Record of the Cancer Treatment Subcommittee of PTAC meeting held at PHARMAC on 18 October 2019 (record for web publishing)

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

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

The Cancer Treatments Subcommittee may:

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

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

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

This Subcommittee meeting record will be reviewed by PTAC at its 20 & 21 February 2020 meeting.

Present from the Cancer Treatment Subcommittee:
Marius Rademaker (Chair)
Scott Babington
Christopher Frampton
Peter Ganly
Tim Hawkins
Richard Isaacs
Allanah Kilfoyle
Anne O'Donnell
Matthew Strother
Lochie Teague
Michelle Wilson

Apologies:
None noted

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1. The role of PTAC Subcommittees and records of meetings

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

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

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

1.4. The Cancer Treatments Subcommittee is a Subcommittee of PTAC. The Cancer Treatments Subcommittee and PTAC and other PTAC Subcommittees have complementary roles, expertise, experience, and perspectives:

- Both PTAC Subcommittees and PTAC are statutory advisory committees established by the PHARMAC Board (external to and separate from PHARMAC staff). Both provide objective advice to PHARMAC on community and hospital pharmaceuticals and their benefits, using the PHARMAC Factors for Consideration. PTAC Subcommittees complement and are separate from PTAC; they are not subordinate.

- PTAC Subcommittees provide objective advice within specific therapeutic areas. PTAC Subcommittees are appointed to reflect specialist knowledge and expertise in health needs and treatments within their own therapeutic groups/areas of clinical practice, including the applicability of evidence to clinical funding settings in New Zealand. The Cancer Treatments Subcommittee provides advice in the therapeutic area of cancer treatments.

- PTAC Subcommittees make recommendations, including providing a priority, within their therapeutic groups of interest. The Cancer Treatments Subcommittee recommends with priority within the context of cancers and their treatments, and within that area of health need and clinical practice.

- PTAC considers Applications or PHARMAC staff proposals across all therapeutic groups in the Pharmaceutical Schedule. It has an overview view of Applications and other items referred to it for clinical advice. PTAC provides and promotes critical appraisal of strength and quality of evidence, applied rigorously, systematically and consistently across all therapeutic groups.

- PTAC Subcommittees and PTAC therefore provide separate and different, if complementary, perspectives and advice to PHARMAC. PTAC examines the same evidence with a different perspective from specialist expert PTAC Subcommittees, as do Subcommittees between them.

The Cancer Treatments Subcommittee and other PTAC Subcommittees may therefore, at times, make recommendations for treatments that differ from PTAC's, including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC may, at times, make recommendations for treatments that differ from PTAC Subcommittees', or PTAC Subcommittees may make recommendations that differ from other PTAC Subcommittees'. PHARMAC considers the recommendations provided by the Cancer Treatments Subcommittee, PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for cancers.

2. Summary of Recommendations

4.12 The Subcommittee **recommended** that carfilzomib for the treatment of relapsed or refractory multiple myeloma be listed with a medium priority, subject to Special Authority criteria.

4.35 The Subcommittee **recommended** that daratumumab for the treatment of relapsed or refractory multiple myeloma be listed with a low priority, subject to Special Authority criteria.

5.3 The Subcommittee **recommended** that the application for pembrolizumab for the adjuvant treatment of resected stage III melanoma be deferred, pending further data to support the benefit of use of pembrolizumab in this setting.

6.3 The Subcommittee considered there is no evidence to suggest any differences in the health benefits or risks between reference and biosimilar rituximab, and

recommended it was clinically acceptable for Riximyo to be listed and be the only available rituximab product for all funded indications, if the cost saving is worthwhile, and supply is secured.

6.4 The Subcommittee **recommended** PHARMAC should consider widening access to rituximab as part of the biosimilar transition, which should include a review of commonly approved rituximab NPPA applications.

7.3 The Subcommittee considered that there is no evidence to suggest any differences in the health benefits or risks between reference and biosimilar trastuzumab, and **recommended** it was clinically acceptable for a biosimilar trastuzumab, such as CT-P6, to be listed and be the only available trastuzumab product for all funded indications, if the cost saving is worthwhile and supply is secured.

7.4 The Subcommittee supported a competitive process and **recommended** that PHARMAC bring any other biosimilar trastuzumab options to CaTSoP, when available in future, for review. The Subcommittee noted that there is sufficient evidence of biosimilarity to reference trastuzumab (Herceptin) and considered that interchangeability or switch data should be reviewed if available in future.

8.3 The Subcommittee **recommended** that obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with indolent non-Hodgkin lymphoma (NHL) who relapsed after, or are refractory to, a rituximab-containing regimen, be funded with a medium priority; subject to Special Authority criteria.

8.4 The Subcommittee **recommended** that obinutuzumab for the first-line induction and maintenance treatment of adult patients with follicular lymphoma (FL) be deferred.

9.4 The Subcommittee **recommended** that ribociclib in combination with an aromatase inhibitor as a first-line treatment of HR-positive, HER2-negative locally advanced breast cancer who have failed previous endocrine therapy be funded with high priority subject to the same Special Authority criteria as previously recommended for palbociclib in this setting.

9.5 The Subcommittee **recommended** that ribociclib in combination with fulvestrant for the second-line treatment of HR-positive, HER2-negative locally advanced breast cancer who have failed previous endocrine therapy be funded with high priority subject to the same Special Authority criteria as previously recommended for palbociclib in this setting.

9.8 The Subcommittee considered that based on currently available data there was a class effect from CDK4/6 inhibitors in the treatment of HR-positive HER2-negative locally advanced breast cancer and **recommended** funding for patients to receive one line of treatment with a CDK4/6 inhibitor in either a first or second-line setting with high priority.

10.3 The Subcommittee **recommended** that pembrolizumab be funded as a bridge to transplant for the treatment for relapsed and refractory HL in individuals eligible for autologous or allogeneic stem cell transplantation who are refractory to a second or subsequent line of chemotherapy or have relapsed after at least three lines of therapy, with a medium priority, subject to Special Authority criteria.

3. Review of items relevant to oncology from May and August PTAC

3.1. The Subcommittee noted the records of the PTAC meetings held on 23 and 24 May 2019 and 22 and 23 August 2019.

3.2. The Subcommittee noted that a number of items considered by PTAC at these meetings were also on the agenda for consideration at this meeting and therefore the record of PTAC's consideration would be considered as part of those agenda items, namely: trastuzumab biosimilar; pembrolizumab for the adjuvant treatment of resected stage III melanoma; and CDK4/6 inhibitors for the treatment of hormone-receptor positive, HER2 negative locally advanced or metastatic breast cancer.

4. Correspondence and Matters Arising

Octreotide LAR potential brand change

Discussion

4.1. The Subcommittee noted that the long-acting depot injection forms of octreotide (somatostatin analogue, octreotide LAR) (prefilled syringe presentations - Inj 10mg, 20 mg and 30mg) were included in the 2018/19 Invitation to Tender (ITT).

4.2. The Subcommittee noted that as a result of bids received in the ITT, there is potential that the funded brand of octreotide LAR may change. The Subcommittee noted that based on the likely Medsafe approval timeframe and supplier lead times for the currently preferred product, a change could be implemented in 2020.

4.3. The Subcommittee noted that octreotide LAR is currently funded subject to the following Special Authority criteria:

> Initial application — (Malignant Bowel Obstruction) from any relevant practitioner. Approvals valid for 2 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has nausea* and vomiting* due to malignant bowel obstruction*; and
> 2. Treatment with antiemetics, rehydration, antimuscarinic agents, corticosteroids and analgesics for at least 48 hours has failed; and
> 3. Octreotide to be given at a maximum dose 1500 mcg daily for up to 4 weeks.
>
> Note: Indications marked with * are unapproved indications.
>
> Renewal — (Malignant Bowel Obstruction) from any relevant practitioner. Approvals valid for 3 months where the treatment remains appropriate and the patient is benefiting from treatment.
>
> Initial application — (Acromegaly) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
> Both:
> 1. The patient has acromegaly; and
> 2. Any of the following:
>   2.1. Treatment with surgery, radiotherapy and a dopamine agonist has failed; or
>   2.2. Treatment with octreotide is for an interim period while awaiting the effects of radiotherapy and a dopamine agonist has failed; or
>   2.3. The patient is unwilling, or unable, to undergo surgery and/or radiotherapy.
>
> Renewal — (Acromegaly) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:
> Both:
> 1. IGF1 levels have decreased since starting octreotide; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment.

Note: In patients with Acromegaly octreotide treatment should be discontinued if IGF1 levels have not decreased after 3 months treatment. In patients treated with radiotherapy octreotide treatment should be withdrawn every 2 years, for 1 month, for assessment of remission. Octreotide treatment should be stopped where there is biochemical evidence of remission (normal IGF1 levels) following octreotide treatment withdrawal for at least 4 weeks

Initial application — (Other Indications) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years for applications meeting the following criteria:
Any of the following:

1. VIPomas and Glucagonomas - for patients who are seriously ill in order to improve their clinical state prior to definitive surgery; or
2. Both:
   2.1. Gastrinoma; and
   2.2. Either:
      2.2.1. Patient has failed surgery; or
      2.2.2. Patient in metastatic disease after H2 antagonists (or proton pump inhibitors) have failed; or
3. Both:
   3.1. Insulinomas; and
   3.2. Surgery is contraindicated or has failed; or
4. For pre-operative control of hypoglycaemia and for maintenance therapy; or
5. Both:
   5.1. Carcinoid syndrome (diagnosed by tissue pathology and/or urinary 5HIAA analysis); and
   5.2. Disabling symptoms not controlled by maximal medical therapy.

Note: The use of octreotide in patients with fistulae, oesophageal varices, miscellaneous diarrhoea and hypotension will not be funded as a Special Authority item.

Renewal — (Other Indications) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 2 years where the treatment remains appropriate and the patient is benefiting from treatment.

4.4. The Subcommittee considered that the majority of prescribing of octreotide LAR was by endocrinologists and in primary care or hospice. Members considered that advice should be sought regarding a potential brand change of this product from those prescribers.

4.5. The Subcommittee considered that use of octreotide for the treatment of malignant bowel obstruction was generally the short-acting preparation, was used to control symptoms and given the natural history of this disease was generally for a short duration.

4.6. The Subcommittee considered that carcinoid patients received monthly injections also for symptom control and many would be on treatment long-term. Therefore, if a brand change were to occur, these patients would need to attend an additional clinic appointment with their medical oncologist to explain and support their transition to a new brand.

4.7. The Subcommittee considered that there were unlikely to be significant issues with a brand change of octreotide LAR provided that any new product was available in appropriate vial sizes and could be readily reconstituted by nursing staff (noting the difficulties with solubility of the currently funded brand).

4.8. The Subcommittee considered that any brand change should include a minimum of 6 month transition window and be supported by education and training for health practitioners particularly around reconstitution.

4.9. The Subcommittee noted that introduction of a generic octreotide LAR product and the associated reduction in pricing could also provide the opportunity for widened access

to provide benefit for additional patient groups. The Subcommittee considered that the groups most likely to benefit from widened access to octreotide LAR would be neuroendocrine tumour populations from the PROMID and CLARINET studies.

Carfilzomib weekly dosing

Application

4.10. The Subcommittee reviewed an additional submission from Amgen for weekly dosing of carfilzomib for the treatment of relapsed or refractory multiple myeloma, based on results of the ARROW clinical trial.

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

Recommendation

4.12. The Subcommittee **recommended** that carfilzomib for the treatment of relapsed or refractory multiple myeloma be listed with a medium priority, subject to the following Special Authority criteria:

> Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
> 2. Carfilzomib to be used as second line treatment; and
> 3. Carfilzomib to be administered in combination with dexamethasone.
>
> Renewal application - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

4.13. The Subcommittee noted that that although there is evidence that carfilzomib provides an improvement in progression-free survival (PFS) and overall survival (OS), carfilzomib would have a significant impact on the health system by way of additional infusion requirements.

4.14. The Subcommittee did not consider a restriction limiting dosing to 70 mg/m^2 once weekly was appropriate, given there is a lack of conclusive evidence supporting this dose having the same health benefit as 56 mg/m^2 twice weekly, which is supported by good quality evidence that is more applicable to the New Zealand setting.

Discussion

4.15. The Subcommittee noted that multiple myeloma is treated with sequential lines of therapy and may include autologous stem cell transplant (ASCT), which can be incorporated into the initial therapeutic regimen or at relapse, depending on patient eligibility. The Subcommittee noted that second-line therapy is usually a thalidomide-based treatment such as melphalan, prednisone and thalidomide (MPT) or cyclophosphamide, thalidomