/m2 on day 1, and 0.5mg/m2 on days 8 and 15 for patients who do not achieve CR/Cri
	Patients not proceeding to a stem cell transplant can take up to a maximum of six cycles:

Comparator(s)	Standard chemotherapy regimen for relapsed/refractory CD22 positive B-Cell ALL currently used in New Zealand
Outcome(s)	• Improved PFS and OS • Improved quality of life while on treatment compared to FLAG-IDA chemotherapy • Fewer (and shorter) hospitalisations since inotuzumab can be provided in an outpatient setting
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.	

8 Cemiplimab - metastatic or locally advanced cutaneous squamous cell carcinoma in adult patients who are not candidates for curative surgery or curative radiation, first-line

Application

8.1 The Subcommittee reviewed an application from Sanofi-Aventis New Zealand Ltd for cemiplimab for the treatment of adult patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced cutaneous squamous cell carcinoma (laCSCC) who are not candidates for curative surgery or curative radiation.

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

Recommendation

8.3 The Subcommittee **recommended** that the application for cemiplimab for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation be **deferred** pending publication of phase II clinical trial evidence supporting longer term response rate, duration of response and quality of life improvements for patients treated with cemiplimab.

8.4 In making this recommendation the Subcommittee considered the lack of long-term published phase II clinical trial data relating to response rate, duration of response, and overall survival benefit, the lack of published relevant QoL data, and that that there were no direct comparator studies available. The Subcommittee considered that data with a median follow up of over two years would be beneficial in the appraisal of the health benefit of cemiplimab.

Discussion

8.5 The Subcommittee noted that the mCSCC is defined as CSCC that has metastasised to lymph nodes (regional or distant) or other distant sites, and laCSCC is CSCC that has not metastasised to lymph nodes (nodal or distant) or other distant sites but may include locally extensive disease. The Subcommittee noted that most CSCC occurs in the head and neck (70-90%), with more than half of the tumours on the anterior scalp, forehead, or ears (Amoils et al. Head Neck. 2017;39:881-885; Newlands et al. J Laryngol Otol. 2016;130:S125-S132).

8.6 The Subcommittee considered the true incidence and prevalence of CSCC is difficult to determine, and that it would be beneficial if epidemiological data was based upon CSCC staging, to enable epidemiological analysis of the size of patient populations that may benefit from targeted treatments.

8.7 The Subcommittee noted that the New Zealand Cancer Registry no longer requires mandatory reporting of non-melanoma skin cancer (NMSC) due to incomplete reporting and difficulty managing the large number of these cancers but considered CSCC are likely to make up approximately 20-30% of NMSC. The Subcommittee noted that the incidence of mCSCC and laCSCC combined ranged from 1.4% up to 3.7% of total CSCC (Brougham et al. J Plast Reconstr Aesthet Surg. 2011;64:273-8; Hollestein et al. Eur J Cancer. 2012;48:2046-53; Robsahm et al. Cancer Med. 2015;4:472-80) with a prevalence of 1.67% reported in one publication (Venables et al. JAMA Dermatol. 2019;155:298-306).

8.8 The Subcommittee noted additional epidemiological data which indicates CSCC is more prevalent among males (55-60%), the elderly (>75 years of age), and those of European descent (non-Māori or -Pacific), with New Zealand and Australia having the highest incidence of CSCC in the world, and considered this likely due to CSCC being a UV associated disease (Elliott et al. NZ Med J. 2018;131:23-29, O'Dea. 2009). The Subcommittee noted that a study in Northland, New Zealand found that of the 890 patients identified with advanced CSCC over a 12-month period, only 9 (1%) patients identified as Māori (Elliott et al. NZ Med J. 2018;131:61-68) and that in New Zealand Cancer Registry data for 2013, 3 of 164 cases (1.8%) were for Māori, all in the 70- to 74-year age group (Ministry of Health 2013 Cancer: New registrations and deaths).

8.9 The Subcommittee noted there is a significant health need for patients with mCSCC and laCSCC as well as their family and whānau. The Subcommittee noted that these patients are typically elderly and suffer from substantial morbidity and high mortality, requiring regular wound dressings and changing, at home nursing care, and regular hospital visits. The Subcommittee noted the presence of distant metastasis correlates to a poor prognosis and a median survival of less than 2 years (Stratigos et al. Eur J Cancer. 2015;51:1989-2007). The Subcommittee also noted the visual disfigurement often associated with mCSCC and laCSCC can reduce quality of life, affecting physical and psychological health and social relationships (Arunachalam et al. Indian J Palliat Care. 2011;17:184-90).

8.10 The Subcommittee noted there is no standard treatment for patients with mCSCC or laCSCC, noting the mainstay of non-mCSCC or laCSCC treatment is surgery and/or radiation. The Subcommittee noted that in clinical practice, best supportive care (BSC) includes surgery, palliative care, and treatments to reduce symptoms and support quality of life. The Subcommittee noted that chemotherapy options in New Zealand include platinum-based and non-platinum-based chemotherapy, namely cisplatin and fluorouracil; however, the Subcommittee considered that due to the age of the likely

patient cohort, many patients present with comorbidities making chemotherapy undesirable due to the associated toxicities.

8.11 The Subcommittee noted that cemiplimab is a fully recombinant human immunoglobulin G4 monoclonal antibody that targets the programmed cell death-1 (PD-1) receptor, thereby potentiating T-cell responses, including anti-tumour responses. The Subcommittee noted the recommended dose for cemiplimab is 350mg every 3 weeks via intravenous infusion over 30 minutes, continued until disease progression or unacceptable toxicity, with a proposed maximum treatment duration of 24 months. The Subcommittee considered that there was a significant correlation between median number of coding somatic mutations per mega-base in CSCC and objective response rate for anti-PD-L1 therapies, consistent with observations of higher responses to anti-PD1 treatment in other solid tumour of high mutational burden (Yarchoan et al. N Engl J Med. 2017;377:25002501).

8.12 The Subcommittee noted that cemiplimab would be an extra line of treatment but would reduce best supportive care costs for eligible patients for a time. The Subcommittee considered that cemiplimab would create an additional burden for infusion and aseptic production services due to an increased demand for treatment for these patients. The Subcommittee considered that patients in rural areas do have difficulty accessing infusion treatments due to travel requirements to regional cancer treatment centres.

8.13 The Subcommittee noted that the supplier has identified two clinical trials as the primary evidence for this application: Study 1423 and Study 1540 (Study 1540 ClinicalTrials.govt (EMPOWER)). The Subcommittee noted that the results discussed below come from the clinical study report (not published in a peer reviewed setting), which provides the most up to date evidence and was provided in the supplier's submission documents.

8.13.1 The Subcommittee noted that Study 1423, a phase I, open label, non-randomised clinical trial, of 26 individuals diagnosed with advanced cutaneous squamous cell carcinoma (laCSCC, nodal mCSCC, distant mCSCC) who were ineligible for surgery and received 3mg/kg cemiplimab every 2 weeks via intravenous infusion. The Subcommittee noted the median age was 73 years (slightly younger than that seen in the New Zealand population), and 58% of patients had received previous systemic therapy and 77% of patients had received previous radiotherapy for CSCC.

8.13.2 The primary end point was noted as overall response rate (ORR), with secondary endpoints of duration of response (DOR), progression free survival (PFS), overall survival (OS) and complete response rate.

8.13.3 The Subcommittee noted that, after a median duration of follow-up of 31.7 months, the objective response rate (ORR) was 60.0% (95% CI 26.2 to 87.8) in laCSCC patients, 43.8% (95% CI 19.8 to 70.1) in mCSCC patients, and 50% (95% CI 29.9 to 70.1) overall.

8.13.4 The Subcommittee noted that the median OS was not reached in laCSCC patients, was 22.0 months (95% CI 13.6 to 'not evaluated') in mCSCC patients, and had not been reached (95% CI 16.2 to 'not reached') in the overall patient population.

8.13.5 The Subcommittee noted that the median PFS was 31.4 months (95% CI 1.1 to 31.4) in laCSCC patients, 16.2 months (95% CI 1.8 to 22.0) in mCSCC

patients, and 22.0 months (95% CI 5.4 to 31.4) in the overall population. The median DOR was not reached in the laCSCC group and was 20.3 months (95% CI 4.6 to 20.3) in the mCSCC group.

8.13.6 The Subcommittee noted that the common treatment-emergent adverse events (TEAEs) for the overall patient population included fatigue (29.6%), nausea, diarrhoea, constipation (19.2% each), dry mouth, decreased appetite, hypercalcaemia, hypophosphataemia, and UTI (15.4% each). The Subcommittee also noted that TEAEs lead to two patients withdrawing from the study, and one death.

8.13.7 The Subcommittee noted that Study 1540, a phase II, ongoing, open-label, multicentre, non-randomised clinical trial of 193 adults who been diagnosed with advanced cutaneous squamous cell carcinoma ineligible for surgery and radiation. The Subcommittee noted patients were divided into three groups; Group 1 included 59 patients with mCSCC, Group 2 included 78 patients with laCSCC, and Group 3 included 56 patients with mCSCC. Group 1 and 2 received 3mg/kg every 2 weeks via intravenous infusion, and those in Group 3 received 350mg every 3 weeks via intravenous infusion.

8.13.8 The Subcommittee noted that, after a median duration of follow up of 15.7 months, the ORR was 50.8% (95% CI 37.5 to 64.1) in Group 1, 44.9% (95% CI 33.6 to 56.6) in Group 2, 42.9% (95% CI 29.7 to 56.8) in Group 3, and 46.1% (95% CI 38.9 to 53.4) in the overall population. The OS was not reached, however the estimated OS at 12 months was 81.3% (95% CI 68.7 to 89.2) in Group 1, 91.8% (95% CI 82.6 to 96.2) in Group 2, 72.5% (95% CI 58.6 to 82.5) in Group 3, and 82.8% (95% CI 76.6 to 87.6) in the overall population. The median DOR was not reached for any group at the time of analysis, however the 6-month DOR was 93.3% for Group 1, 85.7% for Group 2, 95.8% for Group 3, and 91.0% in the overall population.

8.13.9 The Subcommittee noted that 37.8% of patients experienced a severe TEAE, resulting in 19 (9.8%) patients discontinuing the study and 5 deaths (2.6%). The most common TEAEs of grade three or higher included hypertension (4.7%), anaemia, cellulitis (4.1% each), pneumonia (3.6%), fatigue, pneumonitis, and sepsis (2.6% each). The Subcommittee also noted that immune-related reactions occurred in 68.9% of patients, 15.0% of which were grade 3 or higher.

8.13.10 The Subcommittee noted that, over time, the mean change from baseline in global health status/health-related quality of life scores indicate a trend towards improvement, with changes ranging from 4.17 (SD: 19.95) and 15.25 (SD: 22.65) in the overall population, but that these results were not statistically significant. The Subcommittee noted that QoL data shows cemiplimab provides some benefit by improving pain by cycle 3, however there is a delayed response for other QoL domains, indicating that QoL benefits are impacted by time to response.

8.14 The Subcommittee noted the two publications based off Study 1423 and Study 1540:

8.14.1 The Subcommittee noted that Migden et al 2018 reports on Study 1423 (data cut-off date: 2 October 2017) and Group 1 of Study 1540 (Migden et al. N Engl J Med. 2018;379:341-351), and that Migden et al 2020 reports on Group 2 of Study 1540 (Migden et al. 2020).

8.14.2 The Subcommittee noted that in the expansion cohort of Study 1423 after a median follow up of 11 months (range 1.1 to 17.0), Migden et al 2018 reported a response rate (RR) of 50% (95% CI 30 to 70), durable disease control rate (DCR) of 65% (95% CI 44 to 83), and median observed time to response (TTR) of 2.3 months (range 1.7 to 7.3). The Subcommittee noted the (DOR) exceeded 6 months in 7 of the 13 patients who had a response (54%). The Subcommittee noted there were five deaths: three due to disease progression, one due to an unknown cause in a patient who had discontinued treatment because of disease progression and was subsequently lost to follow up, and one due to an adverse event.

8.14.3 The Subcommittee noted that in the metastatic disease cohort (Group 1 of 1540), 56% had received previous systemic therapy and 85% had received previous radiotherapy. The Subcommittee noted that after a median follow up of 7.9 months (range 1.1 to 15.6), Migden et al 2018 reported a RR of 47% (95% CI 34 to 61), DCR of 61% (95% CI 47 to 74), a median observed TTR of 1.9 months (range 1.7 to 6.0). The Subcommittee noted the median DOR had not been reached at the time of this analysis, however, that the DOR exceeded 6 months in 16 of the 28 patients who had a response (57%). It was noted that neither the PFS nor the median OS were reached at the time of data cut-off, however the estimated 12-month PFS was 53% (95% CI 37 to 66) and the estimated 12-month OS was 81% (95% CI 68 to 89).

8.15 The Subcommittee noted the additional studies below provided by the supplier describing best supportive care (BSC) and chemotherapy (CT) treatment in patients with laCSCC or mCSCC as an indirect comparison to patients receiving cemiplimab treatment. The Subcommittee considered these studies provided indirect evidence to compare cemiplimab and BSC, but that chemotherapy has only a limited role in this population group.

- Sun et al. JAMA Dermatol. 2019;155:442-447
- Amaral et al. J Eur Acad Dermatol Venereol. 2019;8:44-51
- Zhu and Chang. J Am Acad Dermatol. 2015
- Hillen et al. Eur J Cancer. 2018;96:34-43
- Jarkowski et al. AM J Clin Oncol. 2016;39:545-548
- Chapalain et al. J Eur Acad Dermatol Venereol. 2019;34;1202-1209
- Ogata et al. Eur J Cancer. 2020;127:108-117
- Hillen et al. Eur J Cancer. 2018;96:34-43

8.16 The Subcommittee considered that while the provided evidence shows some degree of increased PFS and OS for both mCSCC and laCSCC, the overall available evidence is immature. The Subcommittee considered the study population to be similar to New Zealand based on rate of surgery and adjuvant chemotherapy, however that the unknown comorbidity rates in the trial participants make comparison to relevant patient populations difficult. The Subcommittee considered that the studies provided did not clearly define laCSCC or mCSCC and had loose inclusion criteria and considered this would make targeting therapy for the purpose of any funding criteria very difficult.

Furthermore, the Subcommittee considered that patients will likely require several months of treatment with cemiplimab before achieving any initial response. It was considered that published and completed phase II trial data with a longer duration of follow up would be required for the Subcommittee to assess whether cemiplimab has a clinically significant benefit over BSC.

8.17 The Subcommittee noted the cost of funding cemiplimab is high and that there is a risk that patients may remain on cemiplimab beyond disease progression due to difficulty in defining disease progression for the purpose of funding criteria. The Subcommittee noted that the inability to accurately define laCSCC in particular could potentially inflate uptake of cemiplimab and also lengthen the duration of treatment. The Subcommittee considered that in the absence of stringent definitions of CSCC disease stage groupings in the Special Authority criteria for cemiplimab, there was the potential for use of cemiplimab outside of the intended population based on use in patients whose disease was not sufficiently advanced and could be considered amenable to surgery or chemotherapy. The Subcommittee also considered that there is a lack of evidence to support retreatment of patients with cemiplimab.

8.18 The Subcommittee noted there would likely be changes in health sector expenditure if cemiplimab were funded, such as increased use of imaging (PET/CT scans for head and neck locations), increased costs related to infusion services, and costs associated with managing cemiplimab-related immune reactions. The Subcommittee also considered that, compared to current treatment, patients treated with cemiplimab may not require as much surgery and radical radiotherapy, so long as they remained progression free.

8.19 The Subcommittee noted that once a patients' disease progressed, they may typically be offered further palliative radiotherapy and occasionally palliative surgery. The Subcommittee also noted that these palliative treatments were likely to be repeated over time, and that supportive care needs for these patients become increasingly demanding and complex. The Subcommittee considered that patients would be unlikely to continue to visit a medical oncologist or receive further PET or CT imaging once their cancer has progressed.

8.20 The Subcommittee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for cemiplimab if it were to be funded in New Zealand for the treatment of adult patients with mCSCC or laCSCC who are not candidates for curative surgery or curative radiation. 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 Subcommittee'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	Cutaneous squamous cell carcinoma (CSCC), metastatic (mCSCC) or locally advanced (laCSCC), in adult patients who are not candidates for curative surgery or curative radiation, first-line
Intervention	350mg cemiplimab as an intravenous infusion Q3W For up to 24 months, or until progression or unacceptable toxicity

Comparator(s) (NZ context)	Best supportive care with or without chemotherapy (based on supplier estimates) • 24% no treatment • 45% palliative radiotherapy • 20% palliative surgery • 17% on cisplatin • 13% on paclitaxel with or without fluorouracil
Outcome(s)	Improved progression free survival Improved overall survival
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

9 Obinutuzumab - first-line induction and maintenance treatment of follicular lymphoma

Application

9.1 The Subcommittee considered an application from Roche Products (New Zealand) Ltd for the use of obinutuzumab for the first-line induction and maintenance treatment of adult patients with follicular lymphoma (FL).

Recommendation

9.2 The Subcommittee **recommended** that obinutuzumab for the treatment of follicular lymphoma be listed if **cost neutral** to rituximab within the context treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application – (follicular lymphoma)** only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months.
> All of the following:

1. Patient has indolent follicular lymphoma stage III or IV, or stage II bulky disease; and
2. Patient has an ECOG performance status of 0-2; and
3. Patient has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more; and
4. Both
    4.1. Obinutuzumab to be administered at a maximum dose of 1000 mg; and
    4.2. Obinutuzumab to be administered for a maximum of 8 cycles in combination with CHOP, CVP, or bendamustine;

Renewal – (follicular lymphoma) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 24 months for applications meeting the following criteria:
All of the following:

1. Patient has achieved a complete or partial response at the end of obinutuzumab induction therapy; and
2. Obinutuzumab to be administered at a maximum of 1000 mg every 2 months for a maximum of 2 years; and
3. Obinutuzumab to be discontinued at disease progression.

Note: Response to first-line induction treatment in combination with obinutuzumab needs to be assessed 2-4 weeks after the last treatment course. Maintenance therapy should commence at 8 weeks after completion of induction treatment

9.3 In making this recommendation, the Subcommittee noted:

9.3.1 The small reduction in the proportion of patients progressing before 24 months when treated with obinutuzumab compared to rituximab.

9.3.2 The small improvements in progression free survival and time to next anti-lymphoma treatment for patients treated with obinutuzumab compared to those treated with rituximab.

9.3.3 The lack of overall survival or quality of life benefit for patients treated with obinutuzumab compared to rituximab

Discussion

9.4 The Subcommittee noted that this application was first assessed by PTAC in August 2018, and that the Committee recommended that obinutuzumab for use in combination with chemotherapy for the first-line induction and maintenance treatment of follicular lymphoma be deferred until additional data is made available regarding the long-term safety of obinutuzumab and the likely efficacy of obinutuzumab retreatment or rituximab containing regimens at relapse following first-line obinutuzumab. The Committee considered that the preferred option would be to fund rituximab maintenance initially, with obinutuzumab maintenance funded only if cost-neutral to rituximab maintenance.

9.5 The Subcommittee noted that PTAC requested advice from CaTSoP regarding long-term safety data for obinutuzumab, and the likely efficacy of treatment with obinutuzumab or rituximab. The Subcommittee noted that CaTSoP reviewed this application in October 2019, and it recommended that funding be deferred pending more mature progression free survival (PFS) and safety data for this patient group from the GALLIUM trial, however considered that overall survival (OS) data was unlikely to be forthcoming in this patient group.

9.6 The Subcommittee noted that in response to the above recommendations, the supplier has provided further follow-up data from the GALLIUM trial.

9.7 The Subcommittee noted that follicular lymphoma makes up approximately 30% of non-Hodgkin's lymphoma (NHL), equating to approximately 250 patients annually in New Zealand. The Subcommittee noted that the majority of patients are over the age of 45 and considered that the incidence of NHL is consistent across ethnicities and socioeconomic groups. The Subcommittee noted that more than 80% of patients have stage 3 or 4 advanced disease at diagnosis, and that treatment for those with advanced disease is not curative in intent. The Subcommittee noted that localised disease at diagnosis that could be treated surgically, and potentially cured, is rare. The Subcommittee noted that over two thirds of patients require treatment immediately after initial progression, and that the remaining patients are managed with a 'watch and wait' approach. The Subcommittee considered that if obinutuzumab were to be funded for this indication, that approximately 110 patients annually would access obinutuzumab.

9.8 The Subcommittee noted that follicular lymphoma is typically indolent in nature with a median survival in all risk groups of advanced disease of greater than 5 years. The Subcommittee also noted that patients typically have a low symptom burden at diagnosis, and that treatment initiation is based on severity of symptoms (such as bulkiness of disease, systemic symptoms such as weight loss, or bone marrow failure). The Subcommittee considered that the majority of patients will require treatment within 2 years of initial diagnosis. The Subcommittee noted that the majority of patients do not die from their disease, but rather morbidities related to old age and other competing factors.

9.9 The Subcommittee noted that the current first-line treatment option for follicular lymphoma requiring systemic therapy is chemo-immunotherapy – cyclophosphamide, vincristine and prednisone (CVP), cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), or bendamustine chemotherapy with rituximab immunotherapy. The Subcommittee noted that bendamustine was funded in New Zealand in 2018 and is an approved chemotherapy option for follicular lymphoma patients. The Subcommittee noted that, in 2019, access to rituximab was widened to enable patients to continue rituximab treatment for two years as maintenance therapy.

9.10 The Subcommittee noted that upon relapse, patients usually receive further first line therapy or an alternative immunochemotherapeutic regimen. Some patients would receive consolidation with high dose therapy and autologous haematopoietic stem cell transplant (HSCT) with very few patients receiving an allogenic HSCT. Other patients may receive palliative treatments for symptom control (eg. radiotherapy). The Subcommittee noted that relapse of patients with follicular lymphoma within 24 months of treatment, identifies a subset of treated patients as more likely to require further treatment with shorter periods of response and perhaps shorter survival.

9.11 The Subcommittee noted that both rituximab and obinutuzumab are recombinant monoclonal antibodies directed against CD20, but that the two agents recognise different epitopes and have slightly different mechanisms of action. The Subcommittee noted that rituximab has limited direct cytotoxicity, but primarily works through complement-dependent cytotoxicity (CDC) and improvement of natural killer cell and macrophage cytotoxicity through FcγRIIIA binding. The Subcommittee noted that obinutuzumab has increased antibody dependent cell-mediated cytotoxicity (ADCC), with minimal or no CDC, and greatly increases FcγRIIIA affinity. The Subcommittee however considered that that it was unclear if CDC played an important role in the efficacy of treatment of follicular lymphoma.

9.12 The Subcommittee noted that the primary evidence for the use of obinutuzumab for the treatment of patients with previously untreated follicular lymphoma comes from the

phase III randomised GALLIUM study (Marcus R, et al. N Engl J Med. 2017;377:1331-1344) comparing rituximab in combination with chemotherapy with obinutuzumab in combination with chemotherapy in this patient group. The Subcommittee noted that the chemotherapy used was either cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), cyclophosphamide, vincristine and prednisone (CVP) or bendamustine. Patients were treated with rituximab or obinutuzumab with chemotherapy for 6 months, and then rituximab or obinutuzumab alone every two months as maintenance. The Subcommittee considered that the chemotherapy received by patients in this study and the relative proportions was reflective of the New Zealand patient population.

9.13 The Subcommittee noted a health related quality of life study from the GALLIUM trial with a median follow-up of 57.4 months which showed that the minimally clinically important difference (MCID) was not reached in either treatment group for physical wellbeing, emotional wellbeing, social wellbeing and that treatment with rituximab with chemotherapy improved functional wellbeing over the minimally clinically important threshold at follow-up months 36 and 48, obinutuzumab with chemotherapy did not (Davies et al. Ann Hematol. 2020;99:2837-46)

9.14 The Subcommittee noted that updated 5-year follow-up evidence has been provided by the supplier in the form of a conference abstract (Townsend et al. 25th European Hematology Association (EHA) Congress virtual edition June 2020). The Subcommittee noted that the 5-year progression free survival was 70.5% with obinutuzumab and chemotherapy (95% CI 66.4 to 74.1) and 63.2% with rituximab with chemotherapy (95% CI 59.0 to 67.1; HR 0.76; 95% CI 0.62 to 0.92; p=0.0043). The Subcommittee also noted that the 5-year time to next anti-lymphoma treatment was longer for patients who received obinutuzumab compared to those who received rituximab(79.7% versus 72.9%; HR 0.72; 95% CI 0.57 to 0.90; p=0.0039) and that this represented a 28% reduction in the relative risk of requiring another line of treatment within 5 years.

9.15 The Subcommittee noted that the primary issue with treatment of follicular lymphoma is with disease progression, specifically progression of disease within 24 months (POD 24). The Subcommittee noted that these patients with disease progression receive more treatment, have poorer outcomes with their salvage treatment, and experience shorter survival.

9.16 The Subcommittee noted that for patients who progressed within 24 months, there was no difference between the obinutuzumab and rituximab treated groups at a median post-progression follow up of 22.6 months, that overall survival (OS) also did not differ between the two treatment groups (HR 0.87; 95% CI 0.62 to 1.22; p=0.41) (Seymour et al. Haematologica. 2019;104:1202-8). The Subcommittee noted that the incidence of early disease progression (ie within 24 months) was less in the obinutuzumab treated arm compared to the rituximab treated arm (9.2% versus 16.3%, respectively) and the average hazard ratio based reduction in risk of progressing before 24 months with obinutuzumab relative to rituximab was 47.6% (95% CI 27.1 to 62.4). The Subcommittee considered that the evidence for the use of obinutuzumab in the treatment of follicular lymphoma was of good strength and good quality.

9.17 The Subcommittee noted that improved progression-free survival (PFS) was observed for obinutuzumab in combination with chemotherapy, regardless of the backbone chemotherapy received. The Subcommittee noted that, while the different chemotherapy regimens have differing safety profiles, the results of the GALLIUM trial are confounded by the non-random chemotherapy allocation of each patient and that this precludes comparisons between chemotherapy agents. The Subcommittee also

considered that the relative proportions of patients undergoing different chemotherapy treatments from the GALLIUM trial were likely applicable to the New Zealand patient population.

9.18 The Subcommittee noted that the results from the GALLIUM trial indicate that the first dose with obinutuzumab is commonly associated with grade III to V adverse reactions and these were related to infusion reactions. The Subcommittee also noted that obinutuzumab must be administered over 6 hours in a hospital setting for the first dose and 3–4-hour infusions for subsequent doses, while rituximab can be administered in an outpatient setting.

9.19 The Subcommittee noted that patients receiving treatment with rituximab receive a body-surface-area adjusted dose with each cycle of chemotherapy, plus a single dose of rituximab monotherapy every 8 weeks for two years. The Subcommittee also noted that patients receiving treatment with obinutuzumab received larger fixed doses and also received extra doses in the first cycle (3 doses in the first month), but that subsequent dosing frequency was the same as rituximab.

9.20 The Subcommittee noted results from the GAZELLE study, presented at ASCO 2021, which demonstrated that patients could receive 90 minute infusions from the second cycle onwards, without an increase in grade III to V adverse events (Hubel et al. International Conference on Malignant Lymphoma. 2021;39:Supplement). The Subcommittee considered that this would translate to a benefit for patients and infusion services.

9.21 The Subcommittee noted that the response rates, survival outcomes and treatment complications are similar between rituximab and obinutuzumab, but that obinutuzumab treatment decreases the proportion of patients with POD24. The Subcommittee considered that the most benefit would be seen in the small group of patients that experienced POD24 while receiving rituximab that may have otherwise not if they had received obinutuzumab. The Subcommittee considered that on balance, the benefit of obinutuzumab in this patient population would be difficult to model due to the lack of overall survival benefit, uncertain long-term benefit and lack of improvements in quality of life for obinutuzumab compared to rituximab.

9.22 The Subcommittee considered that funding obinutuzumab for this indication would not materially impact health-sector expenditure as while time to next treatment is delayed, there is no demonstrable increased survival for patients after 5 years.

9.23 The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for obinutuzumab if it were to be funded in New Zealand for the treatment of follicular lymphoma. 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 Subcommittee'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	Previously untreated follicular lymphoma
Intervention	Obinutuzumab based therapy During the induction phase, a 1,000 mg vial is administered on days 1, 8, and 15 of Cycle 1 and on day 1 of Cycles 2 to 8 (21-day cycles) or Cycles 2 to 6 (28-day cycles) depending on the companion chemotherapy

	Patients achieving a complete response (CR) or partial response (PR) at the end of induction should continue to the maintenance/monotherapy phase, which consists of a 1,000 mg vial every 2 months until disease progression or up to 2 years. The following companion chemotherapy regimens are recommended for the administration of obinutuzumab during the induction phase: • Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (6 cycles of 21 days plus 2 cycles of 21 days monotherapy, without CHOP) • Cyclophosphamide, vincristine, and prednisone (CVP) (8 cycles of 21 days) • Bendamustine (6 cycles of 28 days).
Comparator(s)	Rituximab based therapy During the induction phase, a dose of 375 mg per square meter of body-surface area on day 1 of each cycle, for 6-8 cycles depending on the companion chemotherapy (as above). Patients achieving a complete response (CR) or partial response (PR) at the end of induction should continue to the maintenance/monotherapy phase, which consists of 375 mg of rituximab per square meter every 2 months for 2 years or until disease progression.
Outcome(s)	PFS gain as shown in GALLIUM trial (hazard ratio [HR] 0.76; 95% CI: 0.62–0.92; p=0.0043; 5-year PFS: 70.5% [95% CI: 66.4–74.1] vs 63.2%) Postponed requirement for salvage therapies.
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 Apalutamide – Prostate cancer, non-metastatic, castration-resistant, high risk

Application

10.1 The Subcommittee considered the application from Janssen-Cilag Pty Ltd for apalutamide for high-risk, non-metastatic, castration-resistant prostate cancer (nmCRPC), following review of the application by PTAC in February 2020 and September 2020, and review of subsequent correspondence from the supplier by PTAC at its February 2021 meeting.

10.2 The Subcommittee noted that there were specific areas for which PTAC considered Pharmac should seek CaTSoP's advice in relation to the application.

10.3 The Subcommittee noted that Pharmac received further correspondence in April 2021 and in September 2021 from the supplier (Janssen-Cilag Pty Ltd) about this application.

Recommendation

10.4 The Subcommittee **recommended** that apalutamide for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer, within the context of treatment of malignancy, with a **high priority** subject to the following Special Authority criteria:

> **APALUTAMIDE**
> **Initial application – (high-risk non-metastatic castration resistant prostate cancer)** only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:

1. Patient has prostate cancer; and
2. Patient does not have distant metastasis, confirmed radiologically by CT scan or similar; and
3. Patient's disease is castration resistant; and
4. Patient has a PSA doubling time of 10 months or less during continuous ADT; and
5. Either:
    5.1. Apalutamide is to be used in combination with androgen deprivation therapy (a gonadotrophin-releasing hormone [GnRH] analogue); or
    5.2. Patient has had a bilateral orchiectomy; and
6. Patient has not had prior subsidised treatment with apalutamide.

Renewal – (high-risk non-metastatic castration resistant prostate cancer) only from a medical oncologist, radiation oncologist, urologist or medical practitioner on the recommendation of a medical oncologist, radiation oncologist or urologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient does not have distant metastasis; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

10.5 In making its recommendation, the Subcommittee considered that:

- There was high-quality randomised controlled trial evidence for a health benefit from apalutamide in terms of overall survival and metastasis-free survival
- Quality of life was improved with apalutamide maintenance treatment likely due to increased metastasis-free survival (MFS) with apalutamide
- Oral treatment with apalutamide would also provide benefits simply due to its convenient formulation, noting concurrent or subsequent treatments for this patient population are injected or infused (ie goserelin or docetaxel)
- Māori and Pacific peoples experience worse outcomes from prostate cancer and are more likely to present with high-risk, non-metastatic, castration-resistant prostate cancer (nmCRPC) disease than non-Māori and non-Pacific peoples.

Discussion

10.6 The Subcommittee noted the prior review of this application as follows:

10.6.1 In February 2020, PTAC reviewed the application and recommended it be deferred due to the lack of a statistically significant change in overall survival (OS), which the Committee considered to be the primary potential benefit of apalutamide, and no reported evidence for quality of life improvement with apalutamide. At that time, PTAC requested Pharmac seek specific advice from CaTSoP to assist in its assessment of the application.

10.6.2 In September 2020, PTAC noted the supplier's response to its February 2020 record, reiterated its previous recommendation to defer the application, and considered that specialised advice from CaTSoP (in the setting of emerging evidence for other similar agents for this indication) remained important to inform assessment of this application. At that time, PTAC noted that, although a health benefit of apalutamide was reported in terms of OS in the SPARTAN trial, there remained reservations about the validity of the estimate of OS in that trial. PTAC also considered that there was an ongoing lack of reported evidence for quality-of-life improvement with apalutamide

and that no additional health-related quality of life data was provided for assessment.

10.6.3 In February 2021, PTAC noted a letter from the supplier regarding the evaluation of the statistical methods utilised in the analysis of the SPARTAN trial. Members considered that there remained some concern regarding the alpha-spending (with potential false positive results) but considered that the survival analyses conducted to account for crossover of patients from placebo to the apalutamide group did support an OS advantage for apalutamide. PTAC had noted that this data was formally published in a peer-reviewed journal and considered that this could be used by Pharmac in a cost-effectiveness analysis of apalutamide. PTAC had noted that the supplier had not provided data summaries that would support a critical appraisal of the views the supplier expressed regarding health-related quality of life for patients receiving apalutamide treatment. PTAC had considered that further advice should still be sought from CaTSoP.

10.7 The Subcommittee noted that Pharmac received correspondence from the supplier in April 2021 (in response to the February 2021 PTAC record) and received further information from the supplier in September 2021 regarding the application for apalutamide, including the 2021 publication of the final OS analysis.

10.8 The Subcommittee noted the high rate of prostate cancer in New Zealand and recognised the health needs of patients with castrate-resistant prostate cancer (CRPC) as previously discussed by PTAC. The Subcommittee noted that there is slightly lower incidence of prostate cancer in Māori compared with non-Māori, but that Māori are more likely to present with advanced disease and therefore have a higher mortality rate. The Subcommittee considered the application for apalutamide targeted a specific population with poor prognosis from prostate cancer and considered that Māori and Pacific peoples more often present at this point in the disease course.

10.9 The Subcommittee noted that the application was for apalutamide for patients whose non-metastatic prostate cancer is no longer responding to androgen deprivation therapy (ADT) (ie castration-resistant) and that ADT would continue alongside treatment with apalutamide. The Subcommittee noted that there are no specific funded treatments for non-metastatic CRPC (nmCRPC). The Subcommittee noted that patients with metastatic disease may receive docetaxel chemotherapy and may be eligible to receive abiraterone acetate.

10.10 The Subcommittee noted the prognostic value of the PSA doubling time (PSADT) in identifying patients at high risk of disease progression, with shorter doubling times representing a worse prognosis. The Subcommittee noted the application proposed a PSADT of 10 months for apalutamide eligibility; members noted that this threshold correlated with a sharp increase in the risk of death from metastatic disease in prostate cancer, as published by Smith et al. (J Clin Oncol. 2013;31:3800-6). The Subcommittee noted that the PSADT threshold used internationally varies between eight to 10 months but that a shorter timeframe of six months is often used in some clinical practice.

10.11 The Subcommittee noted that routine PSA monitoring is performed 3-monthly in New Zealand for patients at high risk of disease progression. On balance, the Subcommittee considered it would be appropriate to use a PSADT of 10 months to identify the high-risk population in the funding criteria for apalutamide because this aligns with the evidence base and would not inappropriately exclude any patients whose PSA doubling occurred between six and 10 months.

10.12 The Subcommittee considered that the supplier's estimate of about 90 patients per year who would be eligible for apalutamide was likely too high based on clinical practice, noting that only about 10 patients per year in Auckland would fit the criteria. The Subcommittee noted that 29% of patients in the SPARTAN trial had a PSADT of between six to 10 months and considered that even with such patients included in the estimate, the true number of eligible patients would be less than proposed. The Subcommittee considered that any increase in access to more sensitive screening methods (eg PSMA PET-CT, currently self-funded) would affect patient numbers by earlier detection of metastatic disease, creating further uncertainty around this number.

10.13 The Subcommittee noted that the evidence for the safety and efficacy of apalutamide comes from the phase III, randomised (2:1) SPARTAN trial, as considered previously by PTAC in February 2020, September 2020 and February 2021. The Subcommittee considered that SPARTAN was a high-quality study and noted that it included participants from the Asia Pacific region but not New Zealand. The Subcommittee noted that 70% of participants had PSADT of less than six months and that participant characteristics were well balanced across the treatment groups. The Subcommittee considered that the key outcome of clinical importance was metastasis-free survival (MFS), and the Subcommittee considered this outcome measure would include bone-related endpoints.

10.14 The Subcommittee noted that median MFS in the SPARTAN primary analysis was 40.5 months with apalutamide vs 16.2 months with placebo (hazard ratio [HR] 0.28; 95% CI: 0.23 to 0.35; P<0.001), although the number of patients remaining in follow-up after 24 months was low (Smith et al. N Engl J Med. 2018:378;1408-18). The Subcommittee considered there was a benefit in MFS from apalutamide regardless of whether PSADT was <6 months or >6 months, supporting apalutamide treatment for those with PSADT of up to 10 months. The Subcommittee noted that the median time to symptomatic disease progression was not reached in either group.

10.15 The Subcommittee noted that overall survival (OS) was a secondary endpoint of SPARTAN and that the final OS analysis was performed after median 50.4 months follow-up (Smith et al. Eur Urol. 2021;79:150-8). As noted by PTAC in September 2020, the authors reported a hazard ratio (HR) for death of 0.78 with apalutamide compared with placebo (95% CI: 0.64 to 0.96; P= 0.016) in the intention-to-treat population with the P value crossing the prespecified O'Brien-Fleming boundary of 0.046; after adjustment for patient crossover from placebo to apalutamide the reported exploratory OS sensitivity analyses' results was (HR 0.69 [95% CI: 0.56 to 0.84]; nominal P = 0.0002). The Subcommittee considered that the trial's statistical analysis was appropriately designed with hierarchical testing of outcomes at interim and final analyses, and with adjusted OS analyses appropriately accounting for treatment crossover. The Subcommittee considered that this provided evidence of an OS benefit from apalutamide in nmCRPC.

10.16 The Subcommittee considered that treatment with apalutamide was well tolerated by SPARTAN trial participants who would otherwise have received ADT alone. The Subcommittee noted that a small proportion of patients discontinued treatment due to adverse events and considered that these events were similar between groups in terms of their management and cost, with rash being the most significant event requiring additional management (GP visits or oncology phone consultation) and tending to occur early in the treatment course.

10.17 The Subcommittee considered that preserving health-related quality of life (HRQoL) was particularly important for patients with nmCRPC during the periods of time between lines of chemotherapy. The Subcommittee noted that HRQoL was not

diminished during maintenance treatment with apalutamide in SPARTAN, and that some HRQoL measures (FACT-P; FACT-G) decreased at relapse as expected (Oudard et al. Prostate Cancer. 2021; EUF-1177). The Subcommittee noted that HRQoL appeared similar between treatment groups until around 18 months, where HRQoL improved with apalutamide maintenance treatment compared with a decrease in HRQoL in the placebo group; the Subcommittee considered this was likely due to increased MFS with apalutamide as opposed to any treatment-specific difference not related to MFS. The Subcommittee considered that this evidence was reasonable for its assessment of the benefit of apalutamide maintenance treatment and that no further HRQoL information was required.

10.18 Overall, the Subcommittee considered that SPARTAN provided evidence of a clinically meaningful benefit in metastasis free survival MFS and an OS benefit from treatment with apalutamide in nmCRPC across all subgroups, with no decrement in HRQOL during maintenance treatment with apalutamide and a tolerable side effect profile.

10.19 The Subcommittee noted the meta-analysis of apalutamide, darolutamide and enzalutamide in nmCRPC (Roumiguié et al. Future Oncol. 2021;17:1811-23). The Subcommittee considered that a cross-trial comparison of these treatments was limited by differences between the clinical trials (eg less chemotherapy received by SPARTAN trial patients and three-quarters of SPARTAN participants subsequently receiving abiraterone acetate with prednisone). However, the Subcommittee considered that survival appeared similar with apalutamide, darolutamide and enzalutamide in nmCRPC and that there may be a class effect among these treatments in this setting with no clear superiority of one treatment over the others. The Subcommittee considered that there may be differences between these treatments in toxicity profiles and their binding properties in the presence of androgen receptor mutations, as noted by PTAC in September 2020.

10.20 The Subcommittee noted that there was an absence of direct evidence to inform the optimal sequencing of apalutamide and abiraterone acetate (which have different mechanisms of action), although some retrospective studies have looked at sequential use and combination use of these treatments. The Subcommittee considered that about 10% of patients may respond to a second therapy and that chemotherapy in between treatments did not appear to offer much additional benefit, although there may be differing views among clinicians. The Subcommittee noted that New Zealand clinicians have experience using abiraterone acetate but considered it was unclear whether abiraterone would be preferred over apalutamide, if both were funded; providing options for metastatic and non-metastatic treatment, respectively; and considered that the best time to use these treatments remained unclear.

10.21 The Subcommittee noted that Pharmac had received funding applications for abiraterone acetate to be used in other indications including hormone sensitive prostate cancer and considered that the application for apalutamide would not affect those indications that are at an earlier point in the disease course. The Subcommittee considered that funding apalutamide for nmCRPC would change the subsequent use of abiraterone acetate for metastatic CRPC (mCRPC) and 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 Subcommittee noted that it would be reasonable for apalutamide to be prescribed by Medical Oncologists, Radiation Oncologists or Urologists, therefore facilitating access across the country from a range of specialist prescribers.

10.22 The Subcommittee considered that radiologic confirmation of non-metastatic disease by CT scan or better (including PSMA PET-CT) would be appropriate to confirm eligibility for funded apalutamide, The Subcommittee considered that monitoring on treatment might include annual imaging if PSA was rising or if there were clinical concerns, however, adding a requirement for radiologic confirmation of non-metastatic disease at renewal would not be appropriate.

10.23 The Subcommittee considered that no additional radiotherapy would be expected with apalutamide as a result of prolonging the time to development of metastasis.

10.24 The Subcommittee considered the type of clinic resource use to manage patients with nmCRPC receiving apalutamide would vary around the country as patients may be monitored by Medical Oncology, Radiation Oncology or Urology depending on the region. The Subcommittee considered that the supplier's estimated resource use was too frequent and that patients might initially have Medical Oncology or GP visits (potentially via phone or Zoom to assess toxicity after one month on treatment, with management for patients who experience rash), followed by three-monthly PSA monitoring and specialist clinic visits every three to four months on average. The Subcommittee considered that management of rash would not be expected to require a hospital visit or incur substantial additional cost.

10.25 The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for apalutamide if it were to be funded in New Zealand for high-risk, non-metastatic, castration-resistant prostate cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee'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 castration-resistant prostate cancer with no distant metastasis and who are at a high risk of developing distant metastases as defined by a PSA doubling time of ≤10 months (HR nmCRPC).
Intervention	Apalutamide (oral tablets) + androgen deprivation therapy (ADT) - The recommended dose of apalutamide is 240mg (four 60mg tablets) administered orally once daily. Treatment ongoing until evidence of metastatic disease.
Comparator(s)	ADT only (goserelin (1x10.8mg subcutaneous injection every 12 weeks)
Outcome(s)	The key therapeutic intent of apalutamide is to delay or prevent metastasis, therefore delaying the decline in quality of life, and reducing risk of death. Key outcome: MFS (see 2018 SPARTAN trial, Smith et al)
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 Enzalutamide - Metastatic castration resistant prostate cancer (sub-group consideration)

Application

11.1 The Subcommittee noted that Pharmac received a funding application from Seqirus (NZ) Ltd for the listing of enzalutamide for the treatment of patients with metastatic

castration-resistant prostate cancer (mCRPC) in May 2016 and that the application was:

11.1.1 Reviewed by PTAC in August 2016, who recommended enzalutamide be funded only if cost neutral to abiraterone acetate, subject to the same Special Authority criteria as abiraterone

11.1.2 Reviewed by CaTSoP in March 2017, who noted and agreed with PTAC and recommended the duration of Special Authority approval in the enzalutamide and abiraterone criteria be amended to six months

11.1.3 Included in Pharmac's October 2020 proposal to decline currently inactive funding applications for medicines that may provide no additional benefits over other funded treatments (in this instance, abiraterone acetate) and for which it is unlikely that the required pricing can be achieved to enable the application to be progressed for funding.

11.2 The Subcommittee noted that Pharmac received responses from consumer experts, clinicians and the supplier of enzalutamide in response to its October 2020 proposal to decline currently inactive funding applications and that the responses supported keeping the application open. The Subcommittee noted that a key element of this feedback was the unmet health need of patients with mCRPC for whom abiraterone acetate is contraindicated and/or not tolerated and noted that Pharmac sought advice from the Subcommittee in light of this new information.

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

Recommendation

11.4 The Subcommittee **recommended** that enzalutamide for patients with metastatic castration-resistant prostate cancer who cannot tolerate abiraterone acetate be funded with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

ENZALUTAMIDE

Special Authority for Subsidy

Initial Application only from a Medical Oncologist, Radiation Oncologist or Urologist or any other 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 prostate cancer; and
2. Patient has metastases; and
3. Patient's disease is castration resistant; and
4. Any of the following:
    - 4.1. All of the following:
        - 4.1.1. Patient is symptomatic; and
        - 4.1.2. Patient has disease progression (rising serum PSA) after second line antiandrogen therapy; and
        - 4.1.3. Patient has ECOG performance score of 0-1; and
        - 4.1.4. Patient has not had prior treatment with taxane chemotherapy; and
        - 4.1.5 Patient has not had prior treatment with abiraterone; or
    - 4.2. All of the following:
        - 4.2.1. Patient's disease has progressed following prior chemotherapy containing a taxane; and
        - 4.2.2. Patient has ECOG performance score of 0-2; and
        - 4.2.3. Patient has not had prior treatment with abiraterone; or
    - 4.3 Both:
        - 4.3.1 The patient has discontinued abiraterone within 3 months of starting treatment due to significant intolerance; and
        - 4.3.2 The cancer did not progress whilst on abiraterone; and

5. Abiraterone treatment is contraindicated; and
6. Enzalutamide to be administered in combination with androgen deprivation therapy.

Renewal only from a Medical Oncologist, Radiation Oncologist or Urologist or any other 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. Significant decrease in serum PSA from baseline; and
2. No evidence of clinical disease progression; and
3. Enzalutamide to be administered as monotherapy; and
4. The treatment remains appropriate and the patient is benefiting from treatment.

11.5 In making this recommendation, the Subcommittee considered the unmet health needs of the patient subgroup with mCRPC who are intolerant of, or contraindicated to, abiraterone acetate, as these patients would not be candidates for docetaxel either and therefore would have no other effective treatment options for their castrate-resistant disease, given androgen deprivation therapy (ADT) provides limited benefit in this state.

11.6 The Subcommittee considered that if enzalutamide were funded for this subgroup with mCRPC, it would be reasonable for Pharmac to review enzalutamide usage within a year from the start of funding.

Discussion

11.7 The Subcommittee noted that in August 2016, PTAC reviewed the application for enzalutamide for mCRPC and had recommended enzalutamide be funded only if cost neutral to abiraterone acetate, subject to the same Special Authority criteria as abiraterone. The Subcommittee noted that PTAC had considered that although there were no head-to-head trials comparing abiraterone with enzalutamide, and taking into account different drug interaction profiles, it was reasonable to consider them clinically equivalent in the treatment of mCRPC. The Subcommittee considered that PTAC's review indicated that the evidence for benefits from enzalutamide, including health-related quality of life (HRQOL), was relevant to the New Zealand population and of good quality

11.8 The Subcommittee noted the feedback relating to enzalutamide for mCRPC that was received in response to Pharmac's October 2020 proposal to decline currently inactive funding applications, including the response from clinicians in Auckland who considered that those who can't have abiraterone should have access to enzalutamide because this small proportion of patients would have no other treatment options. The Subcommittee noted that the consumer feedback from the Prostate Cancer Foundation suggested that access to enzalutamide or abiraterone would be great for patients with mCRPC.

11.9 The Subcommittee noted that Pharmac sought advice from CaTSoP regarding the health need of the subgroup of patients with mCRPC for whom abiraterone acetate is contraindicated or where patients are intolerant to abiraterone treatment eg due to hepatotoxicity or pre-existing liver disease, and the evidence for enzalutamide in this patient subgroup.

11.10 The Subcommittee noted that there are higher rates of hepatitis and chronic liver disease in Māori and Pacific peoples than non-Māori and non-Pacific people, and higher rates in people living in areas of higher deprivation. The Subcommittee considered that intolerances or contraindications to abiraterone that prevent the safe and effective use of funded abiraterone in these populations would have the potential to increase inequitable outcomes.

11.11 The Subcommittee noted that abiraterone acetate is funded with Special Authority criteria and that patients with mCRPC may also be able to receive chemotherapy with docetaxel, usually in combination with prednisone. However, the Subcommittee considered that docetaxel has variable use around the country and might be used in select cases where a clinician has a strong preference for its use (eg as initial treatment for patients with greater disease volume or activity, or those with visceral involvement). The Subcommittee considered that if a contraindication or intolerance results in a patient not being suitable for abiraterone then they are unlikely to be suitable for docetaxel for the same reason, and therefore would have no effective treatment options.

11.12 The Subcommittee noted that liver function test (LFT) abnormalities are known treatment-related toxicities that can occur with abiraterone and with docetaxel. The Subcommittee considered that abiraterone could be contraindicated due to liver disease, hypertension or adrenocorticoid deficiency, although those toxicities could also develop whilst on treatment and such cases would be challenging to disentangle. The Subcommittee considered that a significant intolerance to abiraterone acetate such as grade 3 or 4 hepatotoxicity, heart failure, or fluid retention could result in hospitalisation and/or a decrease in HRQOL. The Subcommittee considered that the clinical trial evidence suggests only 1% of patients would discontinue abiraterone acetate due to unmanageable intolerance.

11.13 The Subcommittee considered that even for those with mCRPC with pre-existing liver disease, most clinicians would commence treatment with abiraterone acetate and closely monitor patients on treatment with an intensity of monitoring relative to the extent of liver disease. The Subcommittee considered that clinicians would try to manage intolerances that arise (eg LFT abnormalities) with dose reductions and therefore that a confirmed intolerance could be observed within the first three- to six months from the start of treatment with abiraterone acetate. The Subcommittee considered that, for patients experiencing a significant intolerance, it would be reasonable for Pharmac to assume that in most cases this would occur within the first three months on abiraterone, as this would align with patient assessment at three-monthly clinic visits.

11.14 The Subcommittee considered that in practice, few patients with mCRPC experience intolerance to abiraterone acetate that cannot be effectively managed and even fewer would have a contraindication that precluded treatment with abiraterone. The Subcommittee considered that it was reasonable to estimate that 10% of patients in the LATITUDE trial of abiraterone plus prednisone in mCRPC (Fizazi et al. N Engl J Med 2017; 377:352-60) might have been excluded at screening due to hepatotoxicity (ie 2.9% of the intention-to-treat population). The Subcommittee noted that about five patients per year in Auckland would be contraindicated to abiraterone and only one or two patients per year would be intolerant to abiraterone, and that smaller numbers per capita would be seen around the rest of the country, since Auckland is a treatment hub serving about 38% of the population. The Subcommittee considered that these assumptions supported an estimate of approximately 20 patients per year nationwide who would be contraindicated to or intolerant of abiraterone, which was lower than Pharmac's estimate of about 33 patients per year.

11.15 The Subcommittee noted the evidence for enzalutamide in mCRPC that had been reviewed and detailed previously by PTAC in August 2016; specifically, from the PREVAIL and AFFIRM trials:

11.15.1 The Subcommittee noted that the first-line PREVAIL trial (Beer et al. NEJM 2014;371:424-33) reported a clear progression-free survival benefit

(PFS) with enzalutamide, but that the overall survival (OS) was not clinically that different to placebo. For PREVAIL, patients were excluded if they had total bilirubin, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper limit of normal (ULN).

11.15.2 The Subcommittee noted that the second-line AFFIRM trial (Scher et al. NEJM 2012;367:1187-97) reported both a PFS and OS benefit. For AFFIRM, patients were excluded if they had total bilirubin, ALT or AST > 2 times the ULN.

11.16 The Subcommittee noted a recent publication of five-year survival data from the PREVAIL trial, which reported the hazard ratio for death with enzalutamide vs placebo was 0.83 (95%CI: 0.75 to 0.93; P< 0.001). (Armstrong et al. Eur Urol. 2020;78:347-57).

11.17 The Subcommittee noted that the PREVAIL and AFFIRM data supported the use of enzalutamide in patients with mCRPC although there appeared not to be any specific data for enzalutamide use in patients who were intolerant of or contraindicated to abiraterone. The Subcommittee noted that the Child-Pugh score, a composite score which can be used to indicate mild, moderate or severe liver disease, was referenced in the Medsafe data sheet for abiraterone acetate although the score is not used in clinical practice in New Zealand nor was it used in the enzalutamide clinical trials. The Subcommittee noted that the clinical trials used standard thresholds for liver function, and patients with liver disease were generally excluded.

11.18 The Subcommittee also noted the following evidence:

- Alumkal et al. Clin Genitourin Cancer. 2017;15:610-17.e3
- Zhu et al. Expert Rev Anticancer Ther. 2018;18:193-8

11.19 The Subcommittee noted that there remains an absence of direct comparative, randomised controlled trial evidence for enzalutamide compared with abiraterone acetate in mCRPC. The Subcommittee considered that the available evidence suggests similar median OS would be expected from each of the two treatments and that there would be similar benefits across patient subgroups, although there was no evidence to suggest that any group would receive a greater benefit from either enzalutamide or abiraterone acetate than any other group.

11.20 The Subcommittee considered that there were some advantages of enzalutamide due to its toxicity profile compared with abiraterone acetate, although central nervous system toxicities were reported with enzalutamide including seizures (in <1%) and falls. The Subcommittee noted that in the subset of patients with visceral liver or lung disease that there were no increased rates of elevated ALT compared with the overall trial population. The Subcommittee considered that the number of patients who discontinued enzalutamide in the clinical trials was relatively low. The Subcommittee considered that enzalutamide offers a treatment option that doesn't have the same risk of LFT abnormalities that can occur with abiraterone acetate (or docetaxel) and considered that there is evidence that enzalutamide would provide a PFS benefit for entire population with mCRPC.

11.21 The Subcommittee considered that the available evidence did not define the target subgroup of patients who were intolerant of or contraindicated to abiraterone. Neither did it provide specific evidence for the safety and efficacy of enzalutamide in that subgroup as opposed to the wider population with mCRPC, nor identify any groups disproportionately affected by contraindications to or intolerance of abiraterone.

However, the Subcommittee considered that there was no evidence to suggest that the efficacy of enzalutamide would be any different in the poorly defined subgroup of people who were intolerant of or contraindicated to abiraterone than the overall population in the trials.

11.22 The Subcommittee noted that there was a lack of good quality evidence to inform the optimal sequencing of treatments with abiraterone acetate and enzalutamide, and noted the following evidence:

- Khalaf et al. Lancet Oncol. 2019;20:1730-9
- Attard et al. J Clin Oncol. 2018;36:2639-46
- Loriot et al. Ann Oncol. 2013;24:1807-12
- Noonan et al. Ann Oncol. 2013;24:1802-07
- de Bono et al. Eur Urol. 2018;74:37-45
- Bianchini et al. Eur J Cancer. 2014;50:78-84
- Schrader et al. Eur Urol. 2014;65:30-6
- CADTH Health Technology Review: Treatment Sequences of Androgen Receptor–Targeted Agents for Prostate Cancer. 2021; Canadian Journal of Health Technologies

11.23 The Subcommittee considered that the evidence provided by Khalaf et al. represented the most robust data which suggested that abiraterone acetate followed by enzalutamide provided better outcomes than the reverse. However, the Subcommittee noted that the chance of receiving a response to a second treatment after disease progression was low. The Subcommittee noted that in the treatment setting being considered, patients with mCRPC would either not have received abiraterone or only received abiraterone briefly until it was intolerable (as opposed to continuing until progression). The Subcommittee considered that it was likely that treatment with enzalutamide after more than three months treatment with abiraterone acetate would provide a lesser benefit and that this available evidence for sequencing supported the proposed three-month timeframe for an intolerance in the funding criteria for enzalutamide.

11.24 The Subcommittee noted that enzalutamide would provide suitability benefits as it is an oral medicine that could enable treatment closer to home, improving quality of life for this subgroup with mCRPC. The Subcommittee noted that enzalutamide would be used in combination with ADT rather than replacing ADT and considered that no other treatments would be expected to be used at the same time. The Subcommittee considered that monitoring whilst on enzalutamide would be done more frequently than for patients receiving ADT alone, with extra clinic visits required while they were on treatment similar to what is performed for patients receiving abiraterone. The Subcommittee considered that no additional resource for management of AEs would be expected as this would be similar to the standard of care already provided. The Subcommittee considered that patients would have blood tests three-monthly and radiologic scans performed as clinically indicated. The Subcommittee considered that patients with mCRPC would likely receive palliative care after disease progression (eg radiotherapy to metastatic bone lesions and medicine for pain) although there was no evidence to suggest that the rate of palliative radiotherapy would change with

enzalutamide treatment. Members considered that the need for radiation therapy may be delayed due to improved disease control.

11.25 The Subcommittee considered that docetaxel would not be a comparator treatment option for the subgroup of patients who are intolerant of or contraindicated to abiraterone acetate, as they are unlikely to be candidates for docetaxel for the same reason. The Subcommittee considered that the estimate of 18% of patients receiving docetaxel upfront before use of enzalutamide (if funded) was plausible. The Subcommittee considered that for low volume disease there would likely be a preference to use abiraterone or enzalutamide ahead of docetaxel, unless there were concerns about disease activity or visceral involvement. The Subcommittee considered that approximately 30% of patients who would receive enzalutamide might not receive docetaxel subsequently, primarily due to comorbidities or the same contraindication they had to abiraterone.

11.26 The Subcommittee considered that the funding criteria for enzalutamide for patients with mCRPC who are contraindicated to or intolerant of abiraterone could target the intended population by requiring a significant intolerance, not further described, within the first three months of treatment with abiraterone. The Subcommittee considered that it would be reasonable for Pharmac to review enzalutamide usage within a year from the start of funding.

11.27 The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for enzalutamide if it were to be funded in New Zealand for patients with mCRPC who are contraindicated to or intolerant of abiraterone. 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 Subcommittee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with mCRPC who are contraindicated or intolerant to abiraterone, have not received previous treatment with enzalutamide. Criteria for treatment are described in the Special Authority criteria above.
Intervention	Enzalutamide administered orally at a dose of 160 mg (4 x 40mg capsules) daily, until unacceptable side effects or confirmed radiographic progression and initiation of chemotherapy. Enzalutamide would be administered in combination with ADT, per EviQ and the AFFIRM and PREVAIL trial protocols.
Comparator(s)	ADT, including: • Goserelin - 10.8mg subcutaneous injection 3 monthly • Bicalutamide 50mg od
Outcome(s)	The therapeutic intent of enzalutamide is to improve overall survival and improve health-related quality of life by extending the duration of progression free survival. Evidence is mainly from the AFFIRM (2nd line) and PREVAIL (1st line) trials, though most patients in the trial populations for these would be eligible for abiraterone, and patients in the population under consideration must be contraindicated or intolerant to abiraterone. The PREVAIL trial found OS of 32.4 months in the enzalutamide group and 30.2 months in the placebo group, and 12-month PFS of 65% and 14% in the two groups respectively. The AFFIRM trial found OS of 14.4 months in the enzalutamide group and 18.4 months in the placebo group.

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.

12 Ibrutinib - Waldenström macroglobulinemia

Application

12.1 The Subcommittee reviewed an application from Janssen for the treatment of first line and relapsed/refractory Waldenström macroglobulinemia (WM).

12.2 The Subcommittee also noted correspondence from a clinician which outlines the unmet need for a BTK inhibitor to treat patients with WM, among other conditions.

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

Recommendation

12.4 The Subcommittee **recommended** that ibrutinib for the treatment of first line Waldenström macroglobulinemia be listed with a **low** priority, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **IBRUTINIB**
> **Initial application – Waldenström Macroglobulinaemia (Lymphoplasmacytic Lymphoma)**
> Applications only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months.
> **Prerequisites** (tick boxes where appropriate):
> 1. The patient has Waldenström Macroglobulinaemia/Lymphoplasmacytic Lymphoma requiring treatment; and
> 2. The patient is treatment naïve; and
> 3. Patient has good performance status.
>
> **Renewal application**
> Applications only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months.
> **Prerequisites** (tick boxes where appropriate)
> 1. No evidence of clinical disease progression and
> 2. The treatment remains appropriate, and the patient is benefiting from treatment

12.5 In making this recommendation, the Subcommittee noted:

12.5.1 the health need of people with WM requiring first line therapy, particularly in those who are unfit for immunochemotherapy and the currently funded treatment options for this population group

12.5.2 the evidence of benefit and improved tolerability of ibrutinib over currently funded treatments for people with WM; although the Subcommittee recognised the absence of direct comparator randomised controlled trials

12.5.3 the improved suitability of an oral treatment option for this patient group if used as monotherapy

12.6 The Subcommittee **recommended** that ibrutinib for the treatment of patients with relapsed/refractory Waldenström macroglobulinemia be listed with a **medium**

priority, within the context of treatment of malignancy, subject to the following Special Authority criteria:

IBRUTINIB
Initial application – relapsed/refractory Waldenström Macroglobulinaemia (Lymphoplasmacytic Lymphoma)
Applications only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months.
Prerequisites (tick boxes where appropriate):

1. The patient has Waldenström Macroglobulinaemia/Lymphoplasmacytic Lymphoma requiring treatment; and
2. Patient has relapsed after or is refractory to a previous line of treatment; and
3. The patient is ibrutinib treatment naïve; and
4. Patient has good performance status.

Renewal application
Applications only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months.
Prerequisites (tick boxes where appropriate)

1. No evidence of clinical disease progression and
2. The treatment remains appropriate, and the patient is benefiting from treatment

12.7 In making this recommendation, the Subcommittee considered:

12.7.1 The health need for those with relapsed/refractory WM including those with early relapse or refractory disease who have fewer treatment options following first line treatment

12.7.2 The evidence of benefit of ibrutinib compared to currently funded treatment options for patients with relapsed/refractory WM; although the Subcommittee recognised the absence of direct comparator randomised controlled trials

12.7.3 The improved suitability of an oral treatment option for this patient group if used as monotherapy.

Discussion

12.8 The Subcommittee noted that the supplier had submitted an abbreviated clinical summary in 2018 to consider funding ibrutinib for patients with WM, which had not previously been considered by CaTSoP or PTAC. The Subcommittee noted that there have been no previous considerations of specific treatments for WM in isolation, however Pharmac currently funds several treatments for patients with indolent lymphomas (eg WM), including bendamustine and rituximab (funded under Special Authority).

12.9 The Subcommittee noted that lymphoplasmacytic lymphoma is an incurable low-grade B-cell non-Hodgkin lymphoma characterised by the infiltration of bone marrow +/-spleen or lymph nodes by a clonal B cell population. The Subcommittee noted that when lymphoplasmacytic lymphoma is associated with an IgM paraprotein, it is referred to as Waldenström macroglobulinemia. For the purposes of the record, WM will be used to reference both lymphoplasmacytic lymphoma and Waldenström macroglobulinaemia. (Leukaemia Foundation Australia 2021).

12.10 The Subcommittee noted that WM is a heterogenous condition. The Subcommittee noted that asymptomatic patients should undergo monitoring and only require treatment if symptomatic disease develops. The Subcommittee noted that WM can cause anaemia, pancytopenia, symptomatic organomegaly or B-symptoms from tissue infiltration, and that symptomatic disease can result from IgM paraprotein associated disorders including hyperviscosity, cold agglutinin

disease, peripheral neuropathy, or cryoglobulinaemia. The Subcommittee noted that these symptoms may impact an individual's quality of life and ability to carry out daily activities. Some complications of WM require urgent therapy, such as symptomatic hyperviscosity, moderate to severe haemolytic anaemia, and symptomatic cryoglobulinemia. The Subcommittee noted that WM is a progressive disease that results in impaired function and quality of life and can lead to early death.

12.11 The Subcommittee noted international estimates of WM incidence of 2-3 cases per million. The Subcommittee noted the supplier's estimate of approximately 12 patients diagnosed with relapsed/refractory WM per year in New Zealand. The Subcommittee considered this to be an underestimate, and that patient numbers in New Zealand could be double that estimated by the supplier. The Subcommittee noted WM is more common in men, and predominantly diagnosed in older patients with a median age at diagnosis of 68 years (Leukaemia Foundation Australia 2021). The Subcommittee noted that the relative incidence of WM in Māori and other disadvantaged groups compared to non-Māori was uncertain.

12.12 The Subcommittee noted that the currently funded treatments for those with WM include bendamustine-rituximab (preferred option), and rituximab-cyclophosphamide-dexamethasone (DRC), or rituximab monotherapy (in those with comorbidities or low tumour burden). The Subcommittee noted that the median progression free survival (PFS) is 69.5 months for bendamustine-rituximab treatment (Rummel et al. Lancet. 2013;381:1203-1210), 34 months (95% CI 23 to 'not reached') for first line DRC treatment (Kastritis et al. Blood. 2015;126:1392-1394),), and 35 months (95% CI 15 to 51) for DRC treatment in relapsed/refractory patients (Paludo et al. BJH. 2017;179:98-105), and 20.3 months for 8 cycles of single agent rituximab (comparator arm of iNNOVATE trial). The Subcommittee considered that patients with relapsed/refractory WM can be retreated with the previous chemotherapy regimen if this was effective in the previous line, an alternative chemotherapy regimen, or rituximab monotherapy. The Subcommittee considered that efficacy of treatment and PFS with each successive line of treatment would be expected to diminish. The Subcommittee noted that autologous or allogenic transplantation were infrequent therapies for patients with WM.

12.13 The Subcommittee noted the following publications as evidence of the use of currently funded agents for the treatment of WM:

- Zheng et al. Onco Targets Ther. 2019;12:2751-2766
- Walewski et al. Br J Haematol. 2020;188;898-906
- Laribi et al. Br J Haematol. 2018;186:146-149
- Kastritis et al. Blood. 2015;126:1392-4

12.14 The Subcommittee noted that bortezomib in combination with dexamethasone +/- rituximab has also been shown to be efficacious in patients with WM. It was noted that the long term follow up of a phase II study of bortezomib, dexamethasone, and rituximab (BDR) has shown a median PFS of 3.5 years, median duration of major response of 5.5 years, and OS rate of 66% at 7 years (Kastritis et al. ESMO. 2018; Gavriatopoulou et al. Blood. 2017;4:456-459). The Subcommittee noted that bortezomib is not currently funded for people with WM and considered that it would like to review bortezomib for the treatment of patients with WM at a future Cancer Treatments Subcommittee meeting.

12.15 The Subcommittee noted elderly patients with WM are more likely to have poorer outcomes due to their increased frailty, comorbidities, and susceptibility to developing adverse reactions to chemotherapy (Morel et al. Blood. 2009;113:4163-70). The Subcommittee also noted those with WM living in rural areas are more likely to experience difficulty in accessing treatment services and thereby more at risk of experiencing poor survival and health outcomes. The Subcommittee considered that the availability of an effective oral treatment option for this patient group would be particularly beneficial.

12.16 The Subcommittee considered the treatment options (rituximab in combination with chemotherapy) to be effective for fit patients with WM and therefore the health need for this group of treatment naïve patients was comparatively low. The Subcommittee considered that the health need for patients with WM is greater for those who are unfit or unable to receive rituximab in combination with chemotherapy due to their frailty or comorbidities, as well as those who have relapsed after, or are refractory to a prior line of treatment, due to the limited treatment options and shorter PFS in later lines of treatment.

12.17 The Subcommittee noted that ibrutinib is an inhibitor of Bruton tyrosine kinase (BTK), and effectively inhibits B-cell receptor and cytokine receptor pathways, thereby hindering malignant B-cell proliferation and survival *in vivo* as well as cell migration and substrate adhesion in vitro. The Subcommittee noted that ibrutinib is Medsafe approved for the treatment of patients with WM. The Subcommittee noted that the recommended dose of ibrutinib for WM is 420mg (three 140mg capsules) once daily until disease progression or if no longer tolerated by the patient, administered either as monotherapy or in combination with rituximab.

12.18 The Subcommittee noted that as ibrutinib can be self-administered by the patient or caregiver in the community, the burden of treatment delivery and need for repeated attendance at a hospital or outpatient facility would be reduced.

12.19 The Subcommittee noted that the key evidence for ibrutinib in the treatment of WM comes from two clinical trials, PCYC-1127-CA (iNNOVATE) and PCYC-1118E.

12.20 The Subcommittee noted that the iNNOVATE trial was a phase III randomised, double-blind, placebo-controlled trial which investigated ibrutinib plus rituximab compared to placebo plus rituximab in 150 adults with previously untreated (n=68) or treated (n=82) WM.

12.20.1 The Subcommittee noted the results of the final analysis of the iNNOVATE trial after a median follow up of 50 (range 0.5-63) months. The Subcommittee noted that the overall median PFS was not reached (95% CI 57.7 months to 'not evaluable' [NE]) in the ibrutinib-rituximab group and 20.3 months (95% CI 13.0 to 27.6) in the placebo-rituximab group. The Subcommittee noted that the median time to next treatment was not reached in the ibrutinib-rituximab group and 18 months in the placebo-rituximab group. The Subcommittee noted that the overall survival (OS) was not reached in either arm. The Subcommittee noted that the ibrutinib-rituximab group had a sustained haemoglobin improvement of 77% versus 43% in the placebo-rituximab group (P<0.0001) (Buske et al. J Clin Oncol. 2021).

12.20.2 The Subcommittee noted that in previously untreated patients, the 54-month PFS rate was not reached in either the ibrutinib-rituximab or placebo-rituximab arm, and that the 48-month PFS rate in these subgroups was 70% and 32%, respectively. It was noted that in previously treated patients, the

54-month PFS rate was 68% with ibrutinib-rituximab versus 20% with placebo-rituximab, with 48-month PFS rates of 71% and 20%, respectively. The Subcommittee noted that ibrutinib-rituximab treatment significantly reduced risk of progression or death versus placebo-rituximab across all prespecified subgroups within the previously treated population, including by serum IgM level, haemoglobin level, and MYD88 mutational status, and within most of these subgroups in the previously untreated population.

12.20.3 The Subcommittee noted that serious adverse events (AEs) occurred in 53% of the ibrutinib-rituximab group, 33% of the placebo-rituximab group, and 52% of the ibrutinib substudy group. The Subcommittee noted that the most common AEs in the ibrutinib substudy group were infections (47% at years 3-4; 50% at years 4-5), hypertension (29% at years 3-4; 36% at years 4-5), and diarrhoea (24% in years 3-4; 7% in years 4-5). The Subcommittee noted that 7 patients in the ibrutinib-rituximab group and 34 patients in the placebo-rituximab group discontinued treatment due to disease progression.

12.20.4 The Subcommittee noted 31 patients from the iNNOVATE trial who were refractory to treatment with rituximab were enrolled into an open label ibrutinib monotherapy substudy. The Subcommittee noted the results of the final analysis of the open label ibrutinib monotherapy substudy after a median follow up of 58 (range 9-61) months. The Subcommittee noted that the median PFS was 39 months (95% CI 25 to NE), with an estimated 18-month PFS of 86% and estimated 60-month PFS rate of 40%. The median OS was not reached (95% CI NE to NE) and the 60-month OS rate was 73% Trotman et al. Clin Cancer Res. 2021).

12.21 The Subcommittee also noted the following additional publications on the iNNOVATE trial:

- Dimopoulos et al. Lancet Oncol. 2017;18:241-250.
- Dimopoulos et al. N Engl J Med. 2018;378:2399-2410.
- Trotman et al. EHA. 2017 abstract.

12.22 The Subcommittee noted that the PCYC-1118E trial was a phase II open-label, prospective, single agent study which investigated ibrutinib monotherapy until disease progression or unacceptable toxicity in 63 symptomatic adults with WM who have received at least one prior treatment (median of two prior treatments) (Treon et al. J Clin Oncol. 2021;39:565-575.; Treon et al. N Engl J Med. 2015; 372:1430-40.). The Subcommittee noted that after a median follow up of 59 months (95% CI 40 to 60), the 5-year PFS was 54% (95% CI 39 to 67) and the 5-year OS was 87%. The Subcommittee noted that the overall response rate (ORR) was 90.5% and the major response rate was 79.4%. The Subcommittee noted that the most common grade 3 or higher AEs that occurred in more than one patient were neutropenia (15.9%), thrombocytopenia (11.1%), and pneumonia (3.2%). The Subcommittee noted that atrial fibrillation occurred in eight patients (12.7%) overall at a median of 15 months (range 3-38 months) after starting treatment.

12.23 The Subcommittee noted that Castillo et al 2021 reported on a phase II, single centre, prospective, single arm study which investigated ibrutinib monotherapy in 30 treatment naïve patients with WM (Castillo et al. Leukaemia. 2021). The Subcommittee noted that after a median follow up of 50 months, the median PFS was not reached and the 4-year PFS rate was 76%, and there was a non-significant lower 4-year PFS rate in patients with than without CXCR4 mutations

(59% versus 92%; P=0.06). The Subcommittee noted that the most common treatment-related AEs were fatigue, upper respiratory infection, and hematoma, and that atrial fibrillation occurred in 20% of patients.

12.24 The Subcommittee noted the additional evidence supporting the use of ibrutinib for patients with WM:

- Gustine, J., K. Meid, and T. Dubeau. American Society of Hematology. 2017 abstract
- Treon et al. ASH. 2017 abstract
- Castillo et al. Hemasphere. 2020;4
- Grunenberg et al. Future Oncol. 2019;15:2687-2697.
- Lim et al. Expert Opin Pharmacother. 2020;21:1555-1564.

12.25 The Subcommittee considered that the evidence provided supports the efficacy of ibrutinib for the treatment of first line and relapsed/refractory WM. The Subcommittee however considered that this evidence was limited, in that it does not include randomised controlled trials comparing ibrutinib to relevant rituximab combination chemotherapy (ie. bendamustine-rituximab or DRC). The Subcommittee considered that the efficacy of rituximab in combination with chemotherapy would be considerably greater than the comparator treatment in the iNNOVATE trial (rituximab monotherapy). The Subcommittee considered the efficacy (PFS) of ibrutinib for patients with previously untreated WM to be somewhat comparable to that of bendamustine-rituximab. The Subcommittee considered that in the absence of direct comparative trials, the benefit of ibrutinib over such comparators is uncertain.

12.26 The Subcommittee considered the toxicity profile of ibrutinib to be manageable and less than that of other currently funded treatments. The Subcommittee considered that the reduced toxicity and reduced treatment burden may correspond to a health-related quality of life benefit. The Subcommittee also considered the improved suitability of ibrutinib as an oral treatment as it allows treatment in the community and management of patients as outpatients. The Subcommittee considered that, when used in combination with rituximab, outpatient attendance for systemic rituximab treatment would be required for up to 8 cycles. The Subcommittee considered that comparators for ibrutinib were of fixed duration (6 cycles) of systemic therapy versus continuous therapy with ibrutinib.

12.27 The Subcommittee considered that for first line treatment of WM, ibrutinib would be of most benefit and may improve PFS for those with comorbidities who are unfit for more intensive rituximab-based chemotherapy regimens. The Subcommittee considered that this patient group would equate to approximately 25% of those with previously untreated WM but that this may vary depending on clinician preference.

12.28 The Subcommittee considered that there is unlikely to be new evidence for the use of ibrutinib for patients with WM, as BTK inhibitors are the standard of care for these patients in other international jurisdictions.

12.29 The Subcommittee considered that ibrutinib would be of particular benefit and would improve PFS for those with WM who relapse early after or are refractory to

rituximab-based chemotherapy, as these individuals have very limited current treatment options.

12.30 The Subcommittee noted the publications below of key clinical trial evidence for other BTK inhibitors for the treatment of WM to assess whether there is a class effect. The Subcommittee considered that a class effect is likely, with each BTK inhibitor presenting differing side effect profiles. The Subcommittee considered that it would welcome a funding application for the use of other BTK inhibitors for this patient group.

- Constantine et al. Blood. 2020;136:2038-2050.
- Sekiguchi et al. Cancer Sci. 2020;111:3327-3337.
- Owen et al. Lancet Haematol. 2020;7:112-121.

12.31 The Subcommittee considered that the response to ibrutinib treatment may also depend on the identified WM mutation subtype and that those with CXCR4 mutations may benefit more than other populations. The Subcommittee considered that CXCR4 subtyping is not currently included in routine WM testing. The Subcommittee considered that there may be changes in health sector expenditure if ibrutinib were funded, with increased testing for CXCR4 mutations to determine treatment preference especially for first line therapy.

12.32 The Subcommittee considered other health sector expenditure costs of ibrutinib would include additional clinic follow up for continuous therapy, outpatient care to manage side effects, and pharmacy dispensing services.

12.33 The Subcommittee considered that if funded, the number of patients receiving ibrutinib would increase over time due to continuous therapy and the long PFS. The Subcommittee considered that the estimated duration of treatment of 47.7 months used to assess the budget impact of ibrutinib is likely an underestimate and considered that patients with WM would likely continue treatment for longer than this. The Subcommittee noted that in the iNNOVATE trial, 45% of patients continued to receive ibrutinib in a commercial setting post-study, indicating that the duration of treatment may be much longer. The Subcommittee considered that if ibrutinib were funded, New Zealand patients may have lower discontinuation rates compared to that seen overseas and in clinical trials due to the lack of other currently funded treatment options available for WM. The Subcommittee considered that the treatment duration and disease course of WM is probably similar to the more well-evidenced CLL patient group treated with BTK inhibitors.

12.34 The Subcommittee considered that comparator treatments for patients who could receive rituximab in combination with chemotherapy would require fewer than two lines of treatment of finite duration over 5 years, consistent with the median PFS of 70 months for patients receiving bendamustine-rituximab and thus the relative cost of treatment compared with ibrutinib would likely be substantially less.

12.35 The Subcommittee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for ibrutinib if it were to be funded in New Zealand for WM. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Subcommittee'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	Relapsed/refractory WM patients with good performance status	First line WM patients with good performance status
Intervention	*Ibrutinib 420mg daily until disease progression combined with an initial 8-week course (two four-weekly cycles split 3 months apart) of rituximab 375mg/m^2.*	
Comparator(s) (NZ context)	Bendamustine-rituximab: 375mg/m^2 of rituximab on day 1 and 90mg/m^2 of bendamustine on days 1 and 2, repeated every 4 weeks, for a maximum of 6 cycles. Or Dexamethasone, rituximab and cyclophosphamide (DRC) every 3 week for 6 cycles OR Rituximab combined with vincristine and prednisone (RCVP) or combined with doxorubicin, vincristine, prednisone RCHOP every 3 weeks for 6 cycles OR Rituximab monotherapy with 6 cycles of rituximab as currently funded or: *8-week course (two four-weekly cycles split 3 months apart) of rituximab 375mg/m^2.*	Same as second line
Outcome(s)	Progression free survival Overall response rate Potential overall survival benefit	

Table definitions:

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

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

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

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

13 Pembrolizumab - Melanoma, Resected Stage III, Adjuvant treatment

Application

13.1 The Subcommittee considered an application from Merck Sharpe and Dohme (MSD) for the use of pembrolizumab (Keytruda) as monotherapy for the adjuvant treatment of resected stage III melanoma, following consideration of the application by PTAC in August 2019 and by CaTSoP in October 2019.

13.2 The Subcommittee noted that in February 2021, Pharmac received a letter from the Melanoma Network of New Zealand (MelNet) in support of publicly funded

pembrolizumab as an adjuvant therapy for patients with surgically resected stage III melanoma

13.3 The Subcommittee noted that Pharmac received updated evidence from the key clinical trial, Keynote-054, from the supplier in February 2021 and April 2021.

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

Recommendation

13.5 The Subcommittee **recommended** that pembrolizumab be funded for the adjuvant treatment of resected stage III melanoma with a **low priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **PEMBROLIZUMAB**
> **Initial application - (resected stage III malignant melanoma)** only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has resected stage IIIB, IIIC or IIID melanoma; and
> 2. Treatment must be adjuvant to complete surgical resection; and
> 3. Treatment must be initiated within 13 weeks of surgical resection, unless delay is necessary due to post-surgery recovery; and
> 4. Pembrolizumab must be administered as monotherapy; and
> 5. The patient must have an ECOG performance score of 0-1; and
> 6. Pembrolizumab to be administered at a fixed dose of 200 mg every 3 weeks.
>
> **Renewal - (resected stage III malignant melanoma)** only from a medical oncologist or on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of disease recurrence; and
> 2. Pembrolizumab must be administered as monotherapy; and
> 3. Pembrolizumab to be administered at a fixed dose of 200 mg for a maximum of 12 months; and
> 4. Treatment to be discontinued at signs of disease recurrence or at completion of 12 months total treatment course; and
> 5. Maximum of three renewals per patient.

13.6 In making this recommendation, the Subcommittee considered:

13.6.1 The unmet health need of people with stage III resected melanoma

13.6.2 That there appears to be a potential clinical benefit of adjuvant pembrolizumab in this setting, however, disease management and staging in the clinical trial evidence is not aligned with current practice in New Zealand.

13.6.3 An overall survival benefit with adjuvant pembrolizumab is uncertain and unlikely to become clear due to substantial crossover within the clinical trial

13.6.4 Adjuvant pembrolizumab is expected to incur a high cost to the pharmaceutical budget and health system resource

13.6.5 Adjuvant pembrolizumab may be associated with side effects including immune-related adverse events for patients who otherwise would not be receiving active treatment.

13.7 The Subcommittee considered that the second criterion of the current Special Authority criteria for pembrolizumab/nivolumab for metastatic (stage IV) melanoma would require

amendment if pembrolizumab were funded for adjuvant treatment of resected stage IIIB, IIIC, and IIID melanoma (proposed changes to relevant Special Authority criteria are shown below in **bold** and ~~strikethrough~~ as applicable):

2. Patient did not experience a recurrence while on treatment or within six months of completing prior therapy with ~~pembrolizumab~~ **a PD-1/PD-L1 inhibitor** in the resected stage III setting; and

Discussion

13.8 The Subcommittee noted that the application for pembrolizumab for the adjuvant treatment of resected stage III melanoma was reviewed by PTAC in August 2019, and at that time, PTAC recommended it be deferred, pending further data to support the benefit of use of pembrolizumab in this setting. PTAC had also requested specific advice from CaTSoP regarding the patient population, surveillance requirements and the interpretation of data for health benefits in this population.

13.9 The Subcommittee noted that in October 2019, CaTSoP reviewed this application and recommended it be deferred, pending further data to support the benefit of use of pembrolizumab in this setting. At that time, CaTSoP:

- provided advice regarding the specific areas that PTAC highlighted and considered that the application should be reviewed once longer-term data was available, including data for 3-year recurrence-free survival (RFS)
- considered that data regarding retreatment with immune checkpoint inhibitors would also be needed to inform further consideration of use of these agents in the treatment of melanoma.

13.10 The Subcommittee noted that the Melanoma Network of New Zealand (MelNet) provided correspondence in February 2021 supporting use of pembrolizumab as an adjuvant therapy for patients with surgically resected stage III melanoma. The Subcommittee noted that key elements of the correspondence were as follows:

- MelNet considered the Keynote-054 trial provided evidence of a significant clinical impact with adjuvant pembrolizumab for resected stage III melanoma with an absolute difference in relapse-free survival of 20% between pembrolizumab and placebo, seen across all subgroups examined
- MelNet considered that this evidence indicates metastatic disease could be prevented in up to 20% of patients with locally advanced melanoma
- MelNet also noted that overall survival data would not likely eventuate from the Keynote-054 trial as patients who received placebo could cross over to receive pembrolizumab.

13.11 The Subcommittee considered that about half of patients with stage III melanoma present de novo at stage III, while the other half progress from stage I/II disease to stage III. The Subcommittee noted that patients with resected stage III melanoma would not currently receive active treatment as part of standard of care in New Zealand, however, noted that patients whose disease progressed to stage IV may be eligible to receive funded pembrolizumab in the metastatic setting, subject to Special Authority criteria.

13.12 The Subcommittee was made aware of survival data from an Australian study of conditional survival in 2,042 patients with stage III melanoma (Haydu et al. J Clin Oncol. 2017;35:1721-9) and a retrospective review of 340 US patients with stage III

melanoma who eventually relapsed (Romano et al. J Clin Oncol. 2010; 28:3042-7). The Subcommittee considered that the conditional survival of patients with melanoma increases with each year of survival, and therefore considered that adjuvant pembrolizumab would likely be of most benefit early in the course of disease.

13.13 The Subcommittee noted that the five-year survival of patients with metastatic (stage IV) melanoma has improved with the use of immune checkpoint inhibitors including pembrolizumab or nivolumab for metastatic melanoma. The Subcommittee was made aware of five-year overall survival (OS) of 34% in patients with metastatic melanoma who received pembrolizumab in the Keynote-001 trial (Hamid et al. Ann Oncol. 2019;30:582-8). The Subcommittee considered that the greatest benefit was received in the first two years of treatment and that responses were durable in patients who received a complete response. Members considered that the implementation of immune checkpoint inhibitors including pembrolizumab had reduced the usefulness of evidence from historical controls, given that comparison with controls treated without immunotherapy for metastatic disease is inconsistent with current practice.

13.14 The Subcommittee noted that pembrolizumab was proposed to be administered at a flat dose of 200mg three-weekly for a maximum duration of 12 months. However, the Subcommittee was made aware of emerging evidence for the less frequent pembrolizumab dosing schedule of 400mg six-weekly which could be effective and appropriate in this setting (Lala et al. Presented at American Association for Cancer Research Annual Meeting, 2020). The Subcommittee considered that pembrolizumab's relatively large vial size and requirement not to share vials among treated patients would result in wastage and artificially inflate the pharmaceutical's cost.

13.15 The Subcommittee noted that the supplier provided updated evidence from the randomised, phase III, placebo-controlled Keynote-054 trial reporting three-year RFS outcomes, results of a secondary analysis, 3.5 year distant-metastasis free survival (DFMS) outcomes and health-related quality of life data. The Subcommittee noted that the trial design and outcomes from the earlier publications of the Keynote-054 trial had been described by PTAC in August 2019 and by CaTSoP in October 2019, and that it had been noted that:

- The AJCC cancer staging was updated to the 8th Edition, which included stage IIID disease (previously part of stage IIIC group); the Keynote-054 trial used AJCC 7th Edition. The Subcommittee considered that including stage IIID disease has prognostic significance.

- Melanoma staging is based on radiology in current practice, rather than pathology of sentinel lymph nodes; Keynote-054 used pathologic staging

- Complete lymph node dissection is no longer performed in all cases for standard of care; complete lymph node dissection was mandated in the Keynote-054 trial

13.16 The Subcommittee noted that three-year RFS rate in the overall population of Keynote-054 was 63.7% with pembrolizumab compared with 44.1% with placebo (HR stratified by stage, 0.56; 95% CI, 0.47 to 0.68; P<.001) as reported in an updated RFS analysis performed after median follow-up of 36.6 months overall (Eggermont et al. J Clin Oncol. 2020;38:3925-36). The Subcommittee noted that the three-year RFS rate in those with programmed death-ligand 1 (PD-L1)–positive tumours was longer with pembrolizumab compared with placebo (HR, 0.57; 99% CI, 0.43 to 0.74). The Subcommittee considered that outcomes did not substantially differ by PD-L1 status, noting the number of patients with PD-L1 negative disease was low. The

Subcommittee considered that subgroups were relatively homogenous and that results were similar regardless of AJCC 7th or 8th Edition staging for stage IIIA disease. The Subcommittee considered that there was a small benefit in stage IIIC disease although this was not statistically significant.

13.17 The Subcommittee noted that after median follow-up 42.3 months in Keynote-054, the 42-month DFMS was 65.3% with pembrolizumab compared with 49.4% with placebo (HR, 0.60; 95% CI, 0.49 to 0.73; P<.0001 (Eggermont et al. Lancet Oncol. 2021;22:643-54; Eggermont et al. Presented at European Society for Medical Oncology (ESMO) Congress 2020). The Subcommittee noted that the 42-months DFMS in PD-L1+ participants was 66.7% with pembrolizumab compared with 51.6% with placebo (HR, 0.61; 95% CI, 0.49 to 0.76; P<0.0001). The Subcommittee considered that a small number of patients were available for follow-up at four years which limited the reliability of these results.

13.18 The Subcommittee noted that immune-related adverse events (irAEs) were reported in 190 (37.4%) of patients who received pembrolizumab compared with 45 (9.0%) who received placebo in Keynote-054 (Eggermont et al. JAMA Oncol. 2020;6:519-27). The Subcommittee noted that about half of the reported irAEs occurred in the first six months of treatment.

13.19 The Subcommittee noted that after median follow-up of 15.1 months in Keynote-054, the reported differences in health-related quality of life (HRQOL) scores were within the five-point clinical relevance threshold and were clinically non-significant, although compliance with the questionnaire was relatively low (Bottomley et al. Lancet Oncol. 2021;22:655-64). The Subcommittee considered that the results indicated there was no significant difference in HRQOL between the adjuvant pembrolizumab treated group and the placebo group and noted that the effect of all toxicity (not just irAEs) seemed to occur early in treatment.

13.20 The Subcommittee considered that the Keynote-054 trial provided evidence for use of adjuvant pembrolizumab in resected stage III melanoma that was of good quality but unclear strength. The Subcommittee considered that a greater proportion of patients would experience longer disease-free survival with adjuvant pembrolizumab, however, this would be associated a greater rate of immune-related adverse events per 100 patients. The Subcommittee considered that the evidence suggested 16% of patients treated with adjuvant pembrolizumab may not experience later relapse within three years, however, the Keynote-054 trial evidence did not provide survival data to inform whether this results in improvement in long-term survival. The Subcommittee considered that, due to the substantial treatment cross-over, OS data is not expected to eventuate.

13.21 The Subcommittee was made aware of real-world evidence from 641 patients in the Netherlands who received 12 months of adjuvant pembrolizumab which reported a 12-month progression-free survival (PFS) of 70% (De Meza et al. Eur J Cancer. 2021;158:234-45). The Subcommittee considered that the survival data was inconclusive given the limitations of this type of evidence and the short period of follow-up. The Subcommittee noted that early discontinuation occurred in 61% of participants primarily in the first three months due to either progression and/or toxicity; discontinuations at nine to 12 months were primarily due to patient and clinician agreement to cease treatment. The Subcommittee noted explanation for patient and clinician agreement to cease treatment was not provided, although members considered that the COVID-19 pandemic may have been a factor in discontinuations. The Subcommittee considered that this patient population was slightly different to the New Zealand patient population with resected stage III melanoma in terms of risk

profile (eg lesion resectability, grade and Breslow score), however, considered that the evidence provided evidence of higher toxicity, greater discontinuation rates but similar recurrence rates to those reported in the clinical trials.

13.22 The Subcommittee noted that different surrogate endpoints for survival were reported in melanoma trials. The Subcommittee was made aware of publications assessing surrogates for OS in advanced melanoma including PFS and RFS; some of the evidence reported an association between endpoints whilst some did not (Branchoux et al. Crit Rev Oncol Hematol. 2019;137:35-42; Nie et al. Ther Adv Med Oncol.2020;12:1758835920929583; Petrelli et al. Medicine (Baltimore). 2016;95:e3997). The Subcommittee considered that there were many contributing factors including the length of follow-up and resulting hazard ratio, and the differences between populations (noting that the forest plots appeared quite consistent but there were differences between patient populations). The Subcommittee considered that there was some evidence of a reasonable correlation between PFS and OS in melanoma, however, no strong data existed for disease-free survival (DFS) or RFS as a surrogate for improved OS. The Subcommittee considered that an association between RFS and OS was theoretical and therefore an OS benefit from increased RFS could not be assumed in cost-effectiveness modelling, however, acknowledged that there could be a moderate correlation between RFS and OS.

13.23 The Subcommittee was made aware of evidence from a systematic review and network meta-analysis of adjuvant immunotherapy in stages IIC to stage IV melanoma, with regimens including ipilimumab, pembrolizumab, nivolumab, nivolumab/ipilimumab, vemurafenib, and dabrafenib/trametinib (Christofyllakis et al. Front Oncol. 2020;10:637161). The authors suggested that treatment benefits are cumulative, however, the magnitude of benefit differed by disease stage. The Subcommittee noted that lesser effects were reported in stage IIIA disease compared with stages IIIB and IIIC, and the greatest effect was seen in stage IIIC. The Subcommittee considered that this may suggest there is a class effect of adjuvant immunotherapy agents in this setting, although noted that evidence for specific use of atezolizumab was not identified in melanoma.

13.24 The Subcommittee were not able to determine whether early adjuvant treatment of stage III melanoma with 12 months of pembrolizumab improved overall survival compared to later treatment of stage IV disease with 24 months of pembrolizumab.

13.25 The Subcommittee considered that subsequent re-treatment/s in the locally advanced or metastatic setting could differ depending on an individual patient's response and the duration of any treatment received in the adjuvant setting. The Subcommittee noted that one out of 20 patients (5%) in the Keynote-054 trial who had a second course of pembrolizumab post-recurrence received a complete response, and that PFS was limited to 4.1 months for the 20 retreated patients (Eggermont et al. Eur J Cancer. 2021;158:156-68; Eggermont et al. J Clin Oncol. 2021;39;15S). The Subcommittee considered that there was limited evidence for a benefit from retreatment with pembrolizumab, ie adjuvant pembrolizumab treatment of stage III followed by retreatment for metastatic stage IV disease. On balance, the Subcommittee considered it reasonable to consider retreatment for patients with metastatic disease who had not relapsed during adjuvant pembrolizumab treatment or within the six months following adjuvant treatment, however, retreatment would likely have a reduced benefit compared to use for treatment-naïve patients.

13.26 The Subcommittee considered that the second criterion of the current Special Authority criteria for pembrolizumab/nivolumab for metastatic (stage IV) melanoma would require amendment if pembrolizumab were funded for adjuvant treatment of resected stage III

melanoma (proposed changes to relevant Special Authority criteria are shown below in **bold** and ~~strikethrough~~ as applicable):

2. Patient did not experience a recurrence while on treatment or within six months of completing prior therapy with ~~pembrolizumab~~ **a PD-1/PD-L1 inhibitor** in the resected stage III setting; and

13.27 The Subcommittee considered that the supplier's proposed criteria for adjuvant pembrolizumab were broadly appropriate and that amendments in line with the published evidence (specifically, changes to disease stage sub-types and ECOG scores) were reasonable.

13.28 The Subcommittee considered that the increase in health sector costs and referral volumes associated with adjuvant pembrolizumab treatment and monitoring could be significant (Wurcel et al. Oncol Ther. 2021;9:167-85; Bensimon et al. J Med Econ. 2019;22:981-93), and that this could include high-cost radiology assessments including PET scans, however, the Subcommittee considered that regular monitoring for patients in observation also incurred a high cost to the health system. The Subcommittee considered that patients may receive a CT scan after six months of adjuvant treatment for melanoma, at the treating clinician's discretion. The Subcommittee considered that in some cases, relapsed disease would be clinically identified due to symptomatic progression rather than being identified by routine radiology assessments.

13.29 The Subcommittee considered that the below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pembrolizumab if it were to be funded in New Zealand for adjuvant treatment of resected stage III melanoma. 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 Subcommittee'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 stage IIIB, IIIC or IIID melanoma who have undergone complete surgical resection and have an ECOG score of 0-1.
Intervention	Pembrolizumab 200mg every 3 weeks for up to 12 months (noting early discontinuation might occur due to toxicity or disease recurrence).
Comparator(s)	Observation until progression
Outcome(s)	Improved recurrence-free survival; distant metastasis-free survival. No data on whether this improves 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.	

14 Pembrolizumab - First-line treatment of recurrent or metastatic head and neck cancer

Application

14.1 The Subcommittee considered updated information and correspondence received for an application from Merck Sharpe and Dohme (NZ) Ltd (MSD) for pembrolizumab as first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (R/M HNSCC), in patients who have not received systemic therapy for recurrent or metastatic disease.

Recommendation

14.2 The Subcommittee **recommended** that 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 be listed with **a low priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

PEMBROLIZUMAB
Initiation – (head and neck squamous cell carcinoma)
Applications only from a medical oncologist. Approvals valid for four months.
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. Pembrolizumab to be used in combination with platinum-based chemotherapy; and
4. The patient has a positive PD-L1 combined positive score (CPS) of >1; and
5. The patient has ECOG performance score of 0-2.

Continuation
Applications only from a medical oncologist. Approvals valid for four months.
1. No evidence of disease recurrence; and
2. The treatment remains appropriate and the patient is benefitting from treatment; and
3. The total treatment received must not exceed 24 months.

14.3 In making this recommendation, the Subcommittee 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.

14.4 The Subcommittee **recommended** that pembrolizumab in combination with chemotherapy for those with recurrent or metastatic head and neck squamous cell carcinoma irrespective of Combined Positive Score (ie. an all-comers population) be **declined**.

14.5 The Subcommittee made this recommendation based on unclear evidence of benefit for this patient group, the lack of survival benefit demonstrated, and the uncertainty resulting from the lack of a common comparator.

Discussion

14.6 The Subcommittee noted that the application for pembrolizumab for the first line treatment of head and neck squamous cell carcinoma (HNSCC) had previously been considered in October 2020, where it was recommended for decline. This recommendation was made based on the consideration of the New Zealand patient population having a high incidence of HPV-positive oropharyngeal cancer with the patient population with HNSCC in the clinical trial evidence having different epidemiology, characteristics and prognosis; the lack of an appropriate comparator treatment in the key clinical trial evidence for the New Zealand context; and the evidence for short-term outcomes of pembrolizumab only. In making this recommendation, the Subcommittee considered the limited applicability of data in the trial population to the clinical population with HNSCC in New Zealand.

14.7 The Subcommittee noted correspondence from the supplier in response to the October 2020 recommendation, which included updated data, clarification of the epidemiology and 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, and the relevance of outcomes to the New Zealand context.

14.8 The Subcommittee noted information regarding the American Joint Committee on Cancer (AJCC) staging of HNSCC as relevant to Ministry of Health Standard of Care Classifications in New Zealand, as well as a detailed breakdown of the AJCC classification of New Zealand data provided by the applicant. The Subcommittee noted the data was intended to clarify the similarities between the current New Zealand classification of HNSCC disease and the classification of patients recruited to the KEYNOTE-048 study. The Subcommittee noted that the supplier utilised the AJCC codes in an analysis of incident and mortality data for New Zealand and considered that the supplier estimates and projections for this are likely accurate.

14.8.1 The Subcommittee considered that this analysis highlights that oropharyngeal cancer is a subgroup of the HNSCC patient population (comprising approximately 38% of the total HNSCC population, and 30% of deaths from HNSCC), and is not presently the majority of the HNSCC population, as was previously considered. The Subcommittee considered, however that there is a trend towards increases in oropharyngeal disease incidence, such that this subgroup may make up 50% of incident HNSCC cases, and 35% of HNSCC deaths, over the next decade.

14.9 The Subcommittee noted data from New Zealand studies report that 76-78% of oropharyngeal squamous cell carcinoma patients have HPV-positivity, the vast majority of which were HPV p16 positive (Lucas Roxburgh et al. PLos One. 2017;12:e0186424). The Subcommittee also noted that previously reviewed publications reported that p16-positive oropharyngeal SCC represent approximately 22% of the patient population (Burtness et al. Lancet. 2019;394:1915-28).

14.10 The Subcommittee noted that, in a subgroup analysis provided by the supplier, patients with positive p16 status seemed to do better with pembrolizumab with chemotherapy than with cetuximab-chemotherapy in the total population, the CPS>20 population and the CPS>1 population however there was no evidence of a statistically significant interaction between p16 status and magnitude of overall survival benefit versus cetuximab; p16 positive patients were a minority. The Subcommittee considered that uncertainty remains regarding whether p16-positive patients respond to treatment the same as the dominant patient population.

14.11 The Subcommittee noted that previous comments raised by CaTSoP regarding p16-positive HNSCC were driven by the consensus that it is a biologically different disease than non-p16 positive HNSCC and is increasing in incidence relative to non-p16 HNSCC; however, acknowledged that the overall proportion of p16-positive oropharyngeal HNSCC may have been previously overestimated The Subcommittee considered that there remains under-representation of p16-positive disease within the KEYNOTE-048 trial which means that findings cannot be applied to the p16-positive subgroup with confidence, and thus the benefit of treatment with pembrolizumab in combination with chemotherapy for this subgroup is unknown.

14.12 The Subcommittee noted material provided by the supplier that stated that CPS may be a better predictor of patient outcomes than p16 status; however, considered that there was no evidence provided to support this statement. The Subcommittee noted that there is evidence that p16 status is a prognostic marker in oropharyngeal HNSCC, where median overall survival of p16-positive relapsing or metastatic oropharyngeal HNSCC was 2.6 years versus 0.8 years for p16-negative patients in a study of 181

relapsing remitting oropharyngeal cancer patients (Fakhry et al. J Clin Oncol. 2014;32:3365-73). The Subcommittee was not aware of any evidence that p16 status has been explored as a predictive biomarker in checkpoint-inhibition based therapies, and that there is mixed data for prediction with radiotherapy or EGFR-based therapy.

14.13 The Subcommittee noted that there is uncertainty surrounding whether PD-L1 expression is a negative prognostic factor in HNSCC, noting a large meta-analysis which found evidence that PD-L1 expression was neither positive nor negative prognostically (Yang et al. Oral Oncol. 2018;86:81-90). The Subcommittee noted that PD-L1 expression testing as a predictive biomarker varies between trials in the types of tests used, the way of testing, which expression cut-offs were used to define subgroups, and in the interpretation of the results. The Subcommittee noted that PD-L1 laboratory testing remains non-interchangeable between the assays and the companion-antibodies used and considered that nationwide training would have to be implemented to ensure consistency should PD-L1 testing be needed for newly funded agents. The Subcommittee noted the availability of supplier sponsored programmes for CPS testing but noted ongoing uncertainty on the extent of training within these programmes, and associated costs.

14.14 The Subcommittee noted one study which reported that PD-L1 expression may change over time with the use of immune checkpoint inhibitors (Karabajakian et al. Oral Oncol. 2021;119:105368). The Subcommittee considered that this implies that patients may have to be re-biopsied over the course of treatment.

14.15 The Subcommittee noted and agreed with the supplier's view that HPV vaccination will take many years to impact the incidence of HNSCC in New Zealand but noted that this is likely to translate into an increased proportion of p16-positive oropharyngeal HNSCC in the overall HNSCC population in the short-medium term. The Subcommittee considered that this highlights the risks associated with insufficient evidence of benefit of pembrolizumab for p16-positive disease, and that the use of pembrolizumab may therefore represent an increasing fiscal risk over the short-medium term.

14.16 The Subcommittee noted the supplier's concern regarding 4-year overall survival data not being explicitly addressed in the October 2020 meeting record. The Subcommittee noted published abstracts are generally considered to be low quality evidence when compared to peer reviewed papers and there is a general Subcommittee preference to review peer reviewed publications. The Subcommittee noted that the P-values in the 4-year overall survival analysis provided were nominal values and unadjusted for multiplicity and considered this data should be taken as hypothesis generating results, rather than providing definitive answers about the magnitude of long-term survival benefit.

14.17 The Subcommittee considered that the statistical plan provided with the submission was complex, compounded by changes in wording over various iterations and amendments associated with hypotheses for progression free survival and overall survival superiority/non-inferiority including changed language from 'observed events" to "expected events". The Subcommittee noted that the overall survival end point was moved from a secondary to a primary endpoint in a 2016 amendment and the 10% CPS sub-population was dropped from analysis in an amendment made in 2017.

14.18 The Subcommittee noted that updated progression-free survival data provided by the supplier indicates approximately 20% of patients treated with pembrolizumab had not progressed at two years, compared to approximately 10% in the control arm (R Geril KN048 ESMO 2020). The Subcommittee noted that this aligns with the 20% of the oropharyngeal patient population known to be p16-positive, and that these patients

typically have a better prognosis, (as indicated by a median overall survival 2-3 years longer than the rest of the HNSCC population). The Subcommittee considered that, as the p16-positive and p16-negative populations are biologically different with different prognostic indicators, mixing the two populations in the analysis meant that interpreting the true benefit of pembrolizumab for either population is difficult.

14.19 The Subcommittee noted the supplier's concern that review of a network meta-analysis provided in the original submission was not recorded in the October 2020 CaTSoP record (Ramakrishan et al. Technical Report. 2019). The Subcommittee noted that this was reviewed at the time and considered to be low quality evidence and it was not included in the record.

14.20 The Subcommittee noted additional clinician correspondence in response to the October 2020 review of this application. The letter outlined the concerns regarding over-estimation of the p16-positive oropharyngeal patient population at the October 2020 meeting, which the Subcommittee noted and acknowledged. The Subcommittee noted that there remained some uncertainty regarding benefit for the p16-positive subpopulation with under-representation in KEYNOTE-048 and considered an approach to minimise the fiscal risk associated with this uncertainty could be to exclude the population with <1% CPS.

14.21 The Subcommittee noted a study by Schoenfeld et al. in which data from KEYNOTE-048 was extracted for Kaplan-Meier curves to estimate the survival of the <1% CPS population which was not provided in the original KEYNOTE-048 manuscript (Schoenfeld et al. Oral Oncol. 2020;105:104762). The Subcommittee noted that cetuximab with chemotherapy may be more beneficial for CPS<1 patients than pembrolizumab with chemotherapy.

14.21.1 The Subcommittee noted the clinician's comments regarding the impact of HPV vaccination on HNSCC incidence and agreed that it is unlikely to have a near-term impact but could be a growing proportion of the biologic subtype of HNSCC.

14.21.2 The Subcommittee noted that the control arm of the KEYNOTE-048 trial included treatment with cetuximab, which is not a funded agent in New Zealand. The Subcommittee considered that the results from KEYNOTE-048 may thus underestimate the potential benefit for the New Zealand population who cannot access cetuximab.

14.22 Overall, the Subcommittee agreed with the supplier's updated analysis of the epidemiology of HNSCC in New Zealand, and that oropharyngeal HNSCC at present does not represent the majority of cases of relapsed/metastatic HNSCC. The Subcommittee considered that the oropharyngeal population is a biologically different disease, is the fastest growing population of HNSCC, has a better prognosis at diagnosis in the relapsed/metastatic setting, and is underrepresented in the KEYNOTE-048 trial. The Subcommittee considered that the data extending the benefit from the broader patient population from KEYNOTE-048 to this subpopulation had substantial uncertainties. The Subcommittee noted that the October 2020 assessment took an "all or none" approach to the request for funding to all relapsed/metastatic HNSCC leading to a recommendation for decline based on a substantive subpopulation in whom the benefit of therapy remains undetermined.

14.23 The Subcommittee considered that the updated data from the supplier indicates that adding chemotherapy to pembrolizumab treatment increases the response rate in the intention to treat population, as well as in the CPS >1 (median overall survival 13.6

months, 95% CI 10.7 months to 15.5 months versus 10.6 months without pembrolizumab, 95% CI 9.1 months to 11.7 months; HR 0.64, 95% CI 0.53 to 0.78; P=0.00001) and CPS >20 subgroups (pembrolizumab overall response rate 23.3%; median duration of response 23.4 months [range 2.7 to 54.4+ months] versus without pembrolizumab overall response rate 36.1%; median duration of response 4.2 months [range 1.2 to 38.2+ months]), and that this benefit may be conservative in the New Zealand population due to the use of cetuximab in the control arm. The Subcommittee therefore considered that pembrolizumab administered in combination with chemotherapy was appropriate to maximise the probability of patients responding to treatment.

14.24 The Subcommittee considered the structure of the statistical design and control of the type 1 error in KEYNOTE-048 was complex and with over 14 primary hypotheses and noted that modifications of the protocol over time added to the difficulty in interpreting the results.

14.25 The Subcommittee noted that the updated data from the supplier indicated that the primary endpoints relating to progression-free survival were not met, while the endpoints relating to overall survival were met, with the exception of overall survival in the monotherapy arm of the intention to treatment population. The Subcommittee considered that this indicated that overall survival is likely to be the main benefit from treatment. The Subcommittee considered that an estimated treatment effect of pembrolizumab of 5 years (as proposed by NICE) seems reasonable. The Subcommittee considered that the benefit in overall survival, but not progression-free survival also indicated that there was no strong association between progression-free survival and overall survival in this patient population.

14.26 The Subcommittee noted that the growth rate in incident patients with HNSCC is unknown but considered that previous estimates of approximately 3.6% seem reasonable. The Subcommittee also considered that the potential increase in the proportion of patients with CPS ≥1 HNSCC is unknown as CPS is not routinely tested for in New Zealand. The Subcommittee considered that the proportion of patients unfit for chemotherapy (and therefore receiving palliative care instead) was uncertain but likely to be low.

14.27 The Subcommittee considered that the supplier's concerns regarding the previous decline recommendation were valid and reasonable but considered that the reliability of benefit and the alignments of the KEYNOTE-048 patient population and subpopulations to the New Zealand patient population remain unclear, with corresponding uncertainty in benefit. The Subcommittee considered there remained a lack of correlation between progression-free survival and overall survival. The Subcommittee considered that there were financial risks associated with funding an "all-comers" patient population, but that these could be reduced by excluding the p16-positive population from the Special Authority criteria due to uncertainty of clinical benefit for these patients.

14.28 The Subcommittee considered that the below table summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pembrolizumab in combination with chemotherapy if it were to be funded in New Zealand for relapsed or metastatic HNSCC patients. 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 Subcommittee'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	1st line R/M HNSCC where tumours express PD-L1 (combined positive score [CPS]≥1) Approx. 85% of R/M HNSCC patients have CPS≥1, based on the Keynote-048 patient population; majority of these patients assumed to be fit for chemotherapy
Intervention	Pembrolizumab 200mg IV q.3weekly or 400mg IV q.6weekly up to maximum of 24 months, in combination therapy with platinum and 5-FU
Comparator(s)	Either: • In most cases, Cisplatin 75 mg/m2 IV on day 1 of each 21-day cycle administered over 4.5 hours (including considerable pre and post treatment therapy); or • If cisplatin is not suitable; Carboplatin 5 AUC on day 1 of each 21-day cycle administered over 30-60 mins And: • Fluorouracil 4,000 mg/m2 (equivalent to 1,000 mg/m2/day) via CIV via pump over 96 hours beginning on day 1 of each 21-day cycle
Outcome(s)	Overall survival gain vs (unfunded) cetuximab (KEYNOTE-048) Based on Vermoken et al. (2008), overall survival gain vs platinum-based chemotherapy Overall survival benefit assumed to persist for 5 years, based on NICE provisional TA129 No progression-free survival benefit vs (unfunded) cetuximab; uncertain benefit in progression-free survival vs platinum-based chemotherapy
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.	