Record of the Cancer Treatments Advisory Committee Meeting held on 12 October & 13 October 2023

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

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

The Cancer Treatments Advisory Committee may:

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

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

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

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

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

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

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

Table of Contents

1. Attendance

Present
Chair – Stephen Munn
Alannah Kilfoyle
Alice Loft
Anne O'Donnell
Chris Frampton
Chris Hemmings
Lochie Teague
Matthew Strother
Oliver Brake
Richard Issacs
Scott Babington
Stephen Munn
Vidya Mathavan

Apologies
Michelle Wilson

2. Summary of recommendations

Pharmaceutical and Indication	Recommendation
• brentuximab vedotin for adults with previously untreated CD30+ non-cutaneous peripheral T-cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) within the context of treatments of malignancy subject to Special Authority criteria	High priority
• netupitant/palonosetron for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic anti-cancer treatments, within the context of treatments of malignancy subject to Special Authority criteria	Medium priority
• pembrolizumab for the first line systemic treatment of recurrent, locally advanced, or metastatic Merkel cell carcinoma within the context of treatment of malignancy within the context of treatments of malignancy subject to Special Authority criteria	High priority
• atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung cancer	Defer
• subcutaneous pertuzumab and trastuzumab for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer in combination with chemotherapy at high risk of recurrence within the context of treatments for malignancy	Medium priority
• subcutaneous pertuzumab and trastuzumab for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel, within the context of treatments for malignancy.	High priority
• ibrutinib and venetoclax in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting for individuals with TP53 intact CLL within the context of treatments of malignancy subject to Special Authority criteria	High priority
• ibrutinib and venetoclax in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting for individuals with del(17p)/TP53 mutation (TP53 disrupted CLL) within the context of treatments of malignancy subject to Special Authority criteria	High priority
• venetoclax and obinutuzumab in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting within the context of treatments of malignancy subject to Special Authority criteria	High priority
• Special Authority criteria for venetoclax in the treatment of CLL be amended to allow retreatment with venetoclax + rituximab at	Medium priority

relapse, following prior treatment with venetoclax + rituximab (VenR) (ie third-line treatment for TP53 intact CLL) within the context of treatments of malignancy subject to Special Authority criteria	
• bruton tyrosine kinase inhibitor (BTKi) for the first-line monotherapy treatment of TP53 intact CLL within the context of treatments of malignancy subject to Special Authority criteria	High priority
• bruton tyrosine kinase inhibitor (BTKi) be listed for the first-line monotherapy treatment of TP53 disrupted CLL within the context of treatments of malignancy subject to Special Authority criteria	High priority
• bruton tyrosine kinase inhibitor (BTKi) be listed for the second-line monotherapy treatment of TP53 intact CLL within the context of treatments of malignancy subject to Special Authority criteria	Low priority
• alternative bruton tyrosine kinase inhibitor (BTKi) be listed for the treatment of TP53 intact CLL for those who progress or experience intolerable side effects with venetoclax+rituximab subject to Special Authority criteria	Cost neutral
• any further bruton tyrosine kinase inhibitor (BTKi) be listed for the treatment of TP53 disrupted CLL for those who progress or experience intolerable side effects to venetoclax subject to Special Authority criteria	Cost neutral
• durvalumab in combination with chemotherapy for the treatment of locally advanced or metastatic biliary tract cancer within the context of treatment of malignancy subject to Special Authority criteria	Low priority
• pembrolizumab for the treatment of triple negative, locally recurrent unresectable or metastatic breast cancer, with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥10 within the context of treatments of malignancy subject to Special Authority criteria	Medium priority
• pembrolizumab for the neoadjuvant treatment followed by adjuvant monotherapy of early stage II or III triple negative breast cancer within the context of treatment of malignancy subject to Special Authority criteria	Low priority

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

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

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

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

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

4. Correspondence and Matters Arising

4.1. Class effect of immune checkpoint inhibitors for urothelial carcinoma

Discussion

4.1.1. The Committee noted updated evidence supporting the use of immune checkpoint inhibitors for the treatment of urothelial carcinoma in the second-line setting.

4.1.2. The Committee noted it had previously considered applications for two immune checkpoint inhibitors in this setting, pembrolizumab and atezolizumab, and recommended funding with medium and low priority respectively (CaTSoP April 2019).

4.1.3. The Committee noted it has also recommended funding pembrolizumab for first-line treatment of metastatic urothelial carcinoma for those who are not eligible for cisplatin. The Committee noted Pharmac had declined this application in March 2022.

4.1.4. The Committee noted additional data from pivotal clinical trials had been published since the applications were last reviewed in 2019.

4.1.4.1. The Committee noted a published 5 year follow up of KEYNOTE-045 reported a durable response and an overall survival benefit compared to chemotherapy alone (10.1 vs 7.2 months (HR 0.72, 95% CI 0.59-0.86)).

4.1.4.2. The Committee noted a published 3 year follow up of IMvigor211 reported a small overall survival benefit compared to chemotherapy alone in the intention-to-treat group (absolute OS difference +0.6 months, HR 0.82, 95% 0.71-0.94). The Committee noted that atezolizumab was withdrawn voluntarily from the USA by the supplier after the FDA withdrew its accelerated approval in November 2022.

4.1.5. The Committee noted there was Phase I and II trial evidence for other immune checkpoint inhibitors (nivolumab, avelumab and durvalumab). The Committee considered that the results from these trials indicated similar response rates, duration of response, progression free survival and overall survival.

4.1.6. Overall, the Committee considered that atezolizumab and pembrolizumab provide similar, but not the same, health benefits for second-line treatment of urothelial carcinoma. The Committee considered that a class effect for these immune checkpoint inhibitors could not be confirmed based on the data available.

4.1.7. The Committee recommended that Pharmac staff model individually the benefits reported for each medicine against their respective costs. The Committee acknowledged that while there is more robust survival data for pembrolizumab, if

other agents modelled substantially better cost-effectiveness, it would be reasonable to fund any one of these to provide a treatment option affordable within Pharmac's fixed budget.

4.1.8. The Committee recommended Pharmac staff amend their health economic modelling and Special Authority criteria to include a maximum of 2 years of treatment. The Committee noted this was consistent with the KEYNOTE-045 trial design.

4.1.9. The Committee noted that the JAVELIN Bladder 100 study has since indicated that there may be significant health benefit from utilising avelumab as a maintenance treatment for tumours that are stable from chemotherapy. The Committee requested Pharmac seek an application for immune checkpoint inhibitors in this setting for consideration at a future meeting, and that this could potentially define a population of patients who may derive the most benefit from immunotherapy in this disease.

4.2. Retreatment with trastuzumab following disease progression in metastatic breast cancer

4.2.1. The Committee reviewed feedback received in response to the June 2023 Pharmac consultation to change to biosimilar trastuzumab, requesting reconsideration of the application for retreatment with trastuzumab following disease progression in metastatic breast cancer. The feedback included additional evidence the Committee had not reviewed previously.

4.2.2. The Committee noted this proposal had been recently reviewed at its January meeting (CTAC January 2023 – record), where it had recommended the application be declined.

Recommendations

4.2.3. The Advisory Committee **recommended** that the application for retreatment with trastuzumab following disease progression be **declined**.

Discussion

4.2.4. The Committee noted it had previously considered a funding application for retreatment with trastuzumab following disease progression in the metastatic setting from the Breast Cancer Special Interest Group in 2010 and again in January 2023. Both times the Committee recommended the application be declined.

4.2.5. The Committee noted the funded treatments available in New Zealand with good efficacy in this setting, being trastuzumab (first-line) and trastuzumab emtansine (second-line). The Committee noted that in previous considerations they had not considered there to be sufficient evidence to support the efficacy of third-line trastuzumab, as retreatment for HER2 positive metastatic breast cancer following the use of trastuzumab emtansine, and had considered that it would not address the unmet health need.

4.2.6. The Committee noted the feedback stated third-line trastuzumab retreatment was outlined in both the National Comprehensive Cancer Network (NCCN) guidelines and the European Society for Medical Oncology (ESMO) guidelines, but in those jurisdictions there were a number of drugs available which are not currently funded in New Zealand.

4.2.6.1. The Committee noted NCCN guidelines focus on defining treatment regimens and do not specify evidence for any particular third-line treatment. The Committee considered these guidelines are a summary of what treatments could be used, but do not dictate when treatments should be used.

4.2.6.2. The Committee noted the ESMO guidelines use the ESMO Scale for Clinical Actionability of Molecular Targets (ESCAT-1A) to describe the suitability of a

molecular target not that of a specific treatment. The Committee noted the guidelines support trastuzumab retreatment on progression, preferably with trastuzumab deruxtecan or tucatanib, but allow trastuzumab in combination with other chemotherapies. ESMO cites Level III evidence for this recommendation, which indicates evidence based on systematic reviews. The Committee, however, noted they had previously reviewed the only published systematic review and considered it did not provide strong evidence to support funding of trastuzumab in combination with various chemotherapy agents (rather than the use of drug conjugates) in this setting (refer to 6.10 - January 2023 CTAC meeting), despite this recommendation.

4.2.7. The Committee noted two studies were provided in the consultation feedback.

4.2.7.1. A retrospective analysis of individuals with HER2-postitve metastatic breast cancer who received trastuzumab-based therapy beyond progression (Dogan et al. Sci Rep. 2023;13:8779).

4.2.7.1.1. The Committee considered this study provided evidence to support treatment holidays for those who have received long-term trastuzumab-based therapy with a durable complete response that continues for a long time. The Committee noted that treatment holidays are funded in New Zealand, and considered this study did not present evidence supporting the use of trastuzumab in the third-line retreatment (or later) setting.

4.2.7.2. An open-cohort, retrospective, patient-level observational study of individuals with metastatic breast cancer who were started on third-line treatment with trastuzumab-based therapy combined with chemotherapy (Tras+CT) compared to chemotherapy (CT) alone (Sanglier et al, The Breast. 2022; 66:262-71).

4.2.7.2.1. The Committee noted the small size of the CT group (n=49) for this retrospective observational study. The Committee considered that while it was unclear why this was the case, it was likely and that this group was less fit compared to the Tras+CT group (n=337), as all patients would potentially have had access to trastuzumab. It was noted that the CT group had comparatively lower oestrogen-receptor positivity (55% vs 71%) and therefore fewer patients would have had potential benefits from hormonal therapy. Overall, the Committee considered the CT group would have had poorer prognosis at baseline compared to the Tras+CT group and that this would likely have a large impact on survival.

4.2.7.2.2. The Committee noted that the CT group was profoundly different compared with the Tras+CT group at baseline in terms of virtually all important clinical features. The vast majority of these features reflected a poorer prognosis that would likely impact on the relative survival of the groups. The Committee noted that propensity-based analysis is appropriate to adjust for this, but considered that with such strong confounding and the small sample size for the CT group the results for both outcomes were not convincing. Presenting the Kaplan Meyer curves out beyond approximately 12 months is potentially misleading given the very few still at risk in the CT group. A number of sensitivity analyses were performed to compensate for imbalance between the groups, but there was still concern over differences in HER2 status between the groups and a lack of detailed information on comorbidities between the groups.

4.2.7.2.3. The Committee noted the Tras+CT group also had a longer duration of response to prior treatments compared to the CT group. The Committee considered this may further confound the results, as those selected for the additional trastuzumab therapy may have had less aggressive disease.

4.2.7.2.4. The Committee noted there was no statistically significant difference in weighted progression free survival between the two groups (HR, 0.71; 95% CI, 0.50-1.01) as numbers of component events were too low to make conclusions, suggesting that there was not a clear difference in PFS from adding trastuzumab to chemotherapy in this analysis. The Committee noted that while an overall survival benefit was observed (HR, 0.29; 95% CI, 0.16-0.53), they considered that there were many profound differences at baseline apparent between the groups, reflecting most significantly, the poorer prognosis of the CT group, and that these would have contributed to this observed relative survival benefit.

4.2.7.2.5. The Committee also noted that 125 individuals in the Tras+CT group received third-line trastuzumab emtansine. The Committee considered the observed overall survival benefit was likely driven to some degree by the efficacy of trastuzumab emtansine and the availability of hormonal therapy to a higher proportion of the Tras-CT group. The Committee considered it was thus difficult to conclude whether any overall survival benefit was gained from trastuzumab retreatment in this setting.

4.2.7.2.6. The Committee considered a separate analysis of only those people who received trastuzumab plus chemotherapy compared to chemotherapy alone would be needed to determine if there was a health benefit specifically from trastuzumab retreatment in this setting. However, such analysis was not part of the study.

4.2.7.3. Overall, the Committee considered the submitted studies did not provide sufficient evidence of improved outcomes from trastuzumab retreatment in the third-line (or later) setting. The Committee considered that well designed randomised controlled trials rather than observational studies are required to understand adequately if there are health benefits from third-line trastuzumab. The Committee considered that New Zealand would be a good setting in which to conduct such a trial.

4.3. Hodgkin lymphoma treatment paradigm

Discussion

4.3.1. The Committee noted that Pharmac sought advice regarding the consequences to the Hodgkin's lymphoma treatment paradigm if pembrolizumab were to be funded for relapsed or refractory classical Hodgkin lymphoma (HL).

4.3.2. The Committee noted that brentuximab has been funded for the treatment of relapsed/refractory Hodgkin's lymphoma since December 2022.

4.3.3. The Committee noted that Hodgkin's lymphoma is a good prognosis disease, with 80% achieving long term remission from first-line treatment.

4.3.3.1. Of the 20% who have relapsed or refractory disease after first-line therapy, 50% will achieve long term remission with salvage chemotherapy and a consolidative autologous stem cell transplant (ASCT).

4.3.3.2. The remaining 50% of individuals who have relapsed or refractory disease following two lines of therapy (10% of all those with HL) have a poor prognosis either due to ineligibility for an auto-SCT (due to disease or age/co-morbidities) or have relapsed following an auto-SCT.

4.3.4. The Committee noted that approximately 100 people are diagnosed with Hodgkin's lymphoma in New Zealand each year.

4.3.5. The Committee noted that 12 NPPA approvals have been granted for pembrolizumab as a bridge to either autologous or allogenic stem cell transplant. This is estimated to be 5-6 people per year.

4.3.6. The Committee noted that Keynote 087(Chen et al. Blood. 2019;134:1144-53) provided primary evidence for pembrolizumab that included 5-year follow-up. The Committee noted ORR for Pembrolizumab of 71.9% (95% CI: 65.3-77.9), was very similar to brentuximab.

4.3.7. The Committee noted that Keynote 204 (Kuruvilla et al. Lancet Oncol. 2021;22:512-24) provided the primary evidence comparing pembrolizumab vs brentuximab for the treatment relapsed/refractory Hodgkin's lymphoma. The Committee noted that median PFS from the pembrolizumab arm was 13.2 months (95% CI: 10.9-19.4) vs 8.3 months (95% CI: 8.7-19.2) for brentuximab.

4.3.8. The Committee considered that based on the evidence from Keynote 204 the preference for most clinicians in the treatment of relapsed/refractory Hodgkin's lymphoma would be pembrolizumab.

4.3.9. The Committee noted that at least 70% of people with Hodgkin's Lymphoma patients with relapsed or refractory disease after two prior lines of therapy will receive both pembrolizumab and brentuximab.

4.3.9.1. 10% of individuals have relapsed or refractory disease after two lines of therapy.

4.3.9.2. 5% are ineligible for transplantation, with 80% of this population accessing a second agent.

4.3.9.3. 5% are eligible for transplantation based on age/co-morbidities.

- Half of this population have relapsed after an autologous stem cell transplant.
  - Pembrolizumab or brentuximab would be used as bridge to an allogenic stem cell transplant (15-25% of individuals receiving these are cured)
  - The remaining 75% could potentially access the second agent.
- Half were previously ineligible for ASCT due to refractory disease.
  - 70% of these people will respond and proceed to autologous SCT (20% cured)
  - 80% could potentially access the second agent.

4.3.10. The Committee considered it reasonable for pembrolizumab, if funded, to have same the Special Authority criteria as brentuximab.

4.3.11. The Committee understood that interpretation of transplant ineligibility in the current Special Authority criteria differs between treatment centres. It is understood that some centres consider individuals who have persistently F-fluorodeoxyglucose (FDG) avid disease after two lines of therapy as transplant ineligible whilst other centres interpret transplant ineligibility independent of disease status and solely based on age/co-morbidities.

4.3.12. The Committee considered that of the 17 people who have received brentuximab in past 12 months, 80% (13) of these people would require a second treatment. Accounting for the 3 people who have received pembrolizumab via NPPA, this results in an additional 10 individuals (based on point 1.9 above) receiving pembrolizumab if funded.

4.4. Consideration of applications for BRCA mutated cancers via Pharmac's exceptional circumstances framework

Discussion

4.4.1. The Committee reviewed Named Patient Pharmaceutical Assessment applications (NPPA) received by Pharmac since 2017 for olaparib in the treatment of various BRCA mutated cancers.

4.4.2. The Committee noted the first NPPA Pharmac received for olaparib was in 2017 to treat an individual with BRCA-mutated low grade endometrial stroma sarcoma. The Committee noted the application had been determined not to meet the NPPA principles as the health need of the individual could not be differentiated from the wider group of BRCA-mutated cancers.

4.4.3. The Committee noted that Pharmac received a Pharmaceutical Schedule application for olaparib for the second line treatment of people with germline BRCA mutated ovarian cancer in February 2017, which was funded in December 2019. The Committee noted that an application for widened access to the first line treatment of germline BRCA mutated ovarian cancer was received in May 2020 and was funded in March 2022.

4.4.4. The Committee noted that since August 2022, Pharmac had received a number of applications for individuals with various BRCA-mutated cancers. Pharmac staff were now seeking the Committee's advice as to whether there were any groups of individuals that could reasonably be determined as exceptional to the wider group with BRCA mutated cancers.

4.4.5. The Committee noted that BRCA-mutations can be defined as either somatic or germline mutations, and that somatic mutations are more common than germline mutations. The Committee noted that depending on the tumour stream, clinical trials varied in their inclusion criteria for either somatic or germline mutations and that this has driven global regulatory approvals specific to a tumour type, without any tumour-agnostic approvals for olaparib to date.

4.4.6. The Committee noted that the efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors seems to vary considerably across BRCA mutated cancers. The Committee considered that tumour-agnostic efficacy of olaparib could not be determined from available clinical trial data at this time.

4.4.7. Due to the differences in demonstrated efficacy of olaparib, the Committee considered it was appropriate to consider tumour streams individually rather than agnostically for the purposes of NPPA. However, the Committee considered that any consideration of exceptionality would need to account for the type of tumour, extent of the exceptional health need and inequities in access to BRCA testing.

4.4.8. The Committee noted that some tumours, such as in prostate cancer and breast cancer are highly prevalent in the New Zealand population and can demonstrate BRCA mutations. The Committee considered this should be taken into account when considering NPPA applications, as exceptionality is a key determinant of funded access to treatment via NPPA.

4.4.9. The Committee noted that outside of the funded indication for olaparib (ovarian cancer), BRCA-mutation testing is funded privately. The Committee considered that

as a result, there are significant inequities in access to testing and therefore only those who could afford to pay for testing would currently be able to be the subject of NPPA for olaparib. The Committee considered that access to olaparib via NPPA would therefore further exacerbate inequities in the health system for those with PARP inhibitor sensitive cancers.

4.4.10. The Committee stated it would appreciate opportunities to review Pharmaceutical Schedule funding applications made to Pharmac for the more prevalent tumour streams (such as in breast cancer and prostate cancer) shown to have some response to PARP inhibitors such as olaparib.

5. Brentuximab - adults with previously untreated CD30+ non-cutaneous peripheral T-cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)

Application

5.1. The Advisory Committee reviewed the application for brentuximab vedotin for adults with previously untreated CD30+ non-cutaneous peripheral T-cell lymphoma (PTCL) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

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

Recommendation

5.3. The Advisory Committee **recommended** that access to brentuximab vedotin be widened with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> BRENTUXIMAB VEDOTIN
>
> **Special Authority for Subsidy**
>
> **Initial application (CD30 positive systemic anaplastic large-cell lymphoma)** - from any relevant practitioner. Approvals valid for 12 months for applications meeting the following criteria: All of the following:
>
> 1. Patient has CD30 positive systemic anaplastic large-cell lymphoma; and
> 2. Patient must have histological confirmation of CD30 expression; and
> 3. Patient must not have received prior treatment with curative intent chemotherapy for this condition; and
> 4. Treatment must be for curative intent; and
> 5. Treatment must be in combination with cyclophosphamide, doxorubicin and prednisone; and
> 6. Treatment must not be more than 8 treatment cycles under this restriction in a lifetime; and
> 7. Brentuximab vedotin is to be administered at doses no greater than 1.8 mg/kg every 3 weeks.

5.4. In making this recommendation, the Advisory Committee considered that:

5.4.1. for previously untreated CD30+ PTCL, the currently funded treatment in New Zealand is accepted practice internationally, with the exception of treatment for individuals with systemic anaplastic large-cell lymphoma subtype. The Committee considered there was currently an unmet health need and poor prognostic outcomes for the latter group of individuals in New Zealand.

5.4.2. current results from the ECHELON-2 trial reported progression-free survival benefit for brentuximab vedotin for previously untreated systemic anaplastic large cell lymphoma but did not provide evidence for additional benefits, compared with currently funded options, in other subtypes of CD30+ PTCL.

5.4.3. although the utilisation of brentuximab vedotin would increase the overall treatment administration time by approximately 20-30 minutes per person, compared to the currently funded treatment, the wider cost to the health

system would be unlikely to noticeably increase. This is due to the small numbers of individuals requiring this treatment.

Discussion

Māori impact

5.5. The Committee discussed the impact of funding brentuximab vedotin for the treatment of previously untreated CD30+ PTCL on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

5.6. The Committee noted that the treatment of lymphoma is not a Pharmac Hauora Arotahi health area of focus.

5.7. The Committee noted that Te Aho o Te Kahu - Cancer Control Agency's *The State of Cancer in New Zealand 2020* report (revised in March 2021), reported NHL as the third most disparate cancer in terms of survival with a cancer-specific excess mortality of approximately 100% for Māori compared with non-Māori. The Committee considered that this disparity is likely influenced by B Cell non-Hodgkin lymphoma rather than T cell non-Hodgkin lymphoma.

5.8. The Committee considered that the little evidence it was aware of, that suggests Māori experience slightly lower incidence of CD30+ PTCL than other ethnicities in New Zealand, is difficult to comment on, due to the rarity of the disease.

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

5.9. The Committee noted the possible impact of funding brentuximab vedotin for the treatment of previously untreated CD30+ PTCL on Pacific, disabled, and other populations who experience inequities. The Committee considered that due to the rarity of the disease, it was difficult to comment on the effects of CD30+ PTCL on groups experiencing inequities.

Background

5.10. The Committee noted that Pharmac has not previously considered any other treatments for previously untreated CD30+ non-cutaneous peripheral T-cell lymphoma (PTCL)

5.11. The Committee noted that in August 2016, PTAC considered an application from a clinician for the funding of brentuximab vedotin and made various recommendations for the treatment of relapsed/refractory Hodgkin lymphoma, and relapsed/refractory systemic anaplastic large-cell lymphoma. The Committee noted that in September 2018, CaTSoP (now CTAC) recommended brentuximab vedotin be funded with a **high priority** for CD30+ Hodgkin lymphoma which has relapsed after two or more cycles of chemotherapy for individuals who are ineligible for auto-SCT, and individuals who have already had an autologous stem cell transplant. The Committee noted that CaTSoP had also recommended brentuximab vedotin be funded with a **medium priority** for the second-line treatment of CD30-positive systemic anaplastic large-cell lymphoma.

5.12. The Committee noted that in November 2022, Pharmac announced the decision to fund brentuximab vedotin for the treatment of Hodgkin and anaplastic large-cell lymphoma, to be prescribed and used in accordance with Section 29 for individuals who consent to treatment and meet the eligibility criteria.

Health need

5.13. The Committee noted that (non-cutaneous) PTCL is a subset of aggressive non-Hodgkin lymphoma (NHL) that develops in the mature T cells within the lymphoid tissues such as the lymph nodes, spleen, gastrointestinal tract and skin, but is distinct

from cutaneous T-cell lymphoma (which involves the skin). The Committee noted that PTCLs comprise 10-15% of NHL, with > 23 different entities. The Committee noted the most common subtypes are PTCL not otherwise specified (NOS) (approximately 25% of PTCL), angioimmunoblastic T cell lymphoma (approximately 18%), anaplastic T cell lymphoma (which may have the mutation status of anaplastic lymphoma kinase (ALK) positive (approximately 5% of PTCL) or negative (approximately 7% of PTCL)), and extra-nodal Natural Killer/T-cell lymphoma (approximately 10% of PTCL) (Vose et al. J Clin Oncol. 2008;26:4124-30).

5.14. The Committee considered that prognosis in PTCL is consistently worse than in B cell NHL, and little progress has been made in the treatment landscape over recent years with 5-year survival rates ranging from 32-70%, depending on the subtype (Vose et al. J Clin Oncol. 2008;26:4124-30). The Committee noted the exception of people with the ALK positive mutation, who have a similar prognosis to B cell NHL and comprise around 10% of the group.

5.15. The Committee noted that for those who experience long-term survival, this is generally seen in individuals without comorbidities.

5.16. The Committee noted that several of the PTCL subtypes are known to express the cell surface marker CD30 and that CD30 is universally expressed and is pathognomonic in systemic anaplastic large cell lymphoma (sALCL) (Savage et al. Blood. 2008; 111:5496-504).The Committee noted that among non-systemic anaplastic large cell lymphoma subtypes CD30 expression is variable, with estimates from approximately 58–64% in peripheral T-cell lymphoma not otherwise specified, 43–63% in angioimmunoblastic T-cell lymphoma, 55% in adult T-cell leukaemia or lymphoma, and 0–100% in enteropathy-associated T-cell lymphoma (Bossard et al. Blood. 2014; 24:2983-6, Sabattini et al. Haematologica. 2013;98:e81-2).

5.17. The Committee noted the estimated incidence of CD30+ PTCL in New Zealand in 2020 provided by the applicant, who made the calculations by utilising the data published by the New Zealand Ministry of Health from the population-based New Zealand Cancer Registry (NZCR) and estimated from the published literature (Bossard et al. 2014, Sabattini et al. 2013, Vose et al. 2008). The Committee considered the estimated annualised incidence rates of 0.4 per 100,000 for Māori, 1.4 per 100,00 for Pacific peoples, and 0.7 per 100,000 for the total New Zealand population to be reasonable. The Committee noted that total numbers of deaths were low due to the rarity of the disease in all ethnicities.

5.18. The Committee noted that it appeared from the above data that Māori experience a slightly lower incidence rate of CD30+ PTCL than other ethnicities. In contrast, Pacific peoples experience a higher incidence rate. The Committee noted that despite having a higher incidence, Pacific peoples experienced relatively low mortality rates. Members considered this likely reflects the subtype pattern observed by ethnicity and that while incidence was high overall for Pacific peoples, the incidence of subtypes which generally have a poor prognosis may be low in these populations. However, the Committee considered that due to the rarity of the disease, it was difficult to comment on the effects of CD30+ PTCL on groups experiencing inequities. The Committee noted that as per *The State of Cancer in New Zealand 2020* report (revised in March 2021), NHL is reported as being the third most disparate cancer in terms of survival, with a cancer specific excess mortality of approximately 100% for Māori compared with non-Māori. The Committee considered that this disparity is likely influenced by B Cell non-Hodgkin lymphoma rather than T cell non-Hodgkin Lymphoma.

5.19. The Committee considered that that New Zealand currently treats CD30+ PTCL with the anthracycline-containing regimen cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) (National Comprehensive Cancer Network (NCCN). 2022) or an

intensified regimen with the addition of etoposide to CHOEP and consolidating stem cell transplant and/or radiotherapy. The Committee noted that this practice is also recommended in Australia, Canada, and the United States of America, and considered there is not a distinct unmet need in the general PTCL population in the first-line setting compared to many other countries. The Committee noted however, that for the sALCL subtype of CD30+ PTCL is an exception as CHOP/CHOEP is not the currently accepted practice for this subtype internationally, and thus this subgroup of affected individuals is experiencing an unmet health need.

5.20. The Committee considered that the impacts of CD30+ PTCL can be lifelong for affected individuals, depending on the extent of disease at diagnosis and/or treatment-related morbidity. The Committee considered that while relapsed disease can be treated with second-line chemotherapy with a view to undergoing a transplant, often relapsed disease is chemotherapy-insensitive and people experience a rapid disease course and associated decline. The Committee considered that the impacts of CD30+ PTCL on a person's care needs can cause significant stress for family and whānau caring for people with CD30+ PTCL given the aggressive nature of the disease and associated poor prognosis.

Health benefit

5.21. The Committee noted that brentuximab vedotin is an antibody-drug conjugate that selectively delivers monomethyl auristatin E (MMAE), an antimicrotubule agent, into CD30 expressing cells. Binding of MMAE to tubulin disrupts the microtubule network, inducing cell cycle arrest and resulting in apoptotic cell death. The Committee noted that brentuximab vedotin is approved by Medsafe for the treatment of adults with previously untreated CD30+ PTCL in combination with cyclophosphamide, doxorubicin, and prednisone (CHP).

5.22. The Committee noted that brentuximab vedotin is recommended: in Australia, brentuximab vedotin for people with previously untreated CD30+ in combination with CHP, and for relapsed sALCL; in Europe for untreated sALCL in combination with CHP, and in relapsed sALCL; and in Canada for previously untreated CD30+ PTCL in combination with CHP.

5.23. The Committee noted that the ECHELON-2 trial provided the primary evidence for the health benefits of brentuximab vedotin in combination with CHP for the treatment of previously untreated CD30+ PTCL (Horwitz et al. Lancet. 2019;393:229-40, Horwitz et al. Ann Oncol. 2022;33:288-98.)

5.23.1. The Committee noted the trial was a double-blind, double-dummy, randomised (1:1), placebo-controlled, active-comparator, phase 3 study in adults (≥18 years) with previously untreated CD30+ PTCL (*N*=452) who received either Brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (A+CHP) for 6-8 cycles (*n*= 226) or Cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) for 6-8 cycles (*n*=226). The Committee considered that most affected individuals in New Zealand would have the addition of etoposide to CHOP, therefore this comparator may be slightly less efficacious than CHOEP which is often used in the New Zealand environment. The Committee considered this was a large study for a rare cancer.

5.23.2. The Committee noted that the study required a 75% enrolment of the sALCL subtype and analysis of this group to fulfil regulatory requirements, which was not reflective of the real-world proportion of sALCL in the CD30+ PTCL population (which is closer to 10%) and limits the study's real-world generalisability. The Committee noted that median follow-up was 48 months, and that post-protocol brentuximab vedotin was permitted in both groups. The Committee considered the study was of good quality.

5.23.3. The Committee noted results for the primary endpoint of progression-free survival (PFS). The Committee noted 5-year PFS of 51.4% (95% Confidence Interval (CI): 42.8 to 59.4) in the A+CHP group compared to 43.0% (95%CI: 35.8 to 50.0) in the CHOP group (Hazard ratio (HR) 0.70 (95% CI: 0.53–0.91). The Committee noted the benefit was greater in the sALCL subgroups (60%) than the total intention-to-treat (ITT) population (48%).

5.23.4. The Committee noted the estimated 5-year overall survival rates (median duration not reached) of 70.1% (95%CI: 63.3 to 75.9) in the A+CHP group compared to 61.0% (95%CI: 54.0 to 67.3) in the CHOP group (HR: 0.72; 95% CI: 0.53–0.99), and 75% (CI 68-81) in the sALCL subgroup compared to 68% (CI 60-75) in the ITT population. However, the Committee considered that due to the overlap of confidence intervals, the increased overall survival in the A+CHP group, and ITT group were not statistically significant.

5.24. The Committee considered that current results from the ECHELON-2 trial showed progression-free survival benefit for brentuximab vedotin for previously untreated systemic anaplastic large cell lymphoma (sALCL) but did not provide evidence for additional benefits compared with other funded options (CHOP) in other subtypes of CD30+ PTCL.

5.25. The Committee considered that current evidence does not show any age, stage, sex and/or ethnicity subgroups clearly benefitting from brentuximab vedotin to a greater extent than other subgroups. The Committee considered that it was likely that greater benefits in survival and quality of life would result from brentuximab vedotin if the treatment is used in the first-line setting, rather than in relapsed disease.

5.26. The Committee considered that the ECHELON-2 trial provided evidence for brentuximab vedotin + CHP having a comparable safety to currently funded treatment.

Suitability

5.27. The Committee noted that vincristine, which was the component of CHOP being replaced by brentuximab vedotin in this application, is administered via intravenous infusion over 5-10 minutes, so utilising brentuximab vedotin would increase administration time by approximately 20-30 minutes per person.

Cost and savings

5.28. The Committee considered it appropriate to limit treatment duration to six cycles in any potential funding criteria.

5.29. The Committee considered the number of people treated for CD30+ PTCL in New Zealand is too small to result in large health system increases or decreases from treatment with brentuximab vedotin in comparison with CHOP/CHOEP.

5.30. The Committee was unaware of any evidence of brentuximab vedotin being used in the relapsed/refractory setting following brentuximab use as first-line treatment. The Committee considered that the Special Authority criteria for relapsed/refractory brentuximab vedotin for sALCL should be reviewed if first-line use was funded.

Funding criteria

5.31. The Committee considered that the current evidence from the ECHELON-2 trial, which currently provides evidence for progression-free survival benefit from brentuximab vedotin, is limited to the treatment of previously untreated systemic anaplastic large-cell lymphoma subtype of CD30+ PTCL. Therefore, the Committee considered that it would be appropriate for funding criteria to limit access to this subgroup of previously untreated CD30+ PTCL.

Summary for assessment

5.32. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for brentuximab if it were to be funded in New Zealand for previously untreated systemic anaplastic large-cell lymphoma subtype of CD30+ PTCL. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

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

Population	Adults with previously untreated systemic anaplastic large cell lymphoma
Intervention	Brentuximab vedotin 1.8 mg/kg, cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2 administered intravenously on day 1 of each treatment cycle and prednisone 100 mg administered orally on days 1 to 5 of the treatment cycle. Treatment for six cycles.
Comparator(s) (NZ context)	Cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m2, vincristine 1.4 mg/m2 administered intravenously on day 1 of the treatment cycle and prednisone 100 mg administered orally on days 1 to 5 of a treatment cycle (CHOP). Addition of etoposide 100 mg/m² on days 1, 2, and 3 of a treatment cycle (CHOEP) in people under approximately 60 years for those whom this treatment is considered tolerable
Outcome(s)	ECHELON-2 Estimated 5 year PFS 60% vs 48% for CHOP; HR for a 30% reduction in PFS events is 0.55 (0.39-0.79) 5 year OS 76% vs 69% for CHOP; HR for survival is 0.72 (0.53-0.99)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

BV: brentuximab vedotin

6. Netupitant/palonosetron - Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic anti-cancer treatments (P-001937)

Application

6.1. The Advisory Committee reviewed an application for netupitant/palonosetron (NEPA) in the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic and moderately emetogenic anti-cancer treatments.

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

Recommendation

6.3. The Advisory Committee **recommended** that netupitant/palonosetron be listed with a **medium priority,** within the context of treatments of malignancy, for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of **highly emetogenic** anti-cancer treatments, subject to the following Special Authority criteria:

> **Initial application** from any relevant practitioner. Approvals valid for 12 months where the individual is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy, for the treatment of malignancy.
>
> **Renewal** from any relevant practitioner. Approvals valid for 12 months where the individual is undergoing highly emetogenic chemotherapy and/or anthracycline-based chemotherapy, for the treatment of malignancy.

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

6.4.1. the clinical evidence indicating NEPA to be effective and safe for the management of chemotherapy induced nausea and vomiting (CINV) during HEC or anthracycline-based chemotherapy.

6.4.2. the potential to simplify the regimen and reduce the risk of medication error associated with a complicated medicines administration regimen.

6.5. The Advisory Committee **recommended** that netupitant/palonosetron for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of **moderately emetogenic** anti-cancer treatments (MEC) **be declined**.

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

6.6.1. the risk of nausea and vomiting emesis in the moderately emetogenic chemotherapy (MEC) group being between 30-90%, which made it difficult to determine if a single funded regime would be appropriate for the whole population at risk.

6.6.2. the risk of nausea and vomiting varies between individuals. Furthermore, if an individual experiences severe vomiting and nausea during their first cycle of MEC, then taking patient risk factors into account, this MEC regime by definition becomes a HEC regime for this individual, and they would meet Special Authority criteria for NEPA for subsequent cycles.

Discussion

Māori impact

6.7. The Advisory Committee noted the health need for individuals including Māori experiencing CINV had previously been considered when PTAC and CTAC had considered had considered aprepitant in August 2021 and when it (CTAC) had considered aprepitant in April 2023 respectively.

Background

6.8. The Advisory Committee noted that aprepitant has been funded in New Zealand in since 2009 for individuals receiving highly emetogenic chemotherapy (HEC) or anthracycline containing (AC) chemotherapy.

6.9. The Committee noted that in August 2021, PTAC had deferred making any recommendation for aprepitant for nausea and vomiting associated with any MEC, pending further advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP, now CTAC). PTAC had recommended further advice be sought on the evidence supporting benefit in this wider population, defining who would most likely benefit and whether aprepitant should be used as a first- or second-line treatment.

6.10. The Committee noted that in April 2023, it (CTAC) had reviewed the funding application regarding aprepitant for nausea and vomiting associated with any MEC, and recommended the Special Authority for aprepitant should remain unchanged, with aprepitant continuing to be funded only for people receiving HEC and/or AC chemotherapy.

6.11. In making this recommendation, the Committee had noted:

6.11.1. the guidelines from MASCC and ESMO Consensus Guidelines for the Prevention of Chemotherapy and Radiotherapy-Induced Nausea and Vomiting: ESMO Clinical Practice Guidelines (MASCC/ESMO), The National Comprehensive Cancer Network (NCCN) 2023 guidelines, and The Anti-Cancer Therapy Nationally Organised Workstreams (ACT-NOW), which had categorised a range of chemotherapy regiments based on their CINV risk.

6.11.2. within the "moderately emetogenic" category, chemotherapy agents ranged from a 30% to 90% chance of causing CINV. The Committee considered it a challenge to provide one treatment that would be suitable for the entire group at risk.

6.11.3. individual-related risk factors, as well as the emetogenicity of chemotherapy agents, influence an individual's susceptibility to experiencing CINV. The Committee had considered a person's initial response to MEC to be predictive of their CINV risk for subsequent chemotherapy cycles, and consequently the regime would be defined as a HEC for the individual, and appropriate prophylaxis for vomiting and nausea can be used.

Health need

6.12. The Committee had previously noted that the management of CINV is a high priority in oncology care and that risk factors for higher rates of emesis at the individual level include previous emesis in pregnancy and the propensity for travel/motion sickness.

6.13. The Committee had previously considered control of CINV to be highly valued by individuals receiving chemotherapy, their whānau, and their wider community. It was considered that poorly controlled CINV negatively impacts the quality of life of both individuals receiving treatment and those around them and leads to higher rates of treatment discontinuation. The Committee noted evidence indicating that poorly controlled CINV can affect treatment outcomes, including progression-free survival and overall survival (Woopen et al. Support Care Cancer. 2020;28:73-8).

6.14. The Committee noted the current anti-nausea/emesis regimen for HEC/AC chemotherapy consists of aprepitant (125 mg on day 1, and 80 mg on days 2 and 3), 5-hydroxytryptamine-3 (5-HT3) receptor antagonist (day 1), dexamethasone (12 mg on day 1, and 8 mg on days 2-4) and olanzapine (prn (ie. as required)). The Committee considered this regimen can be burdensome for an individual receiving HEC/AC to manage and a simplified regimen could improve the individuals' experience.

6.15. The Committee noted the current anti-nausea/emesis regimen for MEC consists of a 5-HT3 receptor agonist (day 1) and dexamethasone (8 mg day 1-4).

6.16. The Committee noted some individuals receiving HEC/MEC can experience severe breakthrough vomiting and nausea and therefore require rescue medication. Rescue medications in addition to dexamethasone and olanzapine can include a scopolamine patch or cyclizine.

Health benefit

6.17. The Committee noted NEPA is a fixed-dose dual-therapy containing 300 mg of the neurokinin 1 (NK1) receptor antagonist (RA) netupitant and 0.5 mg of the second-generation 5-HT3 receptor antagonist palonosetron.

6.18. The Committee noted NEPA requires a single dose administration (netupitant half-life ~88 hours, palonosetron ~40 hours) taken 1-hour prior to chemotherapy on day one and is expected to be effective until day five.

6.19. The Committee noted the NETU-10-29 trial (Gralla et al. Ann Oncol. 2014;25:1333-9, Jordan et al. Support Care Cancer. 2016; 24:4617-25), which was an international, double-blinded Phase 3 study of 413 people randomised 3:1 between NEPA or aprepitant regimen who were receiving HEC or MEC. The trial duration was the first six days of each chemotherapy cycle. The Committee noted:

6.19.1. people receiving AC chemotherapy for breast cancer were excluded from this study but were included in the NETU-08-18 study discussed in following paragraphs of this record.

6.19.2. people receiving HEC chemotherapy received the NEPA regimen (day 1: NEPA and 12 mg dexamethasone, day 2-4: 8 mg dexamethasone) or the aprepitant regimen (day 1: 125 mg aprepitant + 0.5 mg palonosetron + 12 mg dexamethasone, day 2-3: 80 mg aprepitant+ 8 mg dexamethasone). People receiving MEC chemotherapy received the NEPA regime (day 1: NEPA and 12 mg dexamethasone) or the aprepitant regimen (day 1: 125 mg aprepitant + 0.5 mg palonosetron + 12 mg dexamethasone, day 2-3: 80 mg aprepitant); palonosetron is not currently funded in New Zealand, with ondansetron likely to be used instead in the New Zealand setting.

6.19.3. >75% of people received four cycles of chemotherapy, and 41% of people receiving NEPA and 47% of people receiving aprepitant discontinued or did not continue further chemotherapy cycles, predominantly for reasons unrelated to NEPA or aprepitant regimens (Gralla et al. Ann Oncol. 2014).

6.19.4. the complete response rates (CRR) (no emesis or rescue medication) during the delayed phase across six chemotherapy cycles were 81-92% for the NEPA (and 76%-88% for the aprepitant (regimens. The Committee noted the overall CRR (including acute and delayed phases) across HEC cycles were 79-91% for the NEPA group and 58-86% for the aprepitant group. Across MEC cycles CRRs were 80-93% for the NEPA group and 82-89% for the aprepitant group (Gralla et al. Ann Oncol. 2014).

6.19.5. people receiving four cycles of carboplatin-based chemotherapies had similar CRR between both the NEPA (80-93%) and aprepitant (82-90%) groups (Jordan et al. Support Care Cancer. 2016).

6.19.6. the incidence and type of adverse events were comparable for both groups, with the most frequently reported adverse events including constipation and headaches.

6.20. The Committee considered the NETU-10-29 study to be a high-quality trial, with clinically relevant population and endpoints. The Committee considered the efficacy and safety of NEPA comparable to the aprepitant regime for the management of acute and delayed CINV for people receiving HEC and MEC.

6.21. The Committee noted the NETU-08-18 trial (Aapro et al. Ann Oncol. 2014;25:1328-33, Aapro et al. Support Care Cancer. 2017;25:1127-35), an international, double-blind, Phase 3 study where 1455 people receiving AC-chemotherapy were randomised 1:1 to receive NEPA and 12 mg dexamethasone (NEPA group) or 0.5 mg palonosetron and 20 mg dexamethasone (PALO group). The trial duration was six days. Ninety-eight percent of participants were females with breast cancer.

6.21.1. The Committee noted the CRRs (no emesis or rescue medication) were:

- In the acute phase (0-24hr) 88% in the NEPA group and 85% in the PALO group (p=0.047).
- In the delayed phase (>24-120 hr) 77% in the NEPA group and 70% in the PALO group (p=0.001).
- The overall response (0-120 hr) was 74% in the NEPA group and 67% in the PALO group (p=0.001).

6.21.2. The Committee noted that during treatment people reported on whether nausea or vomiting impacted their daily living. Seventy-two percent of the NEPA group and 66% of the PALO group reported they were not affected by nausea and 90% of the NEPA group and 84% of the PALO group they were not affected by vomiting (Aapro et al. Ann Oncol. 2014).

6.21.3. The Committee considered the NETU-08-18 study to be a high-quality trial, with a large study population and clinically relevant endpoints. The Committee considered the efficacy of a NK-1RA and 5-HT3 antagonist to be superior to a 5-HT3 antagonist alone with AC chemotherapy, however noted that in New Zealand people receiving AC chemotherapies receive the aprepitant regimen to manage CINV. The Committee considered it difficult to extrapolate the health benefits experienced by people receiving an AC-chemotherapy to other MEC regimens.

6.22. The Committee noted the Zelek et al. Cancer Med. 2023;12:15769-76 and Zelek et al. Oncologist. 2021; 26: e1870–9 publications of a French multicentre, non-inferiority open-label randomised study, where 430 people receiving MEC or AC chemotherapy received a NEPA regimen (day 1: NEPA and 8 mg dexamethasone, day 2-4 8 mg dexamethasone) or aprepitant regimen (day 1: 125 mg aprepitant and 8 mg intravenous ondansetron and 8 mg dexamethasone, day 2-3: 80 mg aprepitant and 8 mg dexamethasone).

6.22.1. The Committee noted adherence to the NEPA regimen was 100%, whereas only 89% of people in the aprepitant arm received all three aprepitant doses.

6.22.2. The Committee noted the overall CRR (0-120 hr) were 65% in the NEPA group and 54% in the aprepitant group. The Committee noted the study reported NEPA to be non-inferior to aprepitant for the management of CINV in people receiving MEC or AC chemotherapy (Zelek et al. Oncologist. 2021; 26: e1870–e1879).

6.22.3. The Committee noted the post-hoc analysis of the trial (Zelek et al. Cancer Med.2023) of people receiving MEC and having risk factors for emesis (female, male <60 years, male ≥60 years receiving carboplatin, male ≥60 years not receiving carboplatin with anxiety) and noted the following CRRs (no emesis or rescue medication):

- In the acute phase (0-24 hr) were 87% in the NEPA group and 75% in the aprepitant group (p=0.019).
- In the extended phase (>24-144hr) 90% in the NEPA group and 84% in the aprepitant group (p=0.159).
- The overall extended response (0-144hr) was 77% in the NEPA group and 58% in the aprepitant group (p=0.003).

6.22.4. The Committee noted however the Zelek et al. Cancer Med.2023 post-hoc analysis extended the CRR measurement to include day six, which had not been selected prospectively as a trial outcome measure. The Committee

considered the post-hoc analysis data to be of low quality and considered that although this data may suggest NEPA might be superior in the acute phase and beyond 120 hours in people receiving non-AC MEC and those with emetogenic risk factors receiving MEC chemotherapy, there could be little certainty with this.

6.23. The Committee noted the following studies:

6.23.1. Hesketh et al. Ann Oncol.2014;25:1340-1346

6.23.2. Hesketh et al. Support Care Cancer. 2018;26:1151-9

6.23.3. Zhang et al. Ann Oncol. 2018;29:452-8

6.23.4. Navari et al. Future Oncol. 2021;17:3027-35

6.23.5. Piechotta et al. Cochrane Database Syst Rev. 2021;11:CD012775

6.24. The Committee considered the NEPA regimen to have comparable efficacy and safety to aprepitant with 5-HT3 antagonist for the management of CINV in people receiving HEC, AC chemotherapy, and people identified as having HEC (independent of the chemotherapy regimen) following their first cycle of chemotherapy.

6.25. The Committee considered the person receiving NEPA would experience effective control for CINV during chemotherapy cycles and this would translate into a significant improvement in health-related quality of life, which the Committee considered to be passed on to health benefit to family and whānau.

Suitability

6.26. The Committee noted that NEPA is a single tablet, which is advantageous for people who struggle to take tablets while they are experiencing persistent nausea. The Committee considered that this simplification of treatment regimen may reduce the risk of an affected individual forgetting to take aprepitant on the second- and third day following chemotherapy. The Committee considered this reduction in risk would likely be meaningful to the individual concerned, in terms of avoiding breakthrough nausea and emesis.

6.27. The Committee noted there was a lack of clarity around what would happen if an individual forgot to take NEPA or took it later in the treatment regimen.

6.28. The Committee noted that these people have a large number of prescriptions, and a reduced prescription load would likely benefit clinicians as well as the affected individual. Furthermore, a simpler regimen is likely to reduce the risk of medication error. The Committee also considered the simplicity of the NEPA regimen would likely be time saving for clinicians, in comparison to the time they currently need to spend educating individuals about the current CINV management regimen.

6.29. The Committee noted that children require lower doses of anti-nausea/emesis medications and the fixed-dose formulation of NEPA would not be an appropriate choice for some children.

Cost and savings

6.30. The Committee considered given its ease-of-use, NEPA would be the preferred option for clinicians and adults, subject to Special Authority criteria. The Committee noted that clinical evidence indicates there is a likely comparable health benefit between NEPA and aprepitant but considered that people who experience difficulties swallowing pills may experience greater health benefit with if a single tablet was required.

6.31. The Committee noted that having two NK1 agonists listed on the Pharmaceutical Schedule would be advantageous as people may have contraindications to one medicine, and for children for whom NEPA was likely to be unsuitable.

6.32. The Committee considered that if NEPA was funded, there would not be any significant changes in health-sector expenditure other than direct treatment costs.

Funding criteria

6.33. The Committee considered the risk of nausea and vomiting from MEC to be wide and variable between individuals and depending on the medicines used. The Committee considered this made it difficult to determine if one treatment could suitability address the health need of the whole group concerned.

6.34. The Committee considered an individual's response to treatment in the first chemotherapy cycle was likely to predict best whether HEC-related prophylaxis for CINV would be needed in subsequent cycles.

6.35. The Committee considered the current Special Authority for aprepitant to be appropriate if NEPA were to be listed. The Committee considered that specifying risk factors in the Special Authority would be too imprecise (being both too broad and too prescriptive), consequently excluding some individuals who would benefit from NEPA in their subsequent chemotherapy cycles.

Summary for assessment

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

Population	Individuals receiving highly emetogenic chemotherapy and/or anthracycline-based chemotherapy for the treatment of malignancy.
Intervention	Netupitant/palonosetron (1 tablet on day 1) Dexamethasone (8-12 mg on days 1-4) Olanzapine (prn as needed)
Comparator(s)	Aprepitant (125 mg on day 1, and 80 mg on days 2 and 3) 5-HT3 receptor agonist (day 1). Dexamethasone (12 mg on day 1, and 8 mg on days 2-4) Olanzapine (prn as needed)
Outcome(s)	Complete response (no emesis and no rescue medication) Complete protection (no emesis, no rescue medication, and no significant nausea) Total control (no emesis, no rescue medication, and no nausea)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

7. Pembrolizumab - 1st line systemic treatment for recurrent locally advanced or metastatic Merkel cell carcinoma (P-001890)

Application

7.1. The Committee reviewed the application for pembrolizumab for the first line systemic treatment of recurrent, locally advanced or metastatic Merkel cell carcinoma.

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

Recommendation

7.3. The Committee **recommended** that pembrolizumab for the first line systemic treatment of recurrent, locally advanced, or metastatic Merkel cell carcinoma be listed with a **high priority,** within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application — Merkel cell carcinoma
Applications only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Patient has locally advanced or metastatic, recurrent, Merkel cell carcinoma; and
2. Patient has not had chemotherapy for their disease in the palliative setting; and
3. Baseline measurement of overall tumour burden is documented clinically and radiologically.
4. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent).
5. Treatment with pembrolizumab to cease after a total duration of 24 months from commencement (or equivalent of 35 cycles when dosed every 3 weeks)

Renewal — Merkel cell carcinoma
Applications only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. Either:
   - 1.1. Patient's disease has had a complete response to treatment; or
   - 1.2. Patient's disease has had a partial response to treatment; or
   - 1.3. Patient has stable disease; and
2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period; and
3. No evidence of disease progression.
4. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent).
5. Treatment with pembrolizumab to cease after a total duration of 24 months from commencement (or equivalent of 35 cycles when dosed every 3 weeks)

7.4. In making this recommendation the Committee considered the following

- The high health need of individuals with Merkel cell carcinoma (MCC)
- The moderate quality evidence of efficacy
- The potentially high number of comorbidities in individuals with MCC
- The ability to treat those who are not candidates for current chemotherapy treatment

Discussion

Māori impact

7.5. The Committee discussed the impact of funding pembrolizumab for the first line systemic treatment of recurrent, locally advanced or metastatic MCC on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

7.6. The Committee noted that the treatment of neuroendocrine tumours is not a Pharmac Hauora Arotahi health area of focus.

7.7. The Committee noted whilst Māori are less likely to develop MCC, they have a lower 5-year overall survival rate compared to New Zealand European people (Lee et al.

Aus J Dermatol. 2019;60:e284-91). However, the Committee noted that the data to support overall survival rate in Māori is based on very few individuals, with wide variation in reported survival times.

7.8. The Committee considered that if funded, pembrolizumab would provide an additional treatment prior to palliative chemotherapy, which could provide additional health benefits to Māori with MCC, but that due to the low incidence of MCC in Māori, its funding would have minimal impacts on Māori health outcomes at a population level.

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

7.9. The Committee discussed the impact of funding pembrolizumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted Pacific peoples are also less likely to develop MCC than European people, accounting for <1% of the cases reported by Lee et al. 2019 using age-standardised data. Based on four cases, 1-year OS was reported to be 80%. If funded, pembrolizumab would provide an additional treatment prior to palliative chemotherapy, which could provide additional health benefits to Pacific peoples with MCC, however due to the low incidence of MCC it would have minimal impacts on overall Pacific people's health outcomes.

Background

7.10. The Committee noted no medicines specifically for the treatment of Merkel cell carcinoma (MCC) had been considered previously.

Health need

7.11. The Committee noted MCC is a neuroendocrine cancer of the skin that tends to grow fast and metastasises quickly to other parts of the body. It typically appears as a nodule on the face, head, or neck. MCC is predominantly caused by exposure to Merkel cell polyomavirus (MCPyV) or by extensive exposure to ultraviolet (UV) radiation from sunlight.

7.12. The Committee noted internationally, most cases are associated with MCPyV, however, the majority of cases of MCC in New Zealand arise from exposure to UV radiation and only about a third are estimated to be associated with the virus (Woodhouse et al. Br J Dermatol. 2018;179:1197-8).

7.13. The Committee noted the reported incidence of MCC in New Zealand is one of the highest in the world, reported to be between 0.50-0.96 per 100,000 in the population (Lee et al. Aus J Dermatol. 2019;60:e284-91; Robertson et al. Br J Dermatol 2015;173:835-7)

7.14. The Committee noted most cases of MCC in New Zealand occur in people of European or New Zealand European ethnicity (Lee et al. 2019).

7.15. The Committee noted MCC is more likely to occur in older adults and in people who are immunocompromised, such as people with solid organ transplants, human immunodeficiency virus (HIV) infection, haematological malignancy or who are on medicine such as azathioprine.

7.16. The Committee noted the increased likelihood of comorbidities in those with MCC.

7.17. The Committee noted the European consensus guidelines that reported five-year overall survival rates for MCC ranging from 48% and 63% with about a quarter of people having lymph node involvement at diagnosis and 8% being diagnosed with distant metastases (Gauci et al. Eur J Cancer. 2022;171:203-31).

7.18. The Committee noted the applicant reported that a higher proportion of New Zealanders with MCC present with metastatic disease (14.7-18%) and have worse overall 5-year survival rates of 29-31% and relative 5-year survival rates of 45-50%

(unpublished local data, NET registry; Lee et al. 2019). The Committee noted this data had wide confidence intervals but is important to consider as New Zealand specific population data, in the context of clinical trial data generated in single arm trials.

7.19. The Committee noted that although Māori are less likely to develop MCC than European people, those with MCC have poorer survival. The Committee noted that while numbers are small, the proportion of cases in Māori (based on age-standardised data) have been reported to be about 4%, however, 5-year relative survival for Māori with MCC is only 23.7% compared with the expected survival within the New Zealand population matched by age group, sex and year (Lee et al. 2019).

7.20. The Committee noted that Pacific peoples are also less likely to develop MCC than European people, accounting for <1% of the cases reported by Lee et al. 2019 using age-standardised data. Based on four cases, 1-year OS was reported to be 80%.

7.21. The Committee noted Parker et al. which reported that survival for MCPyV negative people (2.2 years on average) is worse than for those with the virus (6 years), although not statistically significant in the cohort.

7.22. The Committee noted current treatments for MCC in New Zealand consist of single agent palliative chemotherapy for locally advanced or metastatic MCC. However, outcomes are poor, and these treatments can be associated with both significant and long-term toxicities.

7.23. The Committee considered that a range of chemotherapy regimens are currently used to treat advanced MCC. The Committee considered that carboplatin with etoposide would be used among people who had good performance status while single-agent paclitaxel or carboplatin were more appropriate among those for whom an etoposide-containing regimen was less appropriate.

7.24. The Committee noted response rates to palliative chemotherapy in locally advanced or metastatic MCC are around 40-60% and there is limited durability of response with median progression-free survival (PFS) of three to five months and median overall survival of 10 months (Cowey et al. Future Oncol. 2017;13:1699-710, Iyer et al. Cancer Med.2016;5:2294-301). The Committee noted that the quality of evidence quantifying the effect of treatment in MCC is poor.

7.25. The Committee noted palliative chemotherapy may be too toxic, especially for many clinically frail individuals with MCC, and when considering the poor durability of response and poor survival outcomes, best supportive care (BSC) without any active anti-cancer treatment may be the preferred approach.

Health benefit

7.26. The Committee noted pembrolizumab is an immune checkpoint inhibitor which binds to the programmed death (PD)-1 receptor on T-lymphocytes, blocking the effects of the PD-L1 and PD-L2 ligands.

7.27. The Committee noted the KEYNOTE-017 phase II, open label, non-randomised, multicentre study in those with metastatic or recurrent MCC. The Committee noted the following publications that reported trial results:

7.27.1. The Committee noted (Nghiem et al. N Engl J Med. 2016; 374:2542-52) that reported at the median follow up of 33 weeks. Primary endpoint of objective response rate (ORR): 56% (95% confidence interval [CI], 35 to 76). 14/25 had a confirmed response: 4 with a complete response (CR) and 10 with a partial response (PR). 1/25 (4%) had stable disease, and 9 (36%) had progressive disease. 12/14 (86%) of confirmed responses were ongoing at last follow-up. Among 14 with an objective response, the response duration ranged from

≥2.2 to ≥9.7 months.10/16 MCPyV positive (62%) and 4/9 (44%) MCPyV negative had an objective response.

7.27.2. The Committee noted Nghiem et al. J Clin Oncol. 2019;37:e002478 that reported at median 14.9 months follow-up (range 0.4 to 36.4+ months). ORR was 56% (95% CI, 41.3% to 70.0%) among all 50 who had at least one on-treatment tumour assessment and one confirmatory assessment ≥4 weeks later (28 responses [12 CR, 16 PR]). Five participants (10%) had stable disease (95% CI, 3.3% to 21.8%), and 16 (32%) had progressive disease (95% CI, 19.5% to 46.7%). No significant difference in response rates between MCPyV positive and negative.

7.27.3. The Committee noted Nghiem et al. J Immunother Cancer. 2021;9:e002478 that reported at median 31.8 months of follow up. ORR to pembrolizumab was 58% (95% CI 43.2 to 71.8); this included 15 with CR and 14 with PR. Among 29 responders, Median response duration was not reached (NR, range 1.0+ to 51.8+ months. At 3 years after treatment initiation, 72.7% of responders remained in response. Most objective tumour regressions occurred soon after treatment initiation, with 90% (26/29) of CRs and PRs documented at the initial ~12-week assessment. Median PFS: 16.8 months (95%CI 4.6 to 43.4)

7.27.4. The Committee considered the population included was appropriate to New Zealand.

7.27.5. The Committee considered the evidence was of moderate quality given the rarity of the cancer.

7.28. The Committee noted the KEYNOTE- 913 Phase III, single arm trial in those with metastatic or recurrent MCC (Mortier et al. Presented at 19th International Congress of Society for Melanoma Research. 2022). The trial reported a Kaplan–Meier estimate of median duration of response (RECIST 1.1) not reached (range 4.8 to 25.4+ months); 79% remaining in response at 18 months. Kaplan–Meier estimate of median PFS: 9.3 months (95% CI 3.0 to 26.6).

7.28.1. The Committee noted this data is unpublished.

7.28.2. The Committee noted there is no control arm in the study.

7.28.3. The Committee noted the inclusion and exclusion criteria for the trial were appropriate.

7.28.4. The Committee noted the data in the poster was immature, with PFS, median duration of response and OS not reached after 31.8 months median follow up.

7.29. The Committee noted a variety of other anti- PD-L1, or PD-1 therapies have been trialled, including avelumab and nivolumab. The Committee noted D'Angelo et al. J Immunother Cancer. 2021;9:e002646 which reported the results of avelumab treatment in MCC. The Committee considered initial results suggested there may be a stronger benefit from other immunotherapies, or possibly a class effect and would like to review applications for these agents if they are received.

7.30. The Committee noted pembrolizumab may be an appropriate treatment for those who are not clinically suitable for systemic chemotherapy. The Committee noted those with MCC in general have a high number of comorbidities due to the advanced age of diagnosis.

Suitability

7.31. The Committee noted that pembrolizumab and palliative chemotherapy are administered as intravenous infusions and therefore are unlikely to affect individuals being treated in terms of suitability.

7.32. The Committee considered that a 6 weekly dosing regimen, or weight-based dosing, with pembrolizumab were likely to be clinically appropriate and potentially more suitable than the 3-weekly pembrolizumab regimen for some individuals.

Cost and savings

7.33. The Committee noted that an estimated 20 to 21 people with advanced/metastatic MCC may be eligible for treatment with pembrolizumab per year, based on an incidence of MCC of 0.96 per 100,000 per year (Lee et al. Australasian J Dermatol. 2019;60: e284-e291) and roughly 40% of cases being locally advanced or metastatic at diagnosis (Robertson et al. Br J Dermatol 2015;173:835-7). The Committee noted that the number of MCC cases per year may rise in the medium-term future due to the oldest age cohorts in New Zealand being exposed to particularly high levels of ultraviolet radiation historically.

7.34. The Committee noted that if pembrolizumab were to be funded for MCC, there was the potential for use outside the intended population because some people who would otherwise receive locoregional therapies, such as surgical resection, may be considered candidates for pembrolizumab treatment. The Committee considered if pembrolizumab were to be funded for these other populations, treatment would most likely occur prior to surgical or radiation treatment.

7.35. The Committee noted funding pembrolizumab for advanced/metastatic MCC would likely increase health system resource use in hospital infusion clinics, as it is administered as a 30-minute intravenous infusion. The Committee noted that this is a shorter infusion time than either cisplatin or etoposide, however, the overall treatment duration may be longer.

7.36. The Committee noted that pembrolizumab was associated with immune-related adverse effects, which may require additional treatment and health system resource.

7.37. The Committee noted that funding pembrolizumab for advanced/metastatic MCC may delay or reduce the use of surgery and other palliative treatments for MCC, a phenomenon that has been observed in the setting of metastatic melanoma. The Committee noted however that the magnitude and materiality of this impact was unclear.

7.38. The Committee considered the uptake would be high if pembrolizumab were funded, with the majority of population with MCC undertaking treatment.

7.39. The Committee considered that few, if any, people would receive subsequent systemic treatments after experiencing disease progression on pembrolizumab due to the population affected being relatively elderly and the modest benefit such treatments would provide.

Factors informing economic assessment

7.40. The Committee noted that because KEYNOTE-017 did not have a comparator arm, any economic assessment of pembrolizumab for MCC would need to indirectly compare pembrolizumab treatment with currently funded chemotherapies. The Committee considered that indirect comparisons, although necessary for some economic assessments, introduce inherent uncertainty into an economic assessment. The Committee noted that they may not produce valid comparisons if the baseline characteristics between two studies are substantially different, or if the treatments used in the studies do not reflect the regimens most commonly used in New Zealand.

7.41. The Committee considered a historical cohort study of people with advanced MCC which could be used to inform survival outcomes in the comparator arm of the economic assessment of pembrolizumab (Cowey et al. Future Med. 2017;13:1699-1710). The Committee noted that in both Cowey et al (2017) and KEYNOTE-017,

participants had not received systemic therapies prior to study inclusion, and immunocompromised individuals were excluded.

7.42. The Committee considered however that it was unclear how comparable the two study populations were because KEYNOTE-017 did not report the ECOG statuses of participants at baseline, as such it was unclear the extent to which differences in survival between the two populations was driven by different baseline characteristics between the populations.

7.43. The Committee considered that the main source of uncertainty in the economic assessment of pembrolizumab for MCC would be survival outcomes in the comparator arm, given the available data is of low quality. The Committee considered that the impact of this uncertainty could be addressed by varying comparator arm survival outcomes widely in sensitivity analysis.

Funding criteria

7.44. The Committee noted that limiting funded access to pembrolizumab to 24 months duration was appropriate considering this was the maximum treatment duration of the clinical trials.

7.45. The Committee considered that response to pembrolizumab would occur quickly after treatment and therefore individuals would only remain on treatment if a response was observed, preventing individuals from remaining on treatment that did not provide health benefit, and reducing related costs.

Summary for assessment

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

Population	People with locally advanced/metastatic or recurrent Merkel cell carcinoma, who have not received prior systemic treatment in the metastatic or recurrent setting.
Intervention	Pembrolizumab, 200mg every three weeks Treatment continued until disease progression or unacceptable toxicity.
Comparator(s) (NZ context)	Among people experiencing good performance status • Carboplatin 5 AUC on day 1 and etoposide 100mg/m^2 on days 1 and 3, every 21 days Among people experiencing poor performance status • Carboplatin 5 AUC on day 1, every 21 days • Paclitaxel 80mg/m^2 on days 1 and 8 and 15, every 21 days Treatment continued until disease progression or unacceptable toxicity.
Outcome(s)	Improved progression-free survival (PFS) • Based on indirect comparison between PFS reported in Cowey et al (Future Oncol. 2017;13: 1699-1710) and KEYNOTE-017 Improved overall survival (OS) • Based on indirect comparison between OS reported in Cowey et al (Future Oncol. 2017;13: 1699-1710) and KEYNOTE-017

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

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

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

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

8. Atezolizumab - adjuvant treatment of Non-Small Cell Lung Cancer (NSCLC), PD-L1 positive

Application

8.1. The Advisory Committee reviewed the application for atezolizumab for the adjuvant treatment of programmed death-ligand 1 (PD-L1) positive non-small cell lung cancer (NSCLC).

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

Recommendation

8.3. The Advisory Committee **deferred** making a recommendation for atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung cancer, pending publication of longer-term overall survival data from the IMpower010 trial. The Committee also requested that the statistical analysis plan be included with the submission of any further evidence.

Discussion

Māori impact

8.4. The Committee discussed the impact of funding atezolizumab for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung cancer on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes. The Committee noted the treatment of lung cancer is one of Pharmac's Hauora Arotahi. The Committee noted that Māori are disproportionately impacted by lung cancer with a higher rate of incidence and presenting at an earlier age compared with non-Māori.

8.5. The Committee note that Māori with lung cancer are usually diagnosed at a late stage of disease when treatment tends to be palliative. The Committee noted lung cancer contributes to inequities in health outcomes, with mortality rates 1.37 times higher for Māori compared with non-Māori (Robson et al 2010).

8.6. The Committee noted that Māori are underrepresented in stage II-IIIA NSCLC and funding atezolizumab in this setting would have limited impact on the health of Māori in general but would provide a benefit to those with stage II-IIIA NSCLC. The Committee considered that if effective and targeted screening programmes were funded to identify lung cancer at an earlier stage, proportionally more Māori would likely receive greater benefit from this funding application.

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

8.7. The Committee discussed the impact of funding atezolizumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted the Te Aho lung cancer quality improvement

monitoring report that reported Pacific peoples have the lowest curative resection rate overall at 12.2% compared with other ethnic groups (13.4% for Māori, 25.0% for Asian people, and 17.2% for NZ European/Other). The Committee considered this is due to later diagnosis, with tumours not curatively unresectable, and therefore the funding of atezolizumab as an adjuvant treatment would have a limited effect in this setting on the health of Pacific peoples without further effort to identify and diagnose lung cancer at an earlier stage.

Background

8.8. The Committee noted that immune checkpoint inhibitors are funded for advanced or metastatic, unresectable NSCLC, with atezolizumab specifically funded for second line monotherapy treatment.

Health need

8.9. The Committee noted it had previously reviewed the health need for those with epidermal growth factor receptor (EGFR) positive stage IB to IIIA NSCLC in July 2023 when considering an application for adjuvant osimertinib. The Committee noted that NSCLC is grouped into five stages, with the current application including stages II to IIIA.

8.10. The Committee noted that approximately 17% of lung cancers are resected in New Zealand, of which approximately two thirds are stage I, and therefore not considered within the application.

8.11. The Committee noted Stage II NSCLC is divided into two subgroups: stage IIA and stage IIB, where the former describes a tumour 4 cm to 5 cm in size that has not spread to the nearby lymph nodes whilst the latter is either a tumour that is 5 cm or less in size that has spread to the lymph nodes within the lung, or more than 5 cm wide that has not spread to the lymph nodes. In stage IIIA cancers, the tumour is 5 centimetres or smaller and has spread to lymph nodes on the same side of the chest as the primary tumour.

8.12. The Committee noted in 2019, a total of 2344 lung cancer registrations were recorded in New Zealand, with an age standardised rate of 27.6 per 100,000 (Ministry of Health, 2021).

8.13. The Committee noted a study in 2007 that analysed 565 cases from regional databases and the New Zealand Cancer Registry. The study reported a high proportion of advanced stage at presentation, with 59% of all cases of NSCLC presenting with either stage IIIB or IV disease (Stevens et al. J Thorac Oncol. 2007;2:481-93).

8.14. The Committee noted early-stage NSCLC may be asymptomatic and often presents with generalised non-specific symptoms, including appetite loss, chest pain, fatigue, shortness of breath, weight loss and unexplained haemoptysis (Bradley et al. Adv Ther. 2019;36:19-30).

8.15. The Committee noted for stage II–III disease, with a higher risk of recurrence, platinum-based chemotherapy (as an adjuvant or neoadjuvant therapy) together with surgery is recommended to reduce the risk of micro-metastases and improve survival outcomes compared with surgery alone (Postmus et al, Ann Oncol. 2017;28(suppl_4):iv1-iv21; Non-Small Cell Lung Cancer - Early and Locally Advanced, National Comprehensive Cancer Network 2023).

8.16. The Committee noted the LACE meta-analysis that reported a small incremental benefit (5-year 5.4% absolute increase in overall survival) for those receiving adjuvant chemotherapy (Pignon et al J Clin Oncol. 2008;26:3552-9).

8.17. The Committee noted the rate of recurrence for individuals with resectable stage I–III NSCLC remains high (NSCLC Meta-analysis Collaborative Group, Lancet. 2014;383:1561-71). Approximately 30% to 55% of individuals with NSCLC develop recurrence and die of their disease despite resection with curative intent (Uramoto et al. Transl Lung Cancer Res. 2014; 3: 242–9).

8.18. The Committee noted that Māori are disproportionately impacted by lung cancer, compared with non-Māori. In 2019, the incidence of lung cancer for Māori was 68.4 per 100,000. Lung cancer also presents at an earlier age in Māori compared with non-Māori, incidence rates peaking at age 70-74 years for Māori (730.3 per 100,000) and age 80-84 years for non-Māori (256.9 per 100,000) (Ministry of Health, 2019).

8.19. The Committee noted a 2008 study that reported after adjusting for age, gender, deprivation, and Charlson comorbidity index, Māori were less likely to have localised disease than European cases (OR: 0.5 [0.3–1.0]); and specifically, they were more likely to have locally advanced rather than localised lung cancer compared with European cases (all cases: [OR]: 2.6 [95% CI: 1.3–5.3], $p < 0.01$; cases with NSCLC: OR: 2.7 [1.3–5.7], $p < 0.01$). The Committee noted for cases with stage I/II NSCLC, stage IIB was more common in Māori ($p = 0.003$) (Stevens et al. J Thorac Oncol. 2008;3:237-44).

8.20. The Committee noted the Te Aho lung cancer quality improvement monitoring report, that reported Māori had a lower curative resection rate overall compared with other ethnic groups (13.4% for Māori, 12.2% for Pacific people, 25.0% for Asian people, and 17.2% for NZ European/Other). In addition, Māori also had the lowest overall survival of all ethnic groups, with 37.7 percent alive one year after diagnosis, 21.6 percent two years after diagnosis and 17.5 percent three years after diagnosis.

8.21. The Committee noted those with lung cancer are usually diagnosed at a late stage of disease when treatment tends to be palliative. Lung cancer contributes to inequities in health outcomes, with mortality rates three to four times higher for Māori compared with non-Māori (Robson et al 2010).

8.22. The Committee noted the Te Aho lung cancer quality improvement monitoring report that reported Pacific peoples have the lowest curative resection rate overall at 12.2% compared with other ethnic groups (13.4% for Māori, 25.0% for Asian people, and 17.2% for NZ European/Other). The Committee considered this is due to later diagnosis, with tumours unresectable, and therefore the funding of atezolizumab in this setting would have a limited effect on the health of Pacific peoples without further efforts to identify and diagnose lung cancer at an earlier stage.

8.23. The Committee noted the State of Cancer in New Zealand 2020 report that reported cancer survival is poorer as socioeconomic deprivation increases.

Health benefit

8.24. The Committee noted atezolizumab is a humanised immunoglobulin monoclonal antibody which targets PD-L1 on tumour infiltrating immune cells or tumour cells.

8.25. The Committee noted that atezolizumab would be administered to those who had undergone surgical resection, been treated with adjuvant chemotherapy, and had PD-L1 expression on ≥1% of tumour cells.

8.26. The Committee noted a meta-analysis (Mauguen et al. Lancet Oncol. 2013;14:619-26) provided by the supplier reported a good level of correlation between disease free survival (DFS) and chemotherapy in the adjuvant chemotherapy setting. The Committee considered these results are not applicable to immunotherapy. The Committee noted that DFS as a surrogate end point has not been adopted as a validated surrogate end point for lung cancer.

8.27. The Committee noted overall survival (OS) is the gold standard end point for NSCLC clinical trials with curative intent.

8.28. The Committee considered that six years disease free survival post-surgery would represent a cure in this setting.

8.29. The Committee noted the IMpower010 multicentre, open-label, phase 3 study in those with completely resected stage IB (tumours ≥4 cm) to IIIA NSCLC. Individuals received either adjuvant atezolizumab or best supportive care after adjuvant platinum-based chemotherapy (1-4 cycles).

8.29.1. The Committee noted the Felip et al. Lancet 2021; 398: 1344–57 publication, which reported IMpower010 trial results at a median follow up of 32.2 months:

- In the stage II–IIIA population, atezolizumab treatment improved DFS compared with best supportive care in the stage II–IIIA population whose tumours expressed PD-L1 on ≥1% of tumour cells (hazard ratio (HR) 0·66; 95% confidence interval (CI) 0·50–0·88; p=0·0039, median not estimable (NE) vs 35.3 months) and all in the stage II–IIIA population (0·79; 0·64–0·96; p=0·020, median 42.3 months vs 35.3 months).
- In the intention to treat (ITT) population, HR for DFS was 0·81 (0·67–0·99; p=0·040) (median NE vs 37.2 months).
- Atezolizumab-related grade 3 and 4 adverse events occurred in 53 (11%) of 495 individuals and four (1%) treatment related deaths.

8.29.2. The Committee noted the Wakelee et al. JTO, 2022, 17, SS2 publication, which reported results of the IMpower010 trial at a median follow up of 46 months:

- OS trend in favour of atezolizumab was reported in the population whose tumours expressed PD-L1 on ≥1% of tumour cells at stage II-IIIA (OS HR, 0.71 [95% CI: 0.49, 1.03]).
- An OS trend in favour of atezolizumab was also observed in PD-L1 on ≥50% of tumour cells at stage II-IIIA subpopulation (OS HR, 0.43 [95% CI: 0.24, 0.78]).
- OS benefit favouring atezolizumab was not observed in the all-randomised stage II-IIIA or intention to treat populations.
- There were no new or unexpected safety signals.

8.29.3. The Committee considered that the majority of the benefit in IMpower010 was in individuals who had PD-L1 expression on ≥50% of tumour cells, where a statistically significant OS benefit was observed. However, the Committee noted that this was not a pre-specified endpoint and was instead analysed as a subgroup post-hoc. Without pre-specification there is additional risk of a false positive finding, so the Committee advised that this result should be interpreted with caution.

8.29.4. The Committee noted the OS data had not reached statistical significance in the intention to treat population, and median OS was also not reached. The Committee noted that the data was immature, with further trial results still to be published.

8.30. The Committee considered that the current uptake of adjuvant chemotherapy in New Zealand is significantly lower than in the trial population, and that these lower uptake rates would need to be considered in the assessment, noting that the availability of a PD-1 inhibitor in this setting may increase the uptake of chemotherapy.

8.31. The Committee noted second-line treatment (ie after progression on atezolizumab or best supportive care) was based on clinician choice and there were a variety of treatments used depending on the trial centre. This could affect interpretation of the OS data in a New Zealand context where some of these treatments are not available (such as bevacizumab and nivolumab). The Committee noted New Zealand did not participate in the pivotal trials.

8.32. The Committee considered the trial data seems to suggest those with anaplastic lymphoma kinase (ALK) or EGFR mutations gain less health benefit from atezolizumab compared to the general population with NSCLC. The Committee noted the evidence in the adjuvant setting is not as mature as the advanced setting. The Committee note that European Society for Medical Oncology (ESMO) guidelines (Passaro et al. Ann Oncol. 2022;33:466-87) reported that EGFR- or ALK-positive tumours rarely derive sufficient responses to immune checkpoint inhibitors, with lower response rates reflected in shorter progression free survival, and a lack of response in high PD-L1 expressing advanced NSCLC tumours with ALK or EGFR mutations when treated with pembrolizumab.

8.33. The Committee noted there was evidence of an increase in the rate of adverse events when a TKI is administered following disease progression after a PD-1 or PD-L1 inhibitor (Schoenfeld et al. Ann Oncol. 2019;30:839-44).

8.34. The Committee noted the following studies:

- Kenmotsu et al. Cancer Sci. 2022;113:4327-38.
- Lee et al. J Thorac Cardiovasc Surg. 2023;166:655-6.
- Spigel et al. J Thorac Oncol. 2018;13:1733-42

8.35. The Committee noted the interim analysis of the KEYNOTE-091 trial (O'Brien et al. Lancet Oncol. 2022;23:1274-86) that investigated the effect of another PD-1 inhibitor, pembrolizumab, in individuals with stage IB-IIIA NSCLC. The median follow up was 35.6 months. The Committee also noted that:

8.35.1. Chemotherapy was not mandatory in the trial, and that the proportion of those with stage III was less than in the IMpower010 study.

8.35.2. In the overall population, median DFS was 53·6 months (95% CI 39·2 to not reached) in the pembrolizumab group versus 42·0 months (31·3 to not reached) in the placebo group (HR 0·76 [95% CI 0·63-0·91], p=0·0014).

8.35.3. In the PD-L1 tumour proportion score (TPS) of ≥50% population, median DFS was not reached in either the pembrolizumab group (95% CI 44·3 to not reached) or the placebo group (95% CI 35·8 to not reached; HR 0·82 [95% CI 0·57-1·18]; p=0·14).

8.35.4. Grade 3 or worse adverse events occurred in 34% vs 26% in pembrolizumab and placebo group respectively. Serious adverse events occurred in 24% vs 15% in pembrolizumab and placebo group respectively. Four deaths occurred in the pembrolizumab group.

8.35.5. The trial reported different outcomes to the IMpower010 trial, with DFS being lower in those with a PD-1 score of ≥50% compared to the whole intention to treat population. The Committee noted the study authors suggested this was due to the placebo group in those with a PD-1 score ≥50% having higher median DFS than in the PD-L1 score 1-49% and ≤1% groups, however there was no obvious baseline characteristic imbalances to explain this. The Committee considered that there was variation in results between PD-1 inhibitors in this indication, between PD-1 score subgroups.

8.36. The Committee noted that international regulatory and health technology assessment (HTA) approvals varied with by PD-L1 score (>1%, >50% and >50% excluding those with ALK/EGFR mutations).

Suitability

8.37. The Committee noted that atezolizumab is administered as an intravenous infusion, initially over 60 minutes, which can be reduced to 30 minutes for subsequent infusions. The Committee noted that this would require individuals to travel to infusion centres, and considered this is particularly difficult for those in rural areas. The Committee considered additional help from whānau, or carers may be needed for individuals to attend these appointments, as well as treatment impacting on an individual's time away from work or whānau.

8.38. The Committee noted PD-L1 testing is required to identify those people suited for the treatment. The Committee noted in the early-stage disease setting, PD-L1 testing is not widely undertaken in New Zealand at present. The Committee noted that there were several assays for PD-L1 testing, with results affected by time to sample processing, fixation time, and sample type isolated. In addition, the assay utilised in the KEYNOTE-091 study is not validated for use in New Zealand, as the machine to read the assay results is not available. The Committee noted a national consistent protocol would be necessary to ensure equitable access.

Cost and savings

8.39. The Committee considered that the use of adjuvant chemotherapy in New Zealand was low, with approximately 30 to 60% of people with stage II-IIIA lung cancer receiving this. The Committee considered this would increase if atezolizumab would be funded, which would place additional demand on infusions services. The Committee also noted that atezolizumab would be funded for more cycles than standard of care chemotherapy.

8.40. The Committee considered approximately 4% of those who received atezolizumab may have an immune adverse event that would require hospitalisation.

8.41. The Committee considered there was no clear evidence on the use of a second immune checkpoint inhibitor after atezolizumab treatment. The Committee noted in the IMpower010 trial there was a low rate of retreating individuals who received atezolizumab after their disease relapsed, with 18% receiving a subsequent immune therapy vs 49% in the control arm. The Committee considered clinician choice might vary depending on the timing of disease relapse, with clinicians less likely to re-treat with an immune therapy if an individual progresses whilst receiving, or soon after completion, of atezolizumab treatment.

8.42. The Committee noted the consideration of further treatments is also affected by the health of the individual and their fitness to receive a further immune checkpoint inhibitor.

Funding criteria

8.43. From the currently available data, the Committee could not determine whether it was appropriate to restrict access to those with PD-L1 expression on ≥50% of tumour cells. The Committee noted more mature data would be needed to make this determination as well as consideration of the statistical analysis plan.

8.44. The Committee noted it had no consensus on the inclusion or exclusion of those with ALK or EGFR mutations, due to deferring its recommendation.

Summary for assessment

8.45. The Advisory Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator,

outcomes) information for atezolizumab if it were to be funded in New Zealand for the adjuvant treatment of PD-L1 positive stage II-IIIA non-small cell lung cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with stage II-IIIA, PD-L1 positive (≥1%), NSCLC who have had their tumour resected and received up to 4 cycles of adjuvant, platinum-based chemotherapy that do not have EGFR or ALK mutations
Intervention	Atezolizumab 1,200 mg every 3 weeks until disease recurrence or unacceptable toxicity, for a maximum of one year (16 cycles). Upon disease recurrence, people would receive additional treatments for advanced disease. A second immune checkpoint inhibitor (pembrolizumab) is likely to be used in the advanced setting for people who did not progress while receiving atezolizumab. .
Comparator(s) (NZ context)	Best supportive care (BSC) Upon disease recurrence, people would receive additional treatments for advanced disease, namely pembrolizumab monotherapy or in combination with chemotherapy
Outcome(s)	• Longer disease-free survival. The median DFS in the Impower010 trial was not reached for the PD-L1 ≥1% atezolizumab group and was 35.3 months for the PD-L1 ≥1% BSC group (HR 0.66, 95% CI 0.50-0.88) • Possibly longer overall survival, pending follow-up results • Higher rates of grade 3-4 adverse events. In the Impower010, 22% of those in the atezolizumab arm had a grade 3-4 adverse event, compared with 12% in the BSC arm

Table definitions:

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

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

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

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

9. Subcutaneous pertuzumab-trastuzumab (pertuzumab and trastuzumab fixed dose SC inj) for the treatment of HER2-positive breast cancer

Application

9.1. The Committee reviewed the application from Roche Products NZ Ltd for the use of subcutaneous pertuzumab and trastuzumab, a combined product containing two treatments that is administered subcutaneously (SC). The Committee noted that the application proposed that this formulation ("pertuzumab-trastuzumab SC") be funded in the community and in hospital as an additional option for people eligible for funded intravenous (IV) pertuzumab and trastuzumab for the following indications:

9.1.1. Neoadjuvant treatment of human epidermal growth factor receptor 2 (HER2)-positive, locally advanced, inflammatory, or early-stage breast cancer at high risk of recurrence

9.1.2. Adjuvant treatment of individuals with HER2-positive early breast cancer at high risk of recurrence in combination with chemotherapy

9.1.3. HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel

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

Recommendation

9.3. The Committee **recommended** that pertuzumab-trastuzumab SC for the neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer in combination with chemotherapy at high risk of recurrence be listed with a **medium priority,** within the context of treatments for malignancy.

9.4. In making this recommendation, the Committee considered:

9.4.1. PTAC's recommendation for CTAC to assess the additional data provided for pertuzumab-trastuzumab SC in the neoadjuvant setting.

9.4.2. There to be reasonable data which suggests that pertuzumab-trastuzumab SC provides non-inferior efficacy to the intravenous formulations.

9.4.3. The potential person-centred advantages of subcutaneous administration including reduced time spent on receiving treatment.

9.5. The Committee **recommended** that pertuzumab-trastuzumab SC for the treatment of HER2-positive metastatic or locally recurrent unresectable breast cancer in combination with docetaxel be listed with a **high priority,** within the context of treatments for malignancy.

9.6. In making this recommendation, the Committee considered:

9.6.1. The evidence of noninferiority between the SC formulation and the current IV standard of care treatment regimen, which is relevant to the treatment of this population with metastatic breast cancer in New Zealand.

9.6.2. Potential suitability benefits of the SC formulation in comparison to IV formulation, which include reduced health system resource requirements, improved experience for people receiving the treatment due to reduced time spent on receiving healthcare, and improved access to treatment, particularly if access to SC treatment was available in rural settings.

9.6.3. The need for a proactive implementation plan supported by Te Whatu Ora to provide training and resources in less urban locations to administer SC treatment and clinically monitor for and manage any adverse effects.

Discussion

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

Māori impact

9.8. The Committee considered the high health need of people with breast cancer in New Zealand, including the high impact on Māori, has been previously considered by CTAC and PTAC. The Committee noted that the treatment of breast cancer is one of Pharmac's Hauora Arotahi (Māori health areas of focus) and considered that the incidence of HER-2 positive breast cancer was likely similar among Māori and non-Māori.

9.9. The Committee noted a study, investigating urban and rural differences in breast cancer characteristics in New Zealand, reported that women with breast cancer living in rural areas tended to be older and were more likely to be Māori. The Committee

noted wāhine Māori living in rural settings tended to be older, more likely to be diagnosed with metastatic disease and less likely to have had their condition diagnosed through screening than Māori residing in urban areas (Lawrenson et al. Int J Environ Res Public Health. 2016;13:1000). The Committee considered that access to subcutaneous treatment would reduce some barriers to treatment for those living rurally, such as travel time, time off work, and transport.

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

9.10. The Committee considered the impact of HER2-positive breast cancer on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system.

9.11. The Committee noted that Pacific women are overrepresented in the target population, as they are more than twice as likely to have HER2-positive breast cancer than Māori and other women (14.2% vs. 6.7% and 6.0%; Lawrenson et al. 2016).

Background

9.12. The Committee noted that PTAC reviewed the application in November 2022, and made the following recommendations:

9.12.1. Neoadjuvant treatment of HER2-positive, locally advanced, inflammatory, or early-stage breast cancer: Deferred recommendation, pending CTAC's assessment of the additional data provided for pertuzumab in the neoadjuvant setting.

9.12.2. Adjuvant treatment of patients with HER2-positive early breast cancer: Deferred recommendation, pending the final overall survival analysis of the APHINITY study planned to be conducted in approximately 2024. CTAC agreed with this recommendation.

9.12.3. HER2-positive metastatic or locally recurrent unresectable breast cancer: Recommended listing only if cost-neutral to the combined cost of the single IV agents.

9.13. The Committee noted that IV pertuzumab is funded for the treatment of metastatic breast cancer and IV trastuzumab is funded for both early breast cancer and metastatic breast cancer, subject to eligibility criteria.

Health need

9.14. The Committee considered that the high health need of people with breast cancer in New Zealand, including the high impact on Māori, has been previously considered by CTAC and PTAC. Members considered that the incidence of HER-2 positive breast cancer was likely similar among Māori and non-Māori.

9.15. The Committee noted a study investigating urban and rural differences in breast cancer in New Zealand reported that women with breast cancer living in rural areas tended to be older and were more likely to be Māori. The Committee noted there were no differences between women living in urban and rural areas in regard to their survival, however, wāhine Māori living in rural settings had worse breast cancer-specific survival and all-cause survival at 10 years (at 72.1% and 55.8%, respectively) compared to Māori living in urban areas (at 77.9% and 64.9% respectively). The Committee noted wāhine Māori living in rural settings tended to be older, more likely to be diagnosed with metastatic disease and less likely to have had their condition diagnosed through screening than Māori residing in urban areas (Lawrenson et al. Int J Environ Res Public Health. 2016;13:1000). The Committee considered that access to SC treatment would reduce some barriers to treatment for those living rurally, such as travel time, time off work, and transport.

Health benefit

9.16. The Committee considered that health benefits of funding pertuzumab-trastuzumab SC were different for the different indications discussed, as funding would mean new treatment options in the adjuvant and neo adjuvant settings, whereas it would mean an additional formulation option only for those with metastatic or locally recurrent unresectable breast cancer.

Early stage breast cancer

9.17. The Committee noted results from the FeDeriCa study; a phase 3, multicentre, randomised (1:1), open-label, non-inferiority study of 500 adult with HER2-positive, operable, locally advanced, or inflammatory stage II–IIIC breast cancer, ECOG performance status of 0-1, and a left ventricular ejection fraction of ≥55% (Tan et al. Lancet Oncol. 2021;22:85-97; Supplementary Appendix; Correction; Comment by Bartsch et al. 2021) which was previously reviewed by PTAC in November 2022. The Committee noted that participants received either IV pertuzumab (840 mg loading dose, then 420 mg maintenance doses) and IV trastuzumab (8 mg/kg loading dose, then 6 mg/kg maintenance doses) or a fixed-dose combination of pertuzumab and trastuzumab for SC injection (1200 mg pertuzumab with 600 mg trastuzumab loading dose in 15 mL, then 600 mg pertuzumab with 600 mg trastuzumab maintenance doses in 10 mL), administered every three weeks with neoadjuvant chemotherapy for both groups

9.17.1. The Committee noted the design of the FeDeriCa study was not powered to assess equivalence of the efficacy of the SC and IV formulations. The Committee noted that the investigator reported a non-inferior rate of pathological complete response in the total intention-to-treat population. However, the Committee considered it was unable to confirm the statistical validity of that assessment from the information provided in the study.

9.18. The Committee was made aware of results from the NEOSPHERE trial, which provides the primary evidence for the efficacy of trastuzumab/pertuzumab IV formulations in the treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer (Gianni et al. Lancet Oncol. 2012;13:25-32). The Committee noted that CaTSoP (now CTAC) reviewed this trial as evidence for efficacy of the treatment in September 2018.

9.19. The Committee was made aware of supporting Bayesian evidence from the I-SPY2 trial that trastuzumab/pertuzumab (IV) was superior to trastuzumab emtansine chemotherapy.

9.20. The Committee was made aware of the Tryphaena study (Schneeweiss et al. Eur J Cancer. 2018:89:27-35) as evidence of cardiac safety for trastuzumab/pertuzumab (IV).

9.20.1. The Committee noted that pathologic complete response (CR) was a secondary endpoint of the study.

9.20.2. The Committee noted that the study was not powered to detect a difference in rate of pathologic CR. However, the Committee considered results from the study support the notion that the combination of trastuzumab/pertuzumab increases the rate of pathologic CR, regardless of chemotherapy ‘backbone’.

9.20.3. The Committee noted that the study included a post-hoc long-term survival phase which reported pathologic CR, but with no comparator.

9.20.4. The Committee noted the study signalled that those who had pathologic CR has better disease-free survival (DFS) than those without but did not consider this sufficient evidence of surrogacy.

9.21. The Committee was made aware of results from the BERENICE study; a phase 2, randomised study between two backbone chemotherapy regimens in the neoadjuvant setting, assessing cardiac safety, reporting relative safety and pathologic CR of trastuzumab/pertuzumab IV (Dang et al. Cancers (Basel). 2022; 14: 2596). The five-year event-free survival (EFS) rates in those who received dose dense doxorubicin and cyclophosphamide followed by paclitaxel (cohort A) or 5-fluorouracil, epirubicin, cyclophosphamide followed by docetaxel (cohort B) both followed by pertuzumab–trastuzumab, were 90.8% (95% CI: 86.5, 95.2) and 89.2% (84.8, 93.6), respectively. The five-year overall survival rates were 96.1% (95% CI: 93.3, 98.9) and 93.8% (90.3, 97.2), respectively. There were no new cardiac issues and a low incidence of Class III/IV heart failure.

9.22. The Committee was made aware of results from the KRISTINE study; a phase 3, randomised, controlled, open-label study which utilised pertuzumab/trastuzumab in the standard of care control-arm (neoadjuvant trastuzumab emtansine plus pertuzumab (T-DM1+P) with docetaxel, carboplatin, trastuzumab plus pertuzumab (TCH+P)) (Hurvitz et al. J Clin Oncol. 2019;37:2206-16). Risk of an EFS event was higher with TDM-1+P (hazard ratio [HR], 2.61 [95% CI, 1.36 to 4.98]) with more locoregional progression events before surgery (15 [6.7%] v 0). Risk of an invasive disease-free survival (IDFS) event after surgery was similar between arms (HR, 1.11 [95% CI, 0.52 to 2.40]). Pathologic CR was associated with a reduced risk of an IDFS event (HR, 0.24 [95% CI, 0.09 to 0.60]) regardless of treatment arm.

9.23. The Committee considered that there is little published evidence post-2012 assessing the efficacy of trastuzumab/pertuzumab, and it is unlikely further studies evaluating the efficacy will be undertaken, given that NEOSPHERE provides the primary evidence for this.

9.24. The Committee reviewed evidence for local and systemic reactions to the IV and SC formulations of trastuzumab/pertuzumab. The Committee noted higher rates of procedural pain reported for pertuzumab-trastuzumab SC, and higher administration related reactions with the IV formulation. The Committee noted that systemic reactions in FeDeriCa were rare. However, the Committee noted that the trials were under-powered to detect differences in systemic reactions between pertuzumab-trastuzumab SC and IV.

9.25. The Committee noted results from the PHranceSCa study; a phase II, randomised (1:1), open-label crossover study reporting patient preference for pertuzumab-trastuzumab SC compared with IV pertuzumab and trastuzumab and capturing perceived and actual time savings (O'Shaughnessy et al. Eur J Cancer. 2021;152:223-32). The Committee noted that preference for subcutaneous treatment was "very strong" in about two-thirds of respondents; main reasons being reduced clinic time and greater comfort during administration.

9.26. The Committee noted results from the 8.4 year follow up of the APHINITY trial, which provides evidence for pertuzumab-trastuzumab SC in the adjuvant setting, reported no significant overall survival advantage compared to chemotherapy and trastuzumab alone. The Committee noted that PTAC deferred making a recommendation for the indication in November 2022, pending the final publication of APHINITY, however considered it unlikely than a statistically significant finding would occur in the final analysis (2024).

Metastatic breast cancer

9.27. The Committee noted that there is no PK equivalence data identified for pertuzumab-trastuzumab SC in the metastatic setting. The Committee considered this an area where there is a theoretical risk of the maximum serum concentration (Cmax) being important (due to risk of underdosing in this population). The Committee considered

there may be a risk of undertreating those with a high burden of disease in the first 1-2 cycles.

Early and metastatic breast cancer

9.28. The Committee noted results from a meta-analysis that characterised the risk of anaphylaxis/hypersensitivity with intravenous pertuzumab plus trastuzumab, the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection or concomitant chemotherapy. The Committee noted the study reported that both formulations were well tolerated, with few grade ≥3 anaphylaxis/hypersensitivity events reported with the IV formulation and no grade ≥3 related events with SC, with most events occurred during chemotherapy. The Committee considered this showed reasonable heterogeneity across disease setting (both early and metastatic) and companion chemotherapy treatments. The Committee considered the meta-analysis poor quality evidence to compare systemic reactions between formulations as the FeDeriCa study provided the only data for neoadjuvant treatment with pertuzumab trastuzumab IV compared with pertuzumab trastuzumab SC in this analysis, but considered it did not signal increased problems with the subcutaneous formulations (Swain et al. Eur J Cancer. 2023;178:70-81).

9.29. The Committee noted the results from a simulation study which compared the performance of body size-based and fixed dosing in reducing pharmacokinetic (PK) and/or pharmacodynamic (PD) variability in adults for 12 monoclonal antibodies (mAbs) with published population PK and/or PD models (Wang et al. J Clin Pharmacol. 2009;49:1012-24).

9.29.1. The Committee considered that there was minimal impact on the area under the curve (AUC) for fixed and weight-adjusted dosing of most monoclonal antibodies (mAbs), including pertuzumab and trastuzumab, at the population level.

9.29.2. The Committee noted that if a PK parameter is sensitive to body weight, extremely low or high body weight can lead to under- or over-exposure with fixed, or adjusted dosing.

9.29.3. The Committee noted that pertuzumab clearance is sensitive to body weight but considered this a relatively low sensitivity and likely to have minimal impact.

9.29.4. The Committee noted trastuzumab has not yet been tested for weight-based PK sensitivities. The Committee therefore considered there to be an unknown impact on trastuzumab clearance.

9.30. The Committee considered that subcutaneous biotherapeutics such as pertuzumab-trastuzumab SC present various potential risks including differences in drug exposure (ie pharmacokinetics) from fixed dosing and administration issues, and consequent different possible responses.

9.31. The Committee considered that current evidence does not show substantial risks for pertuzumab-trastuzumab SC above or different to those expected with IV pertuzumab and trastuzumab for the treatment of HER-2 positive breast cancer. However, the Committee considered that if the individual was not receiving any IV treatment, there would be benefit gained from reduced use of central lines.

Suitability

9.32. The Committee considered that potential suitability benefits of subcutaneous biotherapeutics include reduced health system resource requirements in comparison to IV treatment, improved experience for people receiving the treatment due to

reduced time spent on receiving healthcare, and improved access to treatment, particularly if access to SC treatment was available in rural settings.

Cost and savings

9.33. The Committee noted results from a systematic review of time and resource use costs of subcutaneous versus intravenous administration of oncology biologics in a hospital setting, which reported that, regardless of country setting, IV administration takes longer than SC administration in terms of 'chair-time' required (McCloskey et al. Pharmacoecon Open. 2023;7:3-36).

9.34. The Committee noted results from a New Zealand based time-in-motion study which compared medical resource utilisation for IV and SC trastuzumab in Auckland and Tauranga (North et al. Clinicoecon Outcomes Res. 2015;7:423-30). The Committee noted six people received SC trastuzumab, and 12 received standard-of-care IV trastuzumab. The Committee considered it was unclear if the study provided a fair comparison, as standard of care (IV) was not included in the clinical trial and therefore was likely less controlled than that of the SC formulation which was provided as part of a clinical trial. The Committee noted that some costs, such as IV catheters, were not taken into account. The Committee noted that the study assumed there was available capacity for these services within existing resources.

9.35. The Committee noted that in the PHranceSCa, median administration time was 7.0–8.0 minutes with SC and 60.0–150.0 minutes with IV. The Committee noted that healthcare professionals included in the study considered preparation procedures and associated staff time would be reduced if all IV infusions were switched to SC injections (O'Shaughnessy et al. Eur J Cancer. 2021;152:223-32). The Committee considered this would free up health care professionals and resources for the treatment of other tumour streams, however, considered this benefit would be difficult to quantify.

9.36. However, the Committee considered that there would need to be a proactive implementation plan supported by Te Whatu Ora to provide training and resources in less urban locations to administer subcutaneous treatment and monitor for and manage any adverse effects. The Committee considered that if not adequately supported, introduction of SC treatments would compete with resources available for IV treatment, and not necessarily save resource to the extent possible.

9.37. The Committee considered that, in the early breast cancer setting, the extent to which the use of pertuzumab-trastuzumab SC would likely displace comparator treatments would likely be influenced by the approach of the treatment center and may differ across indications. The Committee considered that in the metastatic setting, it is likely all people would switch from the IV to the SC formulation, however there may still be a need for the IV formulation for those with high disease burden in the first 1-2 cycles.

Summary for assessment

9.38. The Committee considered that the table below summarises its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for pertuzumab-trastuzumab SC if it were to be funded in New Zealand for neoadjuvant treatment of HER-2 positive early breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

9.39. The Committee considered that a PICO reviewed by PTAC in November 2022 for the metastatic setting was appropriate.

Population	People with HER-2 +ve, locally advanced, inflammatory, or early-stage breast cancer who have not received prior chemotherapy
Intervention	Neoadjuvant subcutaneous injection given as a loading dose (1200 mg pertuzumab/ 600 mg trastuzumab) followed by maintenance doses every 3 weeks (600 mg pertuzumab/ 600 mg trastuzumab) in combination with taxane- or anthracycline-based chemotherapy for 3 to 6 cycles depending on the chemotherapy regimen used.
Comparator(s) (NZ context)	Neoadjuvant IV trastuzumab given as a loading dose (8 mg/kg trastuzumab) followed by maintenance doses every 3 weeks (6 mg/kg) in combination with taxane- or anthracycline-based chemotherapy for 3 to 6 cycles depending on the chemotherapy regimen used.
Outcome(s)	• Longer invasive disease-free survival (IDFS) compared to IV trastuzumab + chemotherapy • Possible longer overall survival (OS) compared to IV trastuzumab + chemo, however statistical significance was not reached in the APHINITY trial • Potential savings to the health sector due to shorter administration time for the SC formulation.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

10. First line treatment of CLL and subsequent lines

Application

10.1. The Advisory Committee reviewed the following applications:

- Fixed duration venetoclax and ibrutinib for previously untreated CLL (which was previously reviewed by PTAC)
- Venetoclax with rituximab retreatment in relapsed/refractory CLL.

10.2. The Committee considered there was a need to review all its current CLL recommendations, to align pre-existing recommendations, and to make new recommendations for parts of the treatment paradigm which have not yet been considered. The Committee considered there was a need to reconsider funding priorities for CLL, in the context of newly funded treatment options.

10.3. The Committee considered that the benefits and costs of fixed term regimens needed to be considered as an alternative to continuous therapy treatment options, and that Pharmac should continue to routinely incorporate these in its health economic evaluations.

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

Recommendations

10.5. The Advisory Committee reviewed PTAC's advice and **recommended** that the listings of ibrutinib and venetoclax in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting for individuals with TP53 intact CLL with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

VENETOCLAX
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Person has previously untreated chronic lymphocytic leukaemia; and
2. There is documentation confirming the person does not have 17p deletion or TP53 mutation
3. Venetoclax is to be administered in combination with ibrutinib, beginning at cycle four of ibrutinib therapy.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Venetoclax is to be administered in combination with ibrutinib; and
4. Venetoclax is to be discontinued after a maximum of 12 (28 day) cycles.

IBRUTINIB
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Person has previously untreated CLL; and
2. There is documentation confirming the person does not have 17p deletion or TP53 mutation; and
3. Ibrutinib is to be administered at a maximum dose of 420 mg daily for 3 (28 day) cycles.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Ibrutinib to be administered in combination with venetoclax; and
4. Ibrutinib is to be discontinued after a maximum of 15 (28 day cycles) of treatment.

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

- That the wording "ineligible for chemoimmunotherapy" made in a previous recommendation by PTAC for venetoclax + ibrutinib in this population is unclear and not appropriate to define eligibility for first line treatment with venetoclax + ibrutinib.
- The benefit of an oral, fixed duration, chemotherapy free treatment regimen; that all people with CLL may benefit from this regimen.
- That an additional benefit would be seen for individuals with unmutated IGHV status, as currently the most disadvantaged CLL group are those with IGHV unmutated status who will be treated with chemoimmunotherapy (FCR, R-benda or Obi.Chlorambucil depending on fitness) and exposed to risk of toxicity without the potential benefit of

prolonged progression free survival (PFS) that can be seen with the IGHV mutated group.

10.6. The Advisory Committee **recommended** that the listings of ibrutinib and venetoclax in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting for individuals with del(17p)/TP53 mutation (TP53 disrupted CLL) with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

VENETOCLAX
Initial application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Patient has previously untreated chronic lymphocytic leukaemia; and
2. There is documentation confirming that the patient has 17p deletion by FISH testing or TP53 mutation by sequencing
3. Venetoclax is to be administered in combination with ibrutinib, beginning at cycle four of ibrutinib therapy.

Renewal application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Venetoclax is to be administered in combination with ibrutinib; and
4. Venetoclax is to be discontinued after a maximum of 12 (28 day) cycles.

IBRUTINIB
Initial application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Patient has previously untreated CLL; and
2. There is documentation confirming that the patient has 17p deletion by FISH testing or TP53 mutation by sequencing
3. Ibrutinib is to be administered at a maximum dose of 420 mg daily for 3 (28 day) cycles.

Renewal application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
Both:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment; and
3. Ibrutinib to be administered in combination with venetoclax; and
4. Ibrutinib is to be discontinued after a maximum of 15 (28 day) cycles of treatment.

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

- The relatively good efficacy of current treatment with venetoclax monotherapy in this group
- The comparable suitability of the dual oral regimen relative to venetoclax monotherapy, and the added benefit of the fixed duration of treatment, which may prove cost effective when compared to continuous therapy.
- The level of evidence for venetoclax with ibrutinib is limited, however, the committee noted that the treatment currently available for this population in the first line setting also has little evidence.
- The high priority was recommended due to the potential cost saving that this treatment may provide if it is evaluated to be lower cost than the existing treatment, based on the lower treatment duration.

10.7. The Advisory Committee **recommended** that the listings of venetoclax and obinutuzumab in the Pharmaceutical Schedule be extended to the treatment of CLL in the first line setting with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application** (untreated chronic lymphocytic leukaemia) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. Patient has previously untreated chronic lymphocytic leukaemia; and
> 2. Venetoclax is to be administered in combination with obinutuzumab; and
> 3. Venetoclax to be used to a maximum dose of 400mg and for a total of 12 (28 day cycles)
>
> **Renewal application** (untreated chronic lymphocytic leukaemia) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate and the person is benefiting from treatment; and
> 3. Venetoclax is to be administered in combination with obinutuzumab; and
> 4. Venetoclax is to be discontinued after a maximum of 12 (28 day) cycles.
>
> OBINUTUZUMAB
> **Initial application** (untreated chronic lymphocytic leukaemia) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. Patient has previously untreated chronic lymphocytic leukaemia; and
> 2. Obinutuzumab to be administered at a maximum cumulative dose of 8,000 mg and in combination with venetoclax for a maximum of 6 cycles.
>
> **Renewal application** (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of clinical disease progression; and
> 2. The treatment remains appropriate and the person is benefiting from treatment; and
> 3. Obinutuzumab is to be administered in combination with venetoclax; and
> 4. Obinutuzumab is to be discontinued after a maximum of 6 (28 day) cycles.

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

- Efficacy of this regimen in comparison to current standard of care options for CLL The added benefit of the fixed duration of treatment which may prove cost saving in the small subgroup receiving continuous venetoclax (TP53 disrupted).
- The need for a treatment option for clinically frailer individuals who potentially wouldn't tolerate other unfunded agents and prefer a fixed duration treatment.

10.8. The Advisory Committee **recommended** that the Special Authority criteria for venetoclax in the treatment of CLL be amended to allow retreatment with venetoclax + rituximab at relapse, following prior treatment with venetoclax + rituximab (VenR) (ie third-line treatment for TP53 intact CLL) with a **medium priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> VENETOCLAX RETREATMENT
> **Initial application** (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
> All of the following:
> 1. Patient has received at least one prior immunochemotherapy for CLL; and
> 2. Patient has previously relapsed with venetoclax in combination with rituximab regimen.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

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

- The health needs of individuals with CLL with progression of disease following treatment with venetoclax + rituximab (VenR)
- The final analysis of the MURANO trial provided sub study evidence to support retreatment with VenR
- The potential cost-effectiveness of fixed duration venetoclax re-treatment in comparison to continuous treatment with a bruton tyrosine kinase inhibitor (BTKi)

10.9. The Advisory Committee **recommended** that a bruton tyrosine kinase inhibitor (BTKi) be listed for the first-line monotherapy treatment of TP53 intact CLL with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

Bruton Kinase Inhibitor (BTKi)
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Person has previously untreated chronic lymphocytic leukaemia; and
2. There is documentation confirming the person does not have 17p deletion or TP53 mutation.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

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

- The unmet heath needs of individuals with previously untreated TP53 intact CLL
- That the previously considered BTK inhibitors provide evidence to support the same or similar health benefits across this class and that previous recommendations across this class for use in this indication need to be aligned
- That zanubrutinib would be preferred due to its efficacy and safety profile, followed by acalabrutinib due to its safety profile then ibrutinib. However, the Committee noted that access to any BTKi would be acceptable due to the class effect.

10.10. The Advisory Committee **recommended** that a BTKi be listed for the first-line monotherapy treatment of TP53 disrupted CLL, with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

Bruton Kinase Inhibitor (BTKi)
Initial application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Person has previously untreated chronic lymphocytic leukaemia; and
2. There is documentation confirming the person does have 17p deletion or TP53 mutation.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

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

- The unmet health need of those with TP53 disrupted CLL
- The evidence supporting the health benefit from the use of BTKi's for this indication
- That the previously considered BTK inhibitors provide evidence to support the same or similar health benefits across this class, and that previous recommendations across this class for use in this indication need to be aligned.

10.11. The Advisory Committee **recommended** that a BTKi be listed for the second-line monotherapy treatment of TP53 intact CLL, with a **low priority**, within the context of treatment of malignancy, subject to the following special authority criteria:

Bruton Kinase Inhibitor (BTKi)
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Patient has CLL requiring therapy
2. Patient has received at least one prior immunochemotherapy for CLL; and
3. Patient has not previously received funded venetoclax.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

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

- The need for recommendations made for this indication to align to give a combined recommendation for BTKis, and the need to review wording in criteria such as "more appropriate than venetoclax + rituximab"
- The current health benefit being achieved with VenR treatment
- The suitability of an oral BTKi for those who live rurally.

10.12. The Advisory Committee **recommended** that alternative BTKis be listed for the treatment of TP53 intact CLL for those who progress or experience intolerable side effects with venetoclax+rituximab, only if **cost neutral** to ibrutinib, subject to the following special authority criteria:

Bruton Kinase Inhibitor (BTKi)
Initial application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. Patient has received at least one prior immunochemotherapy for CLL; and
2. Patient has experienced intolerable side effects or relapsed with venetoclax in combination with rituximab regimen; and
3. A BTKi has not previously been used and is to be used as monotherapy.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

10.13. The Advisory Committee **recommended** that any further BTKis be listed for the treatment of TP53 disrupted CLL for those who progress or experience intolerable side effects to venetoclax, only if **cost-neutral** to ibrutinib, subject to the following special authority criteria:

Bruton Kinase Inhibitor (BTKi)
Initial application (untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:
1. There is documentation confirming that patient has 17p deletion or TP53 mutation; and
2. Patient has experienced intolerable side effects or relapsed with venetoclax monotherapy, and:
3. A BTKi has not previously been used and is to be used as monotherapy.

Renewal application (untreated chronic lymphocytic leukaemia without 17p deletion or TP53 mutation) – only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the person is benefiting from treatment.

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

- The health benefit being achieved with ibrutinib, a member of this class, in this population
- That the previously considered BTK inhibitors provide evidence to support the same or similar health benefits across this class and that previous recommendations across this class for use in this indication need to be aligned.
- That zanubrutinib would be preferred due to its efficacy and safety profile, followed by acalabrutinib due to its safety profile, then ibrutinib. However, the Committee considered that access to any BTKi would be acceptable due to the class effect.

10.14. The Committee noted that fixed duration VenR has not yet been considered for the second-line treatment of TP53 disrupted CLL, but considered this may be a relevant alternative to consider if a fixed duration regimen or BTKi were to be used for the indication first-line.

10.15. The Committee reiterated its previous recommendation to remove the 36-month access criteria in the current relevant Special Authority criteria with a **high priority**.

Discussion

Māori impact

10.16. The Committee discussed the impact of funding various treatments for CLL on Māori health areas of focus and Māori health outcomes. The Committee noted that treatment of lymphoma is not specifically one of Pharmac's Hauora Arotahi (Māori health areas of focus). The Committee considered that there is no direct evidence to suggest that incidence of CLL in Māori is any greater than that of other New Zealand populations.

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

10.17. The Committee considered the impact of CLL on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee considered that there is no direct evidence to suggest that incidence of CLL in Pacific peoples is any greater than that of other New Zealand populations.

10.18. The Committee considered that access to treatment for people living in rural locations could be improved through increased use of oral treatment regimens, treatments not requiring tumour lysis syndrome monitoring, and fixed-duration regimens with oral or very limited administration requirements, as these all reduce travel requirements to access healthcare.

Background

10.19. The Committee noted the following currently funded treatments for previously untreated CLL in New Zealand:

- Bendamustine hydrochloride + rituximab for Binet stage B or C, or progressive stage A CLL requiring treatment, chemotherapy naïve, unable to tolerate toxicity of full dose fludarabine + cyclophosphamide + rituximab (FCR).
- Venetoclax monotherapy for previously untreated CLL, confirmed 17p deletion and/or TP53 mutation.
- Obiutuzumab for progressive Binet stage A, B or C CD20+ CLL requiring treatment, obinutuzumab treatment naïve, not eligible for full dose FCR due to comorbidities with a score > 6 on the Cumulative Illness Rating Scale (CIRS) or reduced renal function (creatinine clearance < 70mL/min).
- Rituximab (with fludarabine and cyclophosphamide, bendamustine [or venetoclax]) for Binet stage A, B or C CLL requiring treatment, available as first line (or later line) treatment.

10.20. The Committee noted the following currently funded treatments for relapsed/refractory CLL in New Zealand:

- Venetoclax in combination with rituximab (VenR) when CLL has relapsed/ is refractory following at least one prior treatment and has relapsed within 36 months (noting CTAC recommended to remove the 36-month restriction in April 2023).
- Ibrutinib when CLL is refractory to, or has relapsed within 36 months, of a venetoclax regimen or person has experienced intolerable side effects with venetoclax.

10.21. The Committee noted the following previous recommendations received from Pharmac's CTAC (previously CaTSoP), and PTAC Committees for 17p deleted/TP53 mutated CLL, which will henceforth be referred to as 'TP53 disrupted' CLL throughout this record.

First-line

- Zanubrutinib continuous treatment until disease progression with a high priority
- Ibrutinib continuous treatment with a medium priority if considered "more appropriate than venetoclax monotherapy'

- Acalabrutinib continuous treatment with a medium priority if considered "more appropriate than venetoclax monotherapy'

Second-line

- Zanubrutinib continuous treatment only if cost neutral to currently funded ibrutinib if experienced intolerable side effects to venetoclax
- Zanubrutinib continuous treatment for progression on, or following venetoclax treatment with a high priority
- Acalabrutinib continuous treatment with a high priority if experienced intolerable side effects to venetoclax
- Acalabrutinib continuous treatment for progression on, or following venetoclax treatment with a high priority
- Ibrutinib continuous therapy for progression on venetoclax after the current 36-month time period with a high priority.

10.22. The Committee noted the following current recommendations received from Pharmac's CTAC (previously CaTSoP), and PTAC Committees for CLL without 17p deleted/TP53 mutation, which will henceforth be referred to as 'TP53 intact' CLL throughout this record.

First line

- Venetoclax + ibrutinib (I+V) fixed duration treatment with a high priority for people 'ineligible for chemoimmunotherapy'
- Venetoclax + ibrutinib fixed duration treatment with a medium priority for people who are 'eligible for chemoimmunotherapy'
- Venetoclax + obinutuzumab (V+O) fixed duration treatment with a low priority if fludarabine, cyclophosphamide, rituximab (FCR) is 'not appropriate'
- Continuous ibrutinib with a low priority if 'chemoimmunotherapy is inappropriate'

Second-line

- Zanubrutinib continuous treatment with a high priority if experienced intolerable side effects to venetoclax
- Acalabrutinib continuous treatment with a medium priority if 'more appropriate than venetoclax'
- Ibruintib continuous treatment with a medium priority if 'more appropriate than venetoclax + rituxumab"

Third-line

- Acalabrutinib continuous treatment with a medium priority if an individual experiences disease progression within 36 months of venetoclax + rituximab
- Zanubrutinib continuous treatment if an individual experiences disease progression within 36 months of venetoclax + rituximab, only if cost-neutral to currently funded ibrutinib

10.23. The Committee considered that overall, the current recommendations for unfunded treatments for CLL have become fragmented, due to these applications being received at different times, and the impact of recent funding decisions. The

Committee considered that some of the recommendations previously made now need updating to align with updated evidence, to reflect the unmet need, and to incorporate the consideration of fixed duration first line therapy in the treatment paradigm.

Health need

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

10.25. The Committee considered that historically, the population of people with CLL with TP53 disruption have been considered to have higher health need. The Committee considered that the subsequent funding of venetoclax and ibrutinib at progression/first-line treatment intolerability has improved options for this group. The Committee noted that the group accounts for approximately 5% of individuals with CLL being treated in the first line setting (Campo et al. Haematologica. 2018; 103(12):1956-1968).

10.26. The Committee considered that currently, the population of people with CLL who are experiencing the highest clinical need with currently funded treatment options are those without TP53 disruption and with immunoglobulin heavy chain gene (IGHV) unmutated CLL who would currently be treated with immunochemotherapy and exposed to the associated risk of toxicity, including for FCR 2-8% risk of therapy related MDS/AML, without the potential benefit of prolonged progression-free survival (Thompson et al. Blood. 2023). The Committee considered that although ideally access to BTKi and BCL2i treatment would be widened for all people with CLL, it should be noted that those with unmutated IGHV are currently experiencing high levels of unmet health need from currently funded options.

Health benefit

First line fixed duration regimens

Venetoclax + Obinutuzumab (V+O)

10.27. The Committee noted that the CLL17 trial; a phase 3 multicentre, randomised, prospective, open-label trial of ibrutinib monotherapy versus fixed-duration venetoclax plus obinutuzumab (V+O) versus fixed-duration ibrutinib plus venetoclax (I+V) in individuals with previously untreated CLL is currently recruiting, The Committee noted that a study of acalabrutinib plus venetoclax (A+V) versus venetoclax plus obinutuzumab (ven + obi) in previously untreated chronic lymphocytic leukaemia or small lymphocytic lymphoma is also underway.

10.28. The Committee noted that fixed duration V+O includes a total of nine obinutuzumab intravenous (IV) infusions, alongside orally administered venetoclax. The Committee noted that hospital admission is required for days 1 and 2 of cycle 1 due to the risk of infusion reactions. The Committee noted that the regimen also requires monitoring for tumour lysis syndrome (TLS) during the 'ramp-up' phase of venetoclax treatment.

10.29. The Committee noted 5-year results from the randomised CLL14 study of V+O versus chlorambucil plus Obinutuzumab (chl+obi) for previously untreated CLL (Al-Sawaf et al. Nat Commun. 2023;13:2157). The Committee noted that the study included 432 participants, 25 with TP53 disrupted CLL. The Committee noted the median follow up was 76.4 months, and median PFS was favourable for V+O (76.2 vs 36.4 (Hazard ratio [HR] 0.4, 95% Confidence interval [CI] 0.31-0.52, *P*=0.001), and toxicity was similar across the two groups. The Committee noted the 6-year- overall survival (OS) rate was 78.7% in the Ven-Obi and 69.2% in the chl+obi arm (HR 0.69 [95% CI 0.48–

1.01], *P*=0.052). The Committee considered that this study was relevant to the New Zealand population, as Obinutuzumab + chlorambucil is the current standard of care.

10.30. The Committee noted results from the CLL13 trial, a phase 3, randomised (1:1:1), open-label trial, where 926 participants with TP53 intact CLL received six cycles of chemoimmunotherapy (fludarabine-cyclophosphamide-rituximab or bendamustine-rituximab [FCR/BR]) or 12 cycles of VenR, 12 cycles of ven+obi, or venetoclax+obinutuzumab+ibrutinib until minimal residual disease (Eichorst et al. N Engl J Med. 2023;388:1739-54). The Committee noted that after a median follow up of 38.8 months, PFS was lowest in the FCR/BR group (75.5), and that V+O showed superior PFS (87.7) to the current standard of care.

Venetoclax + ibrutinib (I+V)

10.31. The Committee noted that fixed duration I+V is an orally administered regimen which includes 3 months of oral ibrutinib followed by 12 months of oral I+V. The Committee noted that no TLS monitoring or hospital admissions are required for this regimen.

10.32. The Committee noted 4-year results from the fixed dose (FD) arm of the CAPTIVATE trial (noting that PTAC reviewed the 3-year results in May 2023), where 159 people with untreated CLL (17% with TP53 disruption) were treated with the I+V regimen described above. The Committee noted 4-year PFS of 79% (95%CI 71-84), and 4-year freedom from next treatment of 84% (Barr et al. J Clin Oncol. 2023;41:7535). The Committee considered the TP53 disrupted group did slightly less well than the overall cohort.

10.33. The Committee noted results from the GLOW trial; a phase III randomised open-label trial in individuals with previously untreated CLL who would be considered unfit for treatment with fludarabine based chemoimmunotherapy (CIT) (CIRS>6), who were treated with I+V or chlorambucil in combination with Obinutuzumab (chl+obi). The Committee noted that of the 211 participants, 6.6%, and 1.9% had TP53 disrupted CLL in each arm, respectively. The Committee noted that median PFS was not reached in the I+V arm vs 21 months in the chl+obi arm (HR 0.216, 95%CI 0.131-0.357, *P*<0.001) (Kater et al. NEJM Evid. 2022;1). The Committee noted that that I+V was more toxic than chl+obi, with higher rates of myelosuppression, atrial fibrillation, hypertension, and bleeding.

10.34. The Committee noted PTAC's review of an indirect treatment comparison (ITC) study of fixed-duration I+V vs FCR as first line treatment for CLL (Barrientos et al. Hemasphere. 2022; 6(Suppl): 1758-9). The study compared previously untreated CLL or SLL aged ≤70 y who were treated with I+V in the FD cohort of CAPTIVATE to individuals treated with FCR in E1912. Adjusted treatment effects for PFS, OS, and overall response rate (ORR) were estimated by inverse probability of treatment weighting (IPTW) using propensity scores. After IPTW, PFS was improved with I+V relative to FCR (hazard ratio [HR] 0.42; 95% CI 0.25-0.71), as was OS (HR 0.19; 95% CI 0.05-0.77).

10.35. The Committee considered that in theory, a different BTKi may provide the same or similar health benefits compared to ibrutinib when used alongside venetoclax in a fixed term regimen. However, the Committee considered that, as current evidence is limited to ibrutinib in this indication, and until evidence of efficacy of other BTKi's was available when used in this context, the recommendation for funding was confined to only ibrutinib at this time.

10.36. The Committee considered that while evidence was limited for the subgroup with TP53 disruption, it was possible that in this group, venetoclax and ibrutinib would be cost saving, depending on the pricing offered, given the shorter duration of treatment.

First-line CLL funding preferences

10.37. The Committee considered that funding for the first-line treatment of CLL, both with and without TP53 disruption, should include a fixed duration treatment regimen/s based on the currently available evidence. The Committee noted that those with unmutated IGHV status were most likely to benefit from a fixed duration treatment given the poorer efficacy of currently funded treatments in this front-line setting.

TP53 disrupted

10.38. The Committee was asked to consider relative uptake of proposed treatment options. The Committee estimated that if I+V was funded for TP53 disrupted CLL, approximately 30% of people would receive this treatment, with the others preferring to receive the current continuous venetoclax regimen. The Committee considered that those who would receive I+V instead of venetoclax monotherapy would do so primarily because of convenience of a fixed duration, all oral therapy. The Committee considered that this proportion may be similar if V+O were funded.

10.39. The Committee estimated that if both V+O and I+V were funded, approximately 20% of people would receive V+O, approximately 50% would receive I+V, and 30% would receive currently funded continuous treatment.

10.40. The Committee noted there are no comparative data and potentially could be better outcomes with continuous therapy for this group however fixed duration treatment would be of preference for some. The Committee noted clinicians may chose V+O for those who are more clinically frail or those with certain risk factors including cardiac disease.

10.41. The Committee estimated that if continuous use of a BTKi as an alternative to venetoclax monotherapy for TP53 disrupted CLL were funded, approximately 65% of clinicians would select a BTKi in first line if available. The Committee considered this based on the available evidence supporting the efficacy of a BTKi in this setting compared to venetoclax monotherapy. The Committee, however, considered that if a BTK inhibitor were funded as continuous therapy in the first line setting, that access to venetoclax would need to be made available for those who progress on their first line BTK inhibitor.

10.42. The Committee considered that for both TP53 intact and disrupted CLL the preference for a BTKi would be zanubrutinib, then acalabrutinib, then ibrutinib based on the safety (specifically, ibrutinib exhibits higher cardiac risk than acalabrutinib and zanubrutinib) but that broadly the previously considered BTKi's would provide the same or similar health benefits such that any singular option would be acceptable.

TP53 Intact

10.43. The Committee estimated that if I+V was funded for TP53 intact CLL, approximately 70% of people would receive the treatment. The Committee considered that the remainder would not receive I+V due to pre-existing comorbidity, being clinically frail, or preference for FCR due to the evidence of long-term benefits for IGHV mutated CLL after a defined course of therapy.

10.44. The Committee considered that if only V+O was funded for TP53 intact CLL, all individuals who would have been treated with chl+obi would instead receive V+O due to its superior efficacy. The Committee estimated that approximately 40% of those currently treated with FCR/BR would instead receive V+O, as 40% would have unmutated IGHV and therefore would likely receive substantial benefit compared to FCR.

10.45. The Committee estimated that if both V+O and I+V were funded for TP53 intact CLL, approximately 20% of people would receive V+O, 60% would receive I+V, and 20%

would receive a currently funded FCR. The Committee considered some people would remain on FCR due to the evidence of long-term benefits for individuals with mutated IGHV CLL, while there would be a preference for V+O for those who have pre-existing comorbidity or are clinically frail.

10.46. The Committee considered that BTKi monotherapy in first line CLL for TP53 intact disease would provide a useful treatment option in this setting. The Committee considered that most, but not all, people currently receiving BR or chl+obi would use a BTKi preferentially in this setting (approximated at 90% uptake). The Committee considered that uptake would be lower among people receiving FCR (nearer 40%) for the same reasons as described in Paragraph 10.44.

10.47. The Committee considered that if V+O, I+V, and a BTKi were funded for TP53 intact CLL, approximately 20% of people might receive V+O, 60% I+V, 10% a BTKi, and 10% would continue to receive FCR. The Committee considered reasons for choosing a BTKi would be primarily related to its oral formulation and that there is no need for TLS monitoring. The Committee considered that those with pre-existing comorbidity or are clinically frail would receive V+O or a BTKi (if limited cardiac comorbidity). The Committee considered that fixed duration I+V would be preferred over V+O due to its perceived superior efficacy and being a full oral regimen. The Committee considered that there would still remain a group of people who would receive FCR due to the evidence of long-term benefits for individuals with IGHV mutated after a defined course of therapy.

Relapsed/refractory CLL

TP53 disrupted

10.48. The Committee noted that continuous use of a BTKi in the treatment of TP53 disrupted CLL for those with intolerable side effects to venetoclax monotherapy is already funded. The Committee considered any other funded BTKis in this setting would have to be cost-neutral to currently funded ibrutinib as they would be expected to provide the same or similar health benefits.

TP53 intact

10.49. The Committee considered that continuous use of a BTKi as an alternative to VenR for TP53 intact CLL was less of a priority given the efficacy of fixed duration VenR in this setting. The Committee considered that if a BTKi were funded as an alternative in this setting, the Special Authority criteria would need to allow for VenR treatment to be accessed following BTKi use.

10.50. The Committee considered continuous use of a BTKi in the second line treatment of TP53 intact CLL for those with intolerable side effects is already funded. The Committee considered any other funded BTKis in this setting would have to be cost-neutral to currently funded ibrutinib.

Venetoclax retreatment

10.51. The Committee reviewed results from the final 7-year follow up and retreatment analysis of the MURANO trial; a phase III multicentre open-label parallel-arm randomised controlled trial including individuals aged 18 years or over with relapsed or refractory CLL (Kater et al. Hemasphere. 2023;7(suppl):e492813f). The Committee noted that 25 participants received retreatment with VenR following disease progression after the main study regimen. The Committee noted that of these 25 people, 26% had TP53 disrupted CLL, and 91% had IGHV unmutated CLL. The Committee considered the sub study population representative of the New Zealand group who would receive re-treatment, with the exception of their TP53 disruption

status. The Committee noted that median time between the last venetoclax dose in the main study and venetoclax ramp-up in the sub study was 2.3 years (range 1.2–3.1 years), and median follow up of those in the sub study was 33.4 months. The Committee noted that best ORR to re-treatment was 72.0%, and median PFS was 23.3 months (95%CI 15.6-24.3).

10.52. Members noted anecdotal evidence that most haematologist-oncologists consider retreatment with VenR an acceptable treatment for people with CLL who have been previously treated with the regimen and the disease responded well. The Members further considered the need to reconsider the 36-month criteria. The Committee considered VenR retreatment an effective treatment regimen, which if funded may delay the utilisation of continuous treatments.

10.53. The Committee considered that the appropriateness of retreatment with venetoclax would be affected by its use in prior lines of treatment. The Committee considered that use following progression after I+V or V+O treatment is unknown due to a current lack of evidence. The duration of response to I+V or V+O may determine the appropriateness of currently funded VenR use at relapse. The Committee considered that it is currently unknown if repeated fixed duration treatment with I+V or V+O is appropriate, as is the appropriateness of using I+V after V+O or vice versa but this may be possible. The Committee considered that venetoclax monotherapy following progression after VenR may be an appropriate option. However, the Committee considered that a BTKi would be the preference for progression following V+O and VenR for those with a shorter remission duration until further data is available.

10.54. The Committee considered anecdotal evidence that suggested clinicians in New Zealand would likely consider VenR treatment after progression on a first-line BTKi. The Committee noted the Murano trial included only 2.6% of participants with prior BTKi treatment.

10.55. The Committee considered that for CLL treatment in the second-and-later-line settings, access to venetoclax or ibrutinib would be required following treatment with I+V or V+O. The Committee considered that the currently funded treatment paradigm would remain appropriate however some changes to special authority criteria may be required to allow access to allow earlier access to BTKi for those progressing early on a fixed duration venetoclax regimen.

10.56. The Committee considered that it is unlikely that chemoimmunotherapy (eg FCR) would be used in later lines of therapy if more effective regimens were funded and used in earlier lines of treatment.

Suitability

10.57. The Committee reiterated considerations from PTAC in May 2023 that fixed I+V has a more favourable suitability profile compared to currently available treatment options for previously untreated TP53 intact CLL which require intravenous infusion, due to its oral administration. The Committee reiterated that if I+V were funded for this indication, there would be decreased demand for infusion services which would be associated with health sector cost savings. The Committee noted that these suitability benefits would also exist if a BTKi were funded in this setting. They also noted that with both BTKi and I+V treatments there are less requirements for TLS monitoring.

Cost and savings

10.58. The Committee reiterated considerations from PTAC that noted that currently all first-line treatment options for TP53 intact CLL require intravenously administered infusions, in a clinical facility offering a higher level of treatment support (such as a hospital or infusion centre).

10.59. The Committee considered that if the 36-month criteria were removed from current access criteria for treatments for second line CLL, clinician preference and location would influence the consideration of reducing continuous venetoclax to a shorter treatment duration rather than until disease progression in those with TP53 disrupted CLL. It was estimated that 55% of clinicians may adopt the use of a fixed duration treatment if the 36-month criterion was removed.

10.60. The Committee noted that there may be a benefit of treatment with fixed duration I+V or V+O for people with TP53 disruption, relative to venetoclax monotherapy, and that these may present a useful option in addition to access to venetoclax monotherapy from a clinical perspective. However, the Committee noted that fixed duration regimens would be a finite cost and that this may reduce cost compared to alternative funded and unfunded continuous therapy options. The Committee considered that fixed duration regimens provide improved toxicity profiles, including cardiac toxicity, bleeding risk, immunosuppression, associated with treatments offered as part of fixed duration regimens due to reduced time on treatment. The Committee noted that at the 8-year follow up of the RESONATE-2 trial, 42% of participants remained on ibrutinib, with median progression-free survival (PFS) not yet reached (Barr et al. Blood Adv. 2022;6:3440-50). The Committee considered this indicates that the duration of continuous treatment is often longer than the duration of fixed duration regimens (commonly 1-2 years).

Funding criteria

10.61. The Committee considered that access criteria for fixed-duration treatments for first line CLL need to clearly define the target population, as well as define the maximum dose and duration, in order to best target access to treatment. The Committee noted that currently the most disadvantaged group are those with IGHV unmutated status who are currently treated with chemoimmunotherapy so would be the priority target population.

10.62. The Committee considered that restrictive wording including 'appropriate/inappropriate' and/or 'eligible/ineligible' in access criteria would be ineffective in targeting the intended populations/s, and recommended similar wording be avoided in future funding criteria for CLL treatments.

PICO

10.63. The Advisory Committee considered that the tables below summarise its interpretation of the most appropriate PICO (population, intervention, comparator, outcomes) information for venetoclax-containing regimens and BTKi regimens discussed, if they were to each be funded alone in New Zealand.

10.63.1. The Committee noted that the uptake of treatment among people receiving different treatments currently is an area of particular uncertainty. The rationale for the estimates in the table is described in the text above, though further advice may be needed if these assumptions are highly material to the analysis.

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

Table 1. Abbreviated PICO information for venetoclax-containing regimens

<table>
<tr><th colspan="2">Treatment (paragraph of recommendation)</th><th colspan="3">Ven-I (1.6)</th><th>Ven-I (1.7)</th><th colspan="3">Ven-o (1.8)</th><th>Ven re-treat (1.9)</th></tr>
<tr><td rowspan="4">Population</td><td>Line</td><td colspan="3">1L</td><td>1L</td><td colspan="3">1L</td><td>3L (prior ven-R)</td></tr>
<tr><td>TP53 mutation status</td><td colspan="3">TP53 intact</td><td>TP53 disrupted</td><td>TP53 intact</td><td>TP53 disrupted</td><td>TP53 intact</td></tr>
<tr><td rowspan="2">Uptake (%)</td><td colspan="3">70% in total [4 5 6]</td><td rowspan="2">30% [4]</td><td>30% in total [4]</td><td>30% [4]</td><td>Progression >24 months after starting ven-R[3]</td></tr>
<tr><td>40% of people currently on FCR[6] and 90% of people on BR or Obi-chl switch to ven-i</td><td></td><td>100% of people on Obi-chl and 40% of those on FCR or BR switch to ven-o</td><td colspan="3"></td></tr>
<tr><td colspan="2">Intervention*</td><td colspan="3">Ven-I</td><td>Ven-I</td><td colspan="2">Ven-O</td><td>Ven-O</td><td>Ven-R</td></tr>
<tr><td colspan="2">Comparator(s)</td><td>FCR (40%[5])</td><td>BR (40%[5])</td><td>Obi-chl (20%[5])</td><td>Ven mono</td><td>28%[5] Obi-chl</td><td>39%[5] FCR + 33%[5] BR</td><td>Ven mono</td><td>ibrutinib mono[2]</td></tr>
<tr><td colspan="2">Outcome trial</td><td>ITC[1]</td><td colspan="2">GLOW</td><td>N/A – cost minimisation</td><td>CLL14</td><td>CLL13</td><td>N/A – cost minimisation</td><td>MURANO sub-study</td></tr>
</table>

[1] ITC using CAPTIVATE single arm vs E1912 trial (Barrientos et al. Hemasphere. 2022; 6(Suppl): 1758-9)

[2] Assumes that the 36 month criterion is removed from ibrutinib special authority first

[3] The proportion of people with no progression on treatment would be considered to approximate the percentage with 'good response' – there may be variation on this, since in an informal survey, approx. 55% of clinicians suggested 24+ months remission would be adequate to allow re-treatment while 20% felt 36+ months would be needed and the remainder considered 12+ or 18+ months would be adequate.

[4] Only the uptake for funding the proposal alone have been included at this stage. Further advice may be needed if certain things are funded, to understand the committee's experience of uptake in newly funded treatments and the impact of this on the paradigm.
Note: removal of 36 month criteria is as described in April 2023 record, for venetoclax and ibrutinib (recommendation in paragraph 1.16)

[5] Based on assumptions described in the PTAC record in May 2023 (PICO table). It has been assumed in the absence of other information that half of the 80% on either FCR or BR will receive each FCR and BR. Note that 40% + 20% + 40% x 40% = 70%

[6] Those with the IGHV mutation who can receive FCR are more likely to benefit from FCR so may continue to choose FCR.

Table 2. Abbreviated PICO information for BTKi proposals considered

Treatment (paragraph of recommendation)		**Any BTKi mono (1.10)**			**Any BTKi mono (1.11)**	**Any BTKi mono (1.12)**	**Any other BTKi mono (1.13)**	**Any other BTKi mono (1.14)**
Population	**Line**	1L			1L	2L	3L	2L
	TP53 mutation status	TP53 intact			TP53 disrupted	TP53 intact	TP53 intact	TP53 disrupted
	Uptake (%)	70% in total[4]			65%[3]	50%[1]	100%	100%
		40% of people currently on FCR[4] and 90% of people on BR or Obi-chl switch to ven-i						
Intervention*		ibrutinib, zanibrutinib, acalibrutinib					zanibrutinib, acalibrutinib	
Comparator(s)		FCR (40%[4])	BR (40%[4])	Obi-chl (20%[4])	Ven mono	Ven-R	ibrutinib[2]	ibrutinib[2]
Outcome trial		Best evidence from BTKi trials e.g. RESONATE 2 or equivalent for other agents			Current ibrutinib analysis	Best evidence from BTKi trials e.g. RESONATE or equivalent for other agents	N/A – cost minimisation	N/A – cost minimisation

Table definitions:

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

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

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

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

Notes:

[1] CTAC July 2023 – noting that the other 50% would be expected to receive the BTKi in 3L after Ven-R

[2] Assumes that 36 month criterion removed from ibrutinib special authority first

[3] If venetoclax monotherapy was available at 2L this would rise to 90% (para 10.30 CTAC July 2023)

[4] Based on assumptions described in the PTAC record in May 2023 (PICO table). It has been assumed in the absence of other information that half of the 80% on either FCR or BR will receive each FCR and BR. As described above, it is assumed that 40% of people on FCR will switch to a new treatment. Note that 40% + 20% + 40% x 40% = 70%

11. Durvalumab - locally advanced or metastatic biliary tract cancer in combination with chemotherapy

Application

11.1. The Advisory Committee reviewed the application for durvalumab in combination with chemotherapy for the treatment of locally advanced or metastatic biliary tract cancer.

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

Recommendation

11.3. The Advisory Committee **recommended** that durvalumab in combination with chemotherapy for the treatment of locally advanced or metastatic biliary tract cancer be funded with a **low priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

> **Initial application —advanced, metastatic, or recurrent metastatic biliary tract cancer**
> Applications from any relevant medical practitioner. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following
> 1. Patient has advanced biliary tract cancer (Locally Advanced, Metastatic, or Recurrent Disease); and
> 2. Patient has a WHO performance status of 0-1; and
> 3. Either:
> 3.1. Patient has not received prior systemic therapy; or
> 3.2. Patient has recurrent disease after surgery with curative intent or after adjuvant therapy; And
> 4. Patient will receive concomitant treatment with gemcitabine and cisplatin for up to 8 cycles followed by a maximum of 1500 mg durvalumab every four weeks as a monotherapy.
>
> **Renewal application - advanced, metastatic, or recurrent metastatic biliary tract cancer**
>
> Applications from any relevant medical practitioner. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of disease progression; and
> 2. The treatment remains clinically appropriate, and the individual is benefiting from treatment; and
> 3. The patient will receive a maximum of 1500 mg durvalumab every 4 weeks as a monotherapy until disease progression.

11.4. The Advisory Committee recommended durvalumab based on:

- The modest magnitude of health benefit for overall survival
- The tolerability and relative safety profile of durvalumab
- The high quality of clinical trial evidence for health benefit and safety
- The high unmet health need of those with biliary tract cancer
- Māori are disproportionally affected by biliary tract cancer

Discussion

Māori impact

11.5. The Committee discussed the impact of funding durvalumab in combination with chemotherapy for the treatment of locally advanced or metastatic biliary tract cancer on Pharmac's Hauora Arotahi (Māori health areas of focus) and Māori health outcomes.

11.6. The Committee noted biliary tract cancer is not one of Pharmac's areas of Māori health areas of focus.

11.7. The Committee noted a 2015 New Zealand based study that reported the (non-age standardised) incidence rates of gallbladder carcinoma were higher for Māori tāne and wāhine in comparison to the overall population gender-specific age standardised rates (Lilic et al. ANZ J Surg. 2015;85:260-3). The Committee noted that the total number of Māori cases were too few to be able to calculate age-standardised incidence rates by ethnicity.

11.8. The Committee noted the prevalence of *H. pylori* infections, linked to an increased risk of biliary tract cancer, were found to be increased in Māori compared to Europeans (McDonald et al. Helicobacter. 2015;20:139-45).

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

11.9. The Committee discussed the impact of funding durvalumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted the prevalence of *H. pylori* infections, linked to an increased risk of biliary tract cancer, was reported to be increased in Pacific peoples compared to New Zealand Europeans (McDonald et al. Helicobacter. 2015;20:139-45).

11.10. The Committee noted that children and young people aged under 20 years, experiencing poverty and household overcrowding, as well as refugee children, are at a higher risk of *H. pylori* infection which is linked to an increased risk of biliary tract cancer (Pūrongo Ārai Mate Pukupuku, Cancer Prevention Report, RACP Policy on Refugee and Asylum Seeker Health).

Background

11.11. The Committee noted there have been no previous considerations for the treatment of 'biliary tract cancer', however gemcitabine hydrochloride was funded in 2011 for the treatment of locally advanced or metastatic cholangiocarcinoma.

11.12. The Committee noted durvalumab was funded in 2022 for the treatment of stage III locally advanced, unresectable non-small cell lung cancer where the disease has not progressed following platinum-based chemoradiation therapy.

Health need

11.13. The Committee noted biliary tract cancer, or cholangiocarcinoma, refers to a spectrum of invasive tumours, usually adenocarcinomas, arising from the biliary epithelium of the small ducts in the periphery of the liver (intrahepatic) and the main ducts of the hilum (extrahepatic). Extrahepatic biliary tract cancers include gallbladder cancer, ampullary cancer, and cancer of the pancreatic biliary ducts. (Vogel et al, Ann Oncol. 2023;34:127-40, Bridgewater et al. Am Soc Clin Oncol Educ Book. 2016;35:e194-203). The Committee notes those with ampullary cancer are excluded from this application.

11.14. The Committee noted people with biliary tract cancers can be asymptomatic, and malignancy is identified incidentally, either through detection of abnormal liver function tests or imaging undertaken for unrelated reasons (Valle et al. Lancet 2021; 397: 428–44).

11.15. The Committee noted those with advanced biliary tract cancer often report symptoms including jaundice, abdominal pain, pruritus, nausea, unintentional weight loss, fever, and fatigue (Hunter et al. Cancers (Basel). 2021; 13: 5074). The Committee noted due to the generalised nature of symptoms those with the disease often present at an advanced stage (Valle et al. Lancet 2021; 397: 428–44).

11.16. A 2015 New Zealand based study that identified those with gall bladder malignancy treated in the Waitemata District Health Board from 2003 to 2013, reported the ASI rate of gallbladder carcinoma is 0.60/100 000. The gender-specific ASI rates were 0.21/100 000 (men) and 0.76/100 000 (women). The incidence (not age standardised) for Māori was 0.96/100 000 (men) and 1.37/100 000 (women) (Lilic et al. ANZ J Surg. 2015;85:260-3).

11.17. The Committee note that the total number of Māori cases were too few to be able to calculate ASI.

Infections

11.18. The Committee noted cholangiocarcinoma has been associated with chronic infection with liver fluke and *Clonorchis sinensis,* as well as with chronic inflammation of the biliary tree and hepatic parenchyma (Bridgewater et al. 2016, Valle et al. 2021).The Committee noted that this is not endemic in New Zealand but may affect those who have travelled abroad, as well as refugee or immigrant populations.

11.19. The Committee noted there is a predominance in women, and in people with known risk factors for gallstone disease (age, obesity, multiple pregnancies, family history of gallstones, and low levels of physical activity). Chronic infection with Salmonella (*S.typhi* and *S.paratyphi*) and Helicobacter (*H.bilis* and *H.pylori*), are linked to a risk of between 2.6 and 7.5 per 100,000 respectively (Bridgewater et al. 2016). Choledochal cysts have been reported to a 1% to 15% lifetime risk of developing into gallbladder cancer and cholangiocarcinoma.

11.20. The Committee noted the prevalence of *H. pylori* infection, linked to an increased risk of biliary tract cancer, was found to be increased in Māori and Pacific peoples compared to Europeans (18–57% vs 39-83% vs 7-35% respectively) as reported in a 2015 New Zealand based study (McDonald et al. Helicobacter. 2015;20:139-45).

11.21. The Committee noted a further study in South Auckland that reported prevalence of *H. pylori* infection by ethnic group of 34.8% in Māori and 31.3% in Pacific peoples compared with 7.7% in those of European ethnicity (Hsiang et al. N Z Med J. 2013;126:64-76).

11.22. The Committee noted children and young people aged under 20 years, experiencing poverty and household overcrowding, are at a higher risk of *H. pylori* infection (Pūrongo Ārai Mate Pukupuku, Cancer Prevention Report).

11.23. The Committee noted a report by the Royal Australasian College of Physicians reported that H. pylori was detected in 82% of African refugee children in Australia and New Zealand (RACP Policy on Refugee and Asylum Seeker Health).

11.24. The Committee noted data reported from the Te Whatu Ora Cancer web tool (2016-2020) reported Pacific peoples have both a higher incidence of biliary tract cancer and rate of cancer related death than Māori, European and Asian people. The age standardised rate of biliary tract cancer was 2.96 per 100,00, whilst the rate of other biliary cancers was 2.75 per 100,000 in Pacific peoples compared to 0.71 and 1.01 per 100,000 in Europeans respectively.

11.25. The Committee noted women of all ethnicities have a higher rate of gall bladder cancer per 100,000 (2016-2020) compared to men (Te Whatu Ora Cancer web tool).

11.26. The Committee noted that people with biliary tract cancer have reduced health-related quality of life (HRQoL) due to a combination of tumour and treatment related signs and symptoms and the impact of these on functioning (Patel et al.Oncol Ther. 2021; 9: 557–73).

11.27. The Committee noted for individuals treated with complete resection, the 5-year overall survival rates range from 21% to 63% for intrahepatic cholangiocarcinoma,

30% to 40% for perihilar lesions, and 20% to 54% for distal cholangiocarcinomas managed by pancreaticoduodenectomy. The recurrence patterns differ by primary site in the biliary tract (Bridgewater et al. 2016).

11.28. The Committee noted the current standard of care in New Zealand for first-line treatment, in those with WHO performance status 0-1, is a combination of gemcitabine and cisplatin therapy. Treatment is generally with a palliative intent. Many individuals are considered not clinically well enough at the time of diagnosis to receive chemotherapy. The Committee noted many of those who progress whilst on first line treatment continue progressing rapidly and do not proceed to second line treatment. The Committee considered there was variability in the percentage receiving second line treatments in New Zealand, with approximately 20-50% receiving second line therapy. The Committee considered folinic acid, fluorouracil, and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (CAPOX) were standard second line therapies in New Zealand for those clinically fit enough to receive them.

11.29. The Committee noted the current treatment regime is quite toxic, in addition to the disease symptoms being experienced. For this reason, some people may choose not to undertake treatment.

Health benefit

11.30. The Committee noted durvalumab is a human, high affinity, immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that blocks the interaction of programmed cell death ligand-1 (PD-L1) with PD-1 and CD80.

11.31. The Committee noted durvalumab would be administered in combination with gemcitabine and cisplatin, as an alternative to gemcitabine and cisplatin alone, for first-line treatment of advanced biliary tract cancer.

11.32. The Committee noted Oh et al. NEJM Evid 2022;1 that reported the results of a double-blind, placebo-controlled, phase three study (TOPAZ-1) in individuals with previously untreated unresectable or metastatic biliary tract cancer, or with recurrent disease. The study reported:

- The Committee noted the median duration of follow-up was 16.8 months (95% confidence interval (CI), 14.8 to 17.7) in the durvalumab group and 15.9 months (95% CI, 14.9 to 16.9) in the placebo group.
- The Committee noted the estimated 24-month overall survival (OS) rate was 24.9% (95% CI, 17.9 to 32.5) for durvalumab and 10.4% (95% CI, 4.7 to 18.8) for placebo. The hazard ratio (HR) for progression-free survival (PFS) was 0.75 (95% CI, 0.63 to 0.89; P=0.001). Objective response rates were 26.7% with durvalumab and 18.7% with placebo.
- The Committee noted the OS was significantly longer with durvalumab versus placebo (HR, 0.80; 95% CI, 0.66 to 0.97; P=0.021). Median OS was 12.8 months (95% CI, 11.1 to 14.0) in the durvalumab group and 11.5 months (95% CI, 10.1 to 12.5) in the placebo treatment group.
- The Committee noted the incidences of grade 3 or 4 adverse events were 75.7% and 77.8% with durvalumab and placebo, respectively.

11.32.1. The Committee noted those with ampullary cancer were excluded from the trial.

11.32.2. The Committee noted the study was a multi-site, international trial that enrolled 685 people. The Committee noted the quality of data was high with a high number of participants.

11.32.3. The Committee noted the comparator arm was relevant to the New Zealand standard of care.

11.32.4. The Committee noted that baseline characteristics of participants in both arms were well balanced.

11.32.5. The Committee considered it was likely there would be no difference in quality-of-life following treatment with durvalumab due to treatment adverse effects balancing out reduction in disease symptoms.

11.32.6. The Committee noted that there was no significant change in health benefit based on PD-L1 status. The Committee noted the HR for OS for PD-L1 tumour area positivity (TAP) score of ≥1% with durvalumab versus placebo was 0.79 (95% CI, 0.61 to 1.00) compared to those with a TAP ≤1% HR for OS with durvalumab versus placebo of 0.86 (95% CI, 0.60 to 1.23).

11.32.7. The Committee noted that a high number of participants went on to have subsequent cytotoxic chemotherapy (42% in durvalumab arm vs 49% in placebo), and therefore considered the trial population may be clinically fitter than that observed in New Zealand.

11.33. The Committee noted KEYNOTE-966 (Kelley et al. Lancet. 2023 ;401:1853-65), a phase three trial of pembrolizumab vs placebo, administered together with chemotherapy, in individuals meeting the same eligibility criteria as TOPAZ-1. The study reported:

- A median duration of follow up 25·6 months (IQR 21·7-30·4).
- A median OS was 12·7 months (95% CI 11·5-13·6) in the pembrolizumab group versus 10·9 months (9·9-11·6) in the placebo group (HR 0·83 [95% CI 0·72-0·95]; one-sided p=0·0034 [significance threshold, p=0·0200])
- Grade 3 – 4 adverse effects occurred in 79% of those in the pembrolizumab vs 75% in placebo group.
- A total of 2% in the pembrolizumab group and 1% in the placebo group died due to treatment-related adverse events.

11.33.1. The Committee noted the trial was a similar design to the TOPAZ-1 study with a large number of individuals included.

11.33.2. The Committee considered it would be useful to review a funding application for pembrolizumab in this indication and requested Pharmac staff seek this from the supplier. The Committee noted pembrolizumab is not approved for this indication in New Zealand.

11.34. The Committee considered the consistency between the TOPAZ-1 and KEYNOTE-966 trial results suggest there may be a class effect for these drugs in the treatment of biliary tract cancers, however meta-analysis data would be useful to clarify this effect.

11.35. The Committee noted the following studies:

- Rimini et al. Liver Int. 2023;43:1803-12
- Oh et al. Lancet Gastroenterol Hepato. 2022;7:522-32.
- Doki et al. Cancer Med. 2022;11:2550-60
- Feng et al Biomed Res Int.;2022:1720696.

Suitability

11.36. The Committee noted durvalumab is administered as an intravenous infusion and would require additional infusion time above what is required for currently funded treatments. This increases the time resource required from affected individuals and their whānau to undergo treatment. It would also have impacts on infusion services which are currently operating with constrained capacity.

Cost and savings

11.37. The Committee noted durvalumab is administered as an infusion over 1 hour before infusions of gemcitabine and cisplatin, which are administered as infusions for 30 and 60 minutes respectively, on day one of each cycle. The Committee noted this would result in addition infusion chair time in an overburdened infusion system, and additional nursing time would be required for its administration and monitoring.

11.38. The Committee considered that some New Zealand treatment centres would administer six cycles of gemcitabine and cisplatin, rather than the nine cycles in the clinical trial, before transitioning to durvalumab monotherapy if funded.

11.39. The Committee noted a majority of those eligible for cisplatin and gemcitabine, and without contraindication, would receive durvalumab if funded. Slightly more individuals may choose to receive chemotherapy if it is available in combination with durvalumab.

11.40. The Committee considered that there would be an approximately 1% increase in the number of individuals requiring hospitalisations compared to that of the chemotherapy toxicity.

11.41. The Committee noted those undergoing treatments would have four weekly clinic visits, as well as four weekly computerised tomography (CT) scans for maintenance durvalumab after chemotherapy.

11.42. The Committee considered that ACT-NOW cancer data could be consulted for estimating population numbers for biliary tract cancer.

11.43. The Committee noted individuals would routinely see their oncologists and general practitioners on average about 1.3 times per month each.

11.44. The Committee noted these individuals would not be candidates for intensive care unit support in hospitals.

11.45. The Committee considered that individuals with advanced metastatic pancreatic cancer would be a similar population in terms of additional treatments, hospitalisations, and overall survival. The Committee noted that those with pancreatic cancer may have biliary stents inserted which can result in a higher hospitalisation rate due to sepsis. The Committee considered this may also apply to those with biliary tract cancer.

11.46. The Committee noted that FOLFOX/CAPOX is the most likely second-line treatment following durvalumab, and that uptake for second line treatment in some New Zealand centres would be closer to 20%, as opposed to the 50% indicated in the key clinical evidence. Furthermore, the Committee considered ACT-NOW might provide data on how many people receive second-line treatment in this setting.

11.47. The Committee noted the supplier's estimates of numbers and considered these would be an underestimate. The Committee considered that most people who received cisplatin and gemcitabine would receive durvalumab as an add-on if funded. The Committee considered there would a rapid uptake in those receiving durvalumab, however there would be no incremental increase over time in the number receiving durvalumab if funded due to the high mortality rate of the disease. The Committee considered it would be appropriate for those currently receiving treatment with

chemotherapy to receive durvalumab in the second line setting, however the health benefit associated with this is uncertain.

Summary for assessment

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

Population	Individuals with advanced biliary tract cancer (locally advanced, metastatic or recurrent disease) where biliary tract cancer is defined as intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, or gallbladder cancer. Undergoing concurrent treatment with gemcitabine and cisplatin, the individual has: an ECOG performance score no higher than 1 at treatment initiation, advanced or metastatic disease that is untreated with systemic therapy, or recurrent disease after curative surgery or after adjuvant therapy.
Intervention	**Durvalumab** *Cycles 1 to 8* • 1500 mg IV infusion durvalumab on day 1 of every 3-week cycle • gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 IV infusion, on day 1 and 8 every 3-week cycle *Cycles 9 onwards* • 1500 mg IV infusion durvalumab on day 1, every 4 weeks until disease progression or until unacceptable toxicity *Based on the EviQ guidelines for Biliary and gallbladder advanced cisplatin, gemcitabine and durvalumab, accessed 31/07/2023, and dosing information in the current paper.*
Comparator(s) (NZ context)	*Cycles 1 and further* • Gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 IV infusion, on day 1 and 8 every 3-week cycle
Outcome(s)	Improved overall survival Median overall survival was 12.8 months with durvalumab and 11.5 months in the chemotherapy alone group (HR, 0.80; 95% CI, 0.66 to 0.97; P=0.021). Progression-free survival Median progression-free survival was 7.2 months with durvalumab and 5.7 months with chemotherapy alone (HR, 0.75; 95% CI, 0.63 to 0.89; p=0.001) (Oh et al, NEJM, 2022; 1: NA)
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the target population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

12. Pembrolizumab - breast cancer, triple negative, locally recurrent unresectable or metastatic, CPS >10

Application

12.1. The Advisory Committee reviewed the application for pembrolizumab for the treatment of locally recurrent unresectable or metastatic triple receptor negative breast cancer (TNBC), with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥10.

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

Recommendation

12.3. The Advisory Committee **recommended** that pembrolizumab for the treatment of triple negative, locally recurrent unresectable or metastatic breast cancer, with a programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥10 be funded with a **medium priority** within the context of treatment of malignancy subject to the following Special Authority criteria:

> **Initial application – (breast cancer, metastatic)** only from any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has recurrent or metastatic triple negative breast cancer (that does not express ER, PR or HER2 IHC3+ or ISH+ [including FISH or other technology]); and
> 2. The patient's cancer has a confirmed PDL-1 CPS ≥10
> 3. The patient has received no prior systemic therapy in the recurrent or metastatic setting
> 4. The patient has an ECOG score of 0-1
> 5. Pembrolizumab to be used in combination with chemotherapy
> 6. Baseline measurement of overall tumour burden is documented clinically and radiologically
>
> **Renewal application – (breast cancer, metastatic)** only from any relevant practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Any of the following:
> 1.1. Patient's disease has had a complete response to treatment or
> 1.2. Patient's disease has had a partial response to treatment or
> 1.3. Patient has stable disease and
> 2. Response to treatment in target lesions has been determined by comparable radiologic assessment following the most recent treatment period
> 3. No evidence of disease progression
> 4. The treatment remains appropriate and patient is benefitting from treatment
> 5. Pembrolizumab to be used at a maximum dose of 200 mg every three weeks (or equivalent)

12.4. The Advisory Committee noted the following in their decision:

- The high unmet health need and high mortality rate from the disease
- Māori with TNBC have later diagnosis, less access to treatment and poorer overall survival.
- The potential implementation issues of testing tumours for PD-L1 expression.

Discussion

Māori impact

12.5. The Committee discussed the impact of funding pembrolizumab for the treatment of locally recurrent unresectable or metastatic TNBC, with a CPS ≥10 on Māori health areas of focus and Māori health outcomes.

12.6. The Committee noted breast cancer is one of Pharmac's Hauora Arotahi (Māori health areas of focus).

12.7. The Committee noted the incidence of breast cancer in Māori women was 122.5/100,000 compared with 89.6/100,000 in non-Māori women (Te Whatu Ora, Cancer web tool). Māori women are also diagnosed at a later stage, and experience lower 10 year survival rates than non-Māori women (30,000 Voices: Te Rēhita Mate Ūtaetae – Breast Cancer Foundation National Register 2003-2020).

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

12.8. The Committee discussed the impact of funding pembrolizumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted that Pacific peoples have higher rates of later stage diagnosis and are more likely to experience delays to surgery than any other ethnic group. Pacific women have the lowest rates of survival with breast cancer of all ethnicities in New Zealand (Breast Cancer Foundation National Register 2003-2020).

Background

12.9. The Committee noted that it had previously reviewed atezolizumab (with chemotherapy) for those with TNBC whose tumours have a PDL-1 expression ≥1% in April 2021, which was deferred pending further long term clinical trial data.

12.10. The Committee noted pembrolizumab has been reviewed by PTAC and other Specialist Advisory Committees for a range of other cancers which are outlined on the application tracker. It is currently funded for PDL-1 positive, first-line, monotherapy of non-small cell lung cancer and unresectable or metastatic melanoma.

Health need

12.11. The Committee noted the health need of those with early TNBC was discussed in the context of other applications in this meeting, and had been discussed by the Committee (then CaTSoP) in September 2018 (CaTSoP, September 2018).

12.12. The Committee noted that 4.7% of cases of breast cancer in New Zealand registered between 2003 and 2020 present with the metastatic disease (Breast Cancer Foundation. Informing a better future for breast cancer in Aotearoa New Zealand. Report 2020). The Committee noted TNBC represents approximately 15-20% of all breast cancers (Gennari et al. Ann Oncol. 2021;32:1475-95). The Committee further noted that approximately 16% of metastatic breast cancers are triple negative (Breast Cancer Foundation. Insights Report 2018).

12.13. The Committee noted the 5-year survival for people diagnosed with metastatic breast cancer is 29% and 10-year survival is 16%, compared with 99% and 97%, respectively for people diagnosed with Stage 1 disease (Breast Cancer New Zealand, 2022).

12.14. The Committee noted that individuals with metastatic breast cancer may experience emotional distress, including symptoms of depression and anxiety, as well as existential distress and loneliness (Mosher et al, Breast J. 2013 May-Jun; 19: 285–292). The Committee noted physical symptoms, including pain, fatigue, insomnia, and gastro- intestinal symptoms are also correlated with emotional and physical distress (Mosher et al, 2013).

12.15. The Committee noted individuals with metastatic breast cancer face a wide range of challenges, including frequent medical procedures, chronic side effects (eg pain, fatigue, cognitive impairment, sexual dysfunction), and practical concerns (eg work and family role disruption, financial strain) (Mosher et al, 2013).

12.16. The Committee noted breast cancer is one of Pharmac's Hauora Arotahi (Māori Health Areas of Focus). In 2020, the incidence of breast cancer in Māori women was 122.5/100,000 compared with 89.6/100,000 in non-Māori women (Te Whatu Ora, Cancer web tool).

12.17. The Committee noted the causes of ethnic inequities in cancer survival are complex and likely to include a range of factors related to the demographics of people with breast cancer, tumour biology, along with inequities in access to, and timeliness of treatment and quality of care during the cancer diagnosis and treatment pathway (Tin et al, BMC Cancer. 2018;18:58).

12.18. The Committee noted that breast-cancer specific survival was 84% at 10 years for wāhine Māori, compared to 87% for those of European ethnicity (Breast Cancer Foundation National Register 2003-2020).

12.19. The Committee noted Māori were more likely to have high risk tumours as defined by larger size, higher grade, and higher risk subtype, compared to European women. The Committee noted 49.1% of European ethnicity were diagnosed in Stage 1 compared with 42.6% for Māori. The proportion of stage 3 and 4 cancers was also higher for Māori however, has reduced over time from 25.2% of all Māori diagnoses in 2003-2005 to approximately 15% in 2018-2019 (Breast Cancer Foundation National Register 2003-2020).

12.20. The Committee noted that metastatic breast cancer also disproportionately affects Pacific peoples. The Committee noted that compared with other ethnicities, Pacific women have the lowest proportion of breast cancer diagnoses made through the screening process, the lowest proportion of disease diagnosed at stage 1, and the highest proportion of disease diagnosed at Stage 3 and 4 diseases (Breast Cancer Foundation National Register 2003-2020). In addition, it also noted Pacific women have the lowest survival rates for breast cancer of all ethnicities in New Zealand (Breast Cancer Foundation National Register 2003-2020).

12.21. The Committee noted the current funded treatment in New Zealand for individuals with advanced, metastatic TNBC is chemotherapy. The Committee noted this differs from the European Society for Medical Oncology (ESMO) guidelines which include immunotherapy (Gennari et al. 2021).

12.22. The Committee noted that for TNBC there are no targeted therapies, however some cancers with a BReast CAncer gene (BRCA) mutation can be sensitive to some taxanes, platinum agents, or unfunded poly-ADP ribose polymerase (PARP) inhibitors. The Committee noted many individuals with TNBC still relapse early after treatment with these agents.

Health benefit

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

12.24. The Committee noted pembrolizumab as a single agent had been assessed in the KEYNOTE-012, 086 and 119 trials.

12.25. The Committee noted the KEYNOTE-355 study, a randomised, placebo-controlled, double-blind, phase three trial in 847 individuals with untreated locally recurrent, inoperable, or metastatic TNBC.

12.25.1. The Committee noted Cortes et al. N Engl J Med. 2022 ;387:217-26 that reported results of the KEYNOTE 355 study at a median follow up of 44.1 months:

- In the CPS ≥10 subgroup: median overall survival (mOS) of 23.0 months pembrolizumab-chemotherapy group vs 16.1 months in the placebo-chemotherapy group (hazard ratio (HR) for death, 0.73; 95% confidence interval [CI], 0.55 to 0.95; two-sided P = 0.0185
- In the CPS ≥1 subgroup: mOS was 17.6 vs 16.0 months, respectively (HR, 0.86; 95% CI, 0.72 to 1.04; two-sided P = 0.1125 [not significant])
- In the intention-to-treat (ITT) group: mOS 17.2 vs 15.5 months, respectively (HR, 0.89; 95% CI, 0.76 to 1.05 [significance not tested]).
- Adverse events (AE) of grade 3 -5 related to the trial regimen: 68.1% in pembrolizumab-chemotherapy vs 66.9% placebo-chemotherapy.
- Death in 0.4% in pembrolizumab-chemotherapy vs 0% placebo-chemotherapy
- The Committee considered that the OS data curves from the CPS≥10 group would likely remain parallel beyond 36 months, informed by the prolonged survival observed in those with complete responses to immunotherapy in different cancers (such as non-small cell lung cancer).

12.25.2. The Committee also noted Rugo et al. Annals of Oncology (2021) 32 (suppl_5): S1283-1346. that reported results of the KEYNOTE 355 study at median follow up of 44.1 months.

12.25.3. The Committee noted Cortes et al. Lancet. 2020;396:1817-28 reported the second interim analysis results at a median follow-up of 25·9 months (IQR 22·8-29·9) pembrolizumab-chemotherapy group vs 26·3 months (22·7-29·7) placebo-chemotherapy. Median progression free survival (PFS) in individuals with a tumour CPS≥ 10 was 9·7 months with pembrolizumab-chemotherapy vs 5·6 months placebo-chemotherapy (HR for progression or death, 0·65, 95% CI 0·49-0·86; one-sided p=0·0012). HR was not significant in a CPS of ≤1.

12.25.4. The Committee considered the control arm and end points in the predefined groups were appropriate to the New Zealand population.

12.25.5. The Committee considered the evidence was high quality with mature OS data. The treatment group characteristics were well balanced at baseline, including distribution of PD-L1 groups.

12.25.6. The Committee considered that the trial reported OS benefits due to no cross over being allowed on progression, however this prevents an assessment of whether later line use might provide similar health benefit gains.

12.25.7. The Committee considered that those with a CPS≥10 experienced the greatest health benefit gains from pembrolizumab.

12.26. The Committee noted that 38.9% of participants in KEYNOTE-355 had a PD-L1 CPS of 10 or greater ((Cortes et al. New Engl J Med. 2022;387: 217-26).). The Committee considered however that the percentage of TNBC cases in New Zealand with a CPS of 10 or greater was likely to be higher than this because PD-L1 expression can vary substantially within tumours and factors such as the fixation period can greatly influence the CPS score.

12.27. The Committee noted the following studies:

- Huang et al. Eur J Cancer. 2022;177:45-52
- Egelston et al. Cancer Immunol Immunother. 2023;72:3013-27.
- Hattori et al. Cancer Med. 2023;12:10280-93.

- Shah et al. J Immunother Cancer. 2020;8:e000173
- Leung et al. Expert Opin Drug Saf. 2023;22:243-52

12.28. The Committee noted Khan et al. Front Immunol. 2023;14:1060308 a metanalysis of 20 studies including 3962 individuals. The study reported improved objective response rate (ORR), PFS and OS for those with PDL-1 expression. No significant differences between atezolizumab or pembrolizumab were reported.

12.29. The Committee noted Huo et al. Crit Rev Oncol Hematol. 2021;168:103530 a metanalysis of 4 studies including 3007 individuals. The study reported an improved PFS of PD1-PDL-1 blockade therapy plus chemotherapy vs chemotherapy alone, but no OS benefit.

Suitability

12.30. The Committee noted pembrolizumab is administered as an intravenous infusion and its addition to treatment would thereby require individuals to spend more time receiving treatment at an infusion centre, above that associated with current standard of care treatments.

12.31. The Committee noted that PD-L1 testing is not currently undertaken on a routine basis for this type of cancer across New Zealand and would need to be funded and accessible in all regions to prevent inequities.

12.31.1. The Committee noted that that immunohistochemical analysis testing for PD-L1 requires many components, including a range of commercially available antibodies, testing kits and reagents, and differing platforms and scoring systems, which can result in variability of results. The Committee was informed of one study comparing positivity rates using different antibodies found differing scores across SP263, 5IL3N, SP142 platforms. The Committee noted many of the available antibodies are recommended for use on a specific platform, and the majority of laboratories in New Zealand will only have access to one or perhaps two of these platforms.

12.31.2. For example, in the USA, testing for access to pembrolizumab is mandated to use the 22C3 antibody clone on the Dako platform, whereas testing for access to atezolizumab requires the SP142 antibody clone on the Ventana platform; so two different assays must be performed on two different platforms, to test the same biomarker for the same cancer, for access to two different drugs.

12.31.3. The Committee noted that the SP142 test is currently available for TNBC, funded by a pharmaceutical company supplying atezolizumab. Similarly, the 22C3 antibody is available for CPS scoring (on the Dako platform) at two laboratories nationally (funded by a pharmaceutical company for some tumours including TNBC), but most New Zealand laboratories do not have the Dako platform.

12.31.4. The Committee noted that both assays are affected by a variety of other factors including the type of biopsy taken, time to fixation, duration of fixation, and variables in sample processing. Furthermore, there is interobserver variability in assessment of PDL-1 scores, and specific additional training of pathologists is required for each different scoring system (TPS, CPS and IC scoring). The Committee noted that these variabilities in the implementation of PD-L1 testing and interpretation could affect access to pembrolizumab if funded. The Committee considered that standardisation of testing is required across New Zealand and it is preferable that the testing and interpretation should be confined to a relatively limited cohort of laboratories and well trained pathologists.

12.31.5. The Committee noted that PD-L1 testing is required for access to pembrolizumab monotherapy for advanced non-small cell lung cancer. The Committee considered PD-L1 testing and the proposed CPS scoring may not be an appropriate marker to identify the target group, within the context of TNBC, that may benefit from or respond to pembrolizumab treatment, due to its variability. The Committee considered some individuals who might benefit from treatment, may potentially be excluded due to borderline PD-L1 results, due to potential variability in results dependent on testing variables and the time at which the sample was taken in terms of disease progression. The Committee considered a strict cut off could perpetuate inequity due to test, retest variability and the ability to access laboratory testing.

Cost and savings

12.32. The Committee considered that approximately 50 individuals per year would have advanced TNBC, of which approximately 30 would have a CPS≥ 10 and would be eligible for pembrolizumab if funded under the proposed criteria.

12.33. The Committee noted that pembrolizumab-chemotherapy is associated with 45 minutes additional infusion time per cycle compared to chemotherapy and would therefore be associated with incremental nurse and hospital chair-related costs.

12.34. The Committee noted an individual would typically visit an oncologist once every three weeks, and have a CT scan every two to three months depending on the individuals clinical state and prognostic markers. The Committee noted that due to improved management in recent years with granulocyte colony stimulating growth factors, less than 2% of those with TNBC would require inpatient admission due to breast cancer related complications when receiving standard chemotherapy.

12.35. The Committee understood that in some cases an individual whose tumours have a CPS score result below the eligibility threshold would likely undergo re-testing and obtain an eligible CPS result. The Committee considered that repeat testing would result in higher health system resource utilisation.

Funding criteria

12.36. The Committee considered variation in PD-L1 score, from the use of different assays, could make it harder to identify the population that would gain the most health benefit from pembrolizumab. The Committee considered variation in the score across biopsy time points also makes it challenging to assess if there is an effect size difference between, or within, populations with different PD-L1 scores.

Summary for assessment

12.37. The Advisory Committee considered that the table 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 metastatic or recurrent TNBC with a PD-L1 CPS ≥10. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	People with metastatic or recurrent triple-negative breast cancer, with a PD-L1 Combined Positive Score of 10 or greater, who have not received prior treatment in the metastatic or recurrent setting.
Intervention	Pembrolizumab, 200mg administered every three weeks. In combination with either: • paclitaxel 90mg/m^2 on days 1, 8 and 15, every 28 days, or:

	• gemcitabine 1000mg/m^2 and carboplatin AUC on days 1, 8, every 21 days Treatment continued until disease progression, or unacceptable toxicity, or a maximum of 35 administrations
Comparator(s)	Chemotherapy, comprising one of: • paclitaxel 90mg/m^2 on days 1, 8 and 15, every 28 days, or: • gemcitabine 1000mg/m^2 and carboplatin AUC on days 1, 8, every 21 days 55% of individuals would receive carboplatin with gemcitabine, with the remaining proportion receiving paclitaxel, based on proportions observed in KEYNOTE-355.
Outcome(s)	Improved progression-free survival • KEYNOTE-355 reported that pembrolizumab-chemotherapy was associated with improved PFS compared to placebo-chemotherapy (HR, 0.73 [95% CI 0.55 to 0.95) Improved overall survival. • KEYNOTE-355 reported that pembrolizumab-chemotherapy was associated with improved OS compared to placebo-chemotherapy (HR, 0.66, [95% CI, 0.50 to 0.88])

Table definitions:

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

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

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

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

13. Pembrolizumab - breast cancer, triple negative, early Stage II or III, neoadjuvant treatment followed by adjuvant monotherapy (P-001883)

Application

13.1. The Advisory Committee reviewed the application for pembrolizumab for the neoadjuvant treatment followed by adjuvant monotherapy of early stage II or III triple negative breast cancer (TNBC).

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

Recommendation

13.3. The Advisory Committee **recommended** that pembrolizumab for the neoadjuvant treatment followed by adjuvant monotherapy of early stage II or III triple negative breast cancer be funded with a **low priority,** within the context of treatment of malignancy, subject to the following Special Authority criteria:

> **Initial application – (breast cancer, neoadjuvant)** only from a relevant specialist or any other practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has Stage II or III breast cancer that does not express ER, PR or HER2 IHC3+ or ISH+ (including FISH or other technology); and
> 2. Patient is treatment naïve; and
> 3. Patient is to undergo surgical resection; and
> 4. 6 months' adjuvant treatment with pembrolizumab is planned; and
> 5. Patient has an ECOG score of 0-1; and

6. Pembrolizumab to be administered in combination with chemotherapy for a maximum of 17 doses of 200 mg every 3 weeks or 9 doses of 400 mg every 6 weeks, cumulatively across neoadjuvant and adjuvant treatments.

Initial application – (breast cancer, adjuvant) only from a relevant specialist or any other practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has Stage II or III breast cancer that does not express ER, PR or HER2 IHC3+ or ISH+ (including FISH or other technology); and
2. The patient has undergone surgical resection; and
3. Patient has completed systemic neoadjuvant therapy with pembrolizumab and chemotherapy prior to surgery; and
4. Adjuvant treatment with pembrolizumab to be commenced within 12 weeks of surgery; and
5. Disease has not progressed during neoadjuvant therapy; and
6. Pembrolizumab to be administered in combination with chemotherapy for a maximum of17 doses of 200 mg every 3 weeks or 9 doses of 400 mg every 6 weeks, cumulatively across neoadjuvant and adjuvant treatments.
7. Pembrolizumab to be discontinued at disease progression.

13.4. In making these recommendations the Advisory Committee considered:

- The high unmet health need of those with early TNBC
- The lack of treatment options for those with early TNBC
- The evidence that pembrolizumab offers a benefit in prolonging event-free survival in this setting
- The uncertainty of the additional health benefit from adjuvant treatment following neoadjuvant treatment and resection
- The immature overall survival data available at present

Discussion

Māori impact

13.5. The Committee discussed the impact of funding pembrolizumab for the neo- and adjuvant treatment of early TNBC on Māori health areas of focus and Māori health outcomes.

13.6. The Committee noted breast cancer is one of Pharmac's Hauora Arotahi (Māori health areas of focus).

13.7. The Committee noted the incidence of breast cancer in Māori women was 122.5/100,000 compared with 89.6/100,000 in non-Māori women (Te Whatu Ora, Cancer web tool), as well as being diagnosed at a later stage, and Māori experience lower 10 year survival rates (30,000 Voices: Te Rēhita Mate Ūtaetae – Breast Cancer Foundation National Register 2003-2020).

13.8. The Committee noted data from the Breast Cancer Foundation report that reported 51.6% of Māori were diagnosed at stage II or III, compared to 46.2% for the European population (Te Rēhita Mate Ūtaetae - Breast Cancer Foundation National Register 2003-2020 report). It was also noted that 7.5% of Māori in the register had triple-negative disease, compared to 10.3% of Europeans.

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

13.9. The Committee discussed the impact of funding pembrolizumab on Pacific peoples, disabled people, tāngata whaikaha Māori, and people who have been underserved by the health system. The Committee noted Pacific peoples have the longest delays to surgery, highest rate of mastectomy, and least likely to receive radiation therapy. The Committee note Pacific people have the lowest survival rates for breast cancer of all

ethnicities in New Zealand (Breast Cancer Foundation National Register 2003-2020). The Committee also noted the Te Aho o Te Kahu Cancer Control Agency He Pūrongo Mate Pukupuku o Aotearoa 2021 that reported poverty is a barrier to accessing early diagnosis and best-practice treatment for cancers, leading to inequities in cancer survival between the poor and the affluent.

Background

13.10. The Committee noted pembrolizumab has been reviewed by PTAC and other Specialist Advisory Committees for a range of other cancers which are outlined on the application tracker. It is currently funded for program death ligand (PDL)-1 positive, first-line, monotherapy of non-small cell lung cancer and unresectable or metastatic melanoma.

Health need

13.11. The Committee noted the health need of those with TNBC was discussed in the context of other applications in the meeting.

13.12. The Committee noted TNBC are cancers that do not express any of the following three molecular biomarkers which are routinely tested for at diagnosis: oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor (HER-2).

13.13. The Committee noted TNBCs are mostly poorly differentiated tumours of high mitotic index, more often involving lymph nodes and lymph vascular spaces, and which grow rapidly. In addition they are characterised by their high metastatic potential, higher rates of local and distant disease recurrence and have a particular tendency to metastasise to distant viscera (Vuger et al. Acta Clin Croat. 2020; 59: 97–108).

13.14. The Committee noted individuals with TNBC have the poorest rates of 5-year and 10-year survival (Te Rēhita Mate Ūtaetae - Breast Cancer Foundation National Register 2003-2020 report). This is due to the cancer being therapeutically challenging because of its low response to therapeutics and highly invasive nature (Almansour et al. Front Mol Biosci. 2022; 9: 836417).

13.15. The Committee noted the incidence of TNBC is higher in younger people compared to other age groups, accounting for 14.4% of breast cancers diagnosed in New Zealand individuals aged 19-44 years (Breast Cancer Foundation NZ 2022).

13.16. The Committee noted the frequency of relapse is less favourable with the median time to tumour recurrence reported to be 1.2 years shorter in those with TNBC compared to non-TNBCs (3.88 vs. 5.00 years; p = 0.09) (Parikh et al. Int J Radiat Oncol Biol Phys. 2008;72:1056–63).

13.17. The Committee noted the Dent et al. Clin Cancer Res. 2007;13:4429-34 cohort study that followed 1601 women (180 who had TNBC) with newly diagnosed with breast cancer for 8.1 years. Compared with other breast cancers, those with TNBC had an increased likelihood of distant recurrence (hazard ratio (HR), 2.6; 95% confidence interval (CI), 2.0-3.5; P < 0.0001) and death (HR, 3.2; 95% CI, 2.3-4.5; P < 0.001) within five years of diagnosis but not thereafter. The risk of distant recurrence peaked at approximately three years and declined thereafter.

13.18. The Committee considered it was reasonable to assume that people with TNBC were more likely to have more advanced disease at presentation, and therefore had a lower probability of being diagnosed at an early stage than for individuals with other breast cancer types.

13.19. The Committee noted breast cancer treatment-related effects range from side effects that impact quality of life, to those that affect their family members and friends. These include three side effects due to chemotherapy (hair loss, nausea, and fatigue) that

cause distress and trauma. Moreover, women who undergo mastectomy report more anxiety and depression in comparison to women who have breast conserving surgery. Depression was also shown to be more prevalent among older and single individuals, while anxiety is higher in individuals residing in rural regions compared to urban areas (DeMiglio et al. Rep Pract Oncol Radiother. 2020; 25: 913–91).

13.20. The Committee noted the European Society for Medical Oncology (ESMO) guidelines (Cardoso et al. Ann of Oncol, ,2019,30,1194-1220) that outline early breast cancer treatment algorithms for TNBC.

13.21. The Committee noted in New Zealand the standard of care for neoadjuvant treatment is chemotherapy, followed by adjuvant chemotherapy in individuals that do not have pathological complete response following surgery. The Committee considered that many centres in New Zealand follow the Create-x treatment paradigm (Masuda et al. N Engl J Med 2017; 376:2147-159) for those with TNBC, with those whose cancers do not show complete pathological response, receiving six cycles of capcitabine in the adjuvant setting. The Committee noted some individuals would receive a dose dense chemotherapy regimen.

13.22. The Committee considered it was difficult to estimate precise numbers for the likely outcomes for people who experience local or locoregional recurrence, and that this was likely to differ between affected individuals. The Committee considered that individuals with recurrent disease would typically be treated with curative intent. This treatment would typically be surgical re-excision and/or adjuvant radiation (if not previously received), with systemic chemotherapy administered if other approaches were not possible. The Committee considered it was difficult to estimate outcomes based on clinical experience, due to the overall low numbers of affected individuals. The Committee considered that outcomes following subsequent surgery would be worse compared to the primary surgery, however it was difficult to estimate the magnitude of this. There is a paucity of literature to guide such estimates.

Health benefit

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

13.24. The Committee noted Yee et al. JAMA Oncol. 2020; 6: 1–9 that reported the results of a phase 2 trial in those undergoing neoadjuvant treatment with stage II-III breast cancer. The study reported pathological complete response may be a prognostic biomarker for long term outcomes including event free survival (EFS) and distant recurrence free survival. The Committee considered this to be true for those with TNBC.

13.25. The Committee noted Gyawali et al. EClinicalMedicine. 2021:32:100730 and Gion et al . Ther Adv Med Oncol. 2021:13:17588359211059587. The Committee considered that EFS is a clinically relevant endpoint, but that the ability to predict OS from EFS remains uncertain and exploratory. The Committee considered that the evidence suggests there is a reasonable correlation between EFS and OS, but that this evidence is neither strong nor of good quality at this time, given the small number of studies.

13.26. The Committee noted the KEYNOTE-522 study a phase 3 randomised, double-blind, placebo-controlled trial in 1174 with untreated stage II or III TNBC.

13.26.1. Schmid et al. N Engl J Med 2020; 382:810-21 reported the first interim analysis:

- Pathological complete response was 64.8% (95% CI, 59.9 to 69.5) pembrolizumab–chemotherapy group vs 51.2% (95% CI, 44.1 to 58.3)

placebo–chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P<0.001).

- After a median follow-up of 15.5 months (range, 2.7 to 25.0) 7.4% in the pembrolizumab–chemotherapy group vs 11.8% placebo–chemotherapy group had disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumour, or died from any cause (HR, 0.63; 95% CI, 0.43 to 0.93).
- Treatment-related adverse events of grade 3≤ occurred in 78.0% of the pembrolizumab–chemotherapy group vs 73.0% of the placebo–chemotherapy group, including death in 0.4% (n=3) and 0.3% (n=1), respectively.

13.26.2. Schmid et al. N Engl J Med 2022; 386:556-67 reported trial results at a median follow up of 39.1 months:

- Estimated event-free survival at 36 months: 84.5% (95% CI, 81.7 to 86.9) pembrolizumab–chemotherapy vs 76.8% (95% CI, 72.2 to 80.7) placebo–chemotherapy group (HR for event or death, 0.63; 95% CI, 0.48 to 0.82; P<0.001).
- No change in adverse event profile.

13.26.3. The Committee considered the strength and quality of the data to be moderate, with overall survival data remaining immature.

13.26.4. The Committee considered the standard of care in the comparator arm is relevant to New Zealand practice.

13.26.5. The Committee considered the improvements in EFS, distant recurrence and pathological complete response in the pembrolizumab group compared to placebo were clinically meaningful improvements in end points that translate to individual health benefit.

13.26.6. The Committee noted Ghisoni et al. Eur J Cancer. 2021:149:153-64 that reported immune checkpoint inhibitors treatment can result in late-onset and long-lasting immune related adverse events, that are underreported, but common events during and post treatment.

13.26.7. The Committee noted that incidence of treatment related adverse events were similar at both analysis timepoints reported from the KEYNOTE-522 study, however, considered longer term follow up may be needed, which could be in the form of observational data.

13.26.8. The Committee noted an increase in treatment related toxicity leading to discontinuation in the pembrolizumab arm compared to the placebo arm.

13.27. The Committee noted Dent et al. Annals of Oncology.2022;33 : S55-S84 that reported the patient reported outcomes on health related quality of life (HRQoL) for KEYNOTE-522. The study reported that the addition of pembrolizumab did not have a negative clinically meaningful impact on HRQoL. The Committee noted these results are considered exploratory, and that longer term follow up would add value to the data.

13.28. The Committee considered that the evidence suggested that neoadjuvant and adjuvant treatment with pembrolizumab offered a health benefit compared with standard of care. However, the Committee considered that it remains unclear about the extent to which this is driven by the neoadjuvant treatment period, noting that pembrolizumab as neoadjuvant treatment only has not been investigated. The Committee considered that the Loibl et al. Ann Oncol. 2022;33:1149-58 is investigating the use of durvalumab (a PD-L1 inhibitor) as neoadjuvant treatment

only, and that limiting treatment to the neoadjuvant period only may be a more cost-effective treatment strategy. The Committee noted that this application and the Special Authority criteria should be reviewed once more mature data regarding the health benefit neoadjuvant only treatment period is available.

13.29. The Committee noted the following studies:

- Tarantino et al. Crit Rev Oncol Hematol. 2021;159:103223
- Mital et al. J Cancer Res Ther. 2022;18:1754-65
- Miyashita et al. Breast J. 2020;26:1717-28
- Liang et al. Front Endocrinol (Lausanne). 2023;14:1137464
- Latif et al. Expert Rev Anticancer Ther. 2022;22:229-35.
- Schmid et al. Ann Oncol. 2020;31:569-81
- Nanda et al. JAMA Oncol. 2020;6:676-84

Suitability

13.30. The Committee noted pembrolizumab is administered as an intravenous infusion over 30 minutes, and therefore individuals would be required to spend additional time in the infusion chair.

13.31. The Committee noted that infusions could be administered six weekly instead of three weekly, to reduce individuals having to travel to infusion clinics as frequently.

Cost and savings

13.32. The Committee considered that it is uncertain how many people choose to take up capecitabine as adjuvant treatment in New Zealand. The Committee considered that it was also uncertain as to how many people would receive pembrolizumab in combination with capecitabine as adjuvant treatment, if pembrolizumab were to be funded, and that there were mixed opinions about whether this combination treatment would be standard practice due to the risks of overlapping toxicities. The Committee considered some clinicians may choose to use capecitabine alone in this situation, and the Breast Cancer Special Interest Group could be asked to comment on this to provide more concrete estimates.

13.33. The Committee considered that the evidence from cohort studies and historical evidence strongly suggested that the majority of TNBC disease relapse occur in the first 3-5 years after diagnosis. The Committee considered that the historical evidence is suggestive of a significant degree of flattening in the EFS curves after the first 3-5 years, but that there would likely still be a small number of individuals who would relapse after this time point. The Committee considered that there should therefore be a degree of flattening in the EFS curves for both pembrolizumab and the comparator.

13.34. The Committee considered that the estimates provided by the supplier, which used different parametric functions to model EFS in each treatment arm, and which suggested a relatively steep EFS curve in the comparator arm and a flattening EFS curve in the intervention arm, were not plausible. The Committee considered that it was more plausible to assume a flattening in both treatment arms. The Committee considered that the magnitude of EFS gain after 3-5 years was unlikely to increase.

13.35. The Committee considered that while there is a goal for 80% of those eligible for neoadjuvant treatment to receive such treatment, that uptake is likely to be somewhat lower than this. The Committee considered that a recent presentation of data from a single New Zealand centre suggested uptake of neoadjuvant treatment was currently 46% but noted there was also likely to be regional variation.

Summary for assessment

13.36. The Advisory Committee considered that the table 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 neo- and adjuvant treatment of early-stage triple negative breast cancer. This PICO captures key clinical aspects of the proposal and may be used to frame any future economic assessment by Pharmac staff. This PICO is based on the Advisory Committee's assessment at this time and may differ from that requested by the applicant. The PICO may change based on new information, additional clinical advice, or further analysis by Pharmac staff.

Population	Individuals with triple-negative stage II or III breast cancer who have not had treatment and who are to receive surgical resection
Intervention	**Neoadjuvant setting** 200mg pembrolizumab every 3 weeks until progression, death, unacceptable toxicity, or up to 8 cycles. Pembrolizumab is used in combination with - Cycles 1-4 (weeks 1-12): Paclitaxel 80mg/m^2 once-weekly and carboplatin 5AUC (area under the curve) every 3 weeks - Cycles 5-8 (weeks 13-24): Cyclophosphamide every 3 weeks, and either doxorubicin 60mg/m^2 or epirubicin 90mg/m2 **Adjuvant setting** Pembrolizumab 200mg every three weeks until progression, death, unacceptable toxicity, or up to 9 cycles, in combination with: Scheduled radiation therapy It is possible that some people may receive adjuvant pembrolizumab in combination with capecitabine, however the extent of this is unclear.
Comparator(s)	Comparator assumed to be similar to KEYNOTE-522, i.e.: **Neoadjuvant setting** - Cycles 1-4 (weeks 1-12): Paclitaxel 80mg/m^2 once-weekly and carboplatin 5AUC every 3 weeks - Cycles 5-8 (weeks 13-24): Cyclophosphamide every 3 weeks, and either doxorubicin 60mg/m^2 or epirubicin 90mg/m2 **Adjuvant setting** - Scheduled radiation therapy Capecitabine was not allowed in KEYNOTE-522 as adjuvant therapy, however a proportion of people would be expected to receive this in New Zealand. However, rates of uptake of capecitabine in practice are unclear.
Outcome(s)	Improved rates of event-free survival compared to placebo in KEYNOTE-522 (36-month EFS 84.5% vs 76.8%, HR 0.63) EFS assumed to be associated with OS in this setting, but magnitude is uncertain – see results of (Huang et al. Future Oncol 2023, online ahead of print) Magnitude of EFS gains long-term are uncertain, however it is likely that the EFS curves are likely to become significantly flatter after 3-5 years (with most relapsed disease occurring in this earlier period) Magnitude of likely OS gain is uncertain and dependent on several factors, including the extent that EFS flattens over time, and the outcomes after local recurrence for TNBC.
Table definitions:	

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

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

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

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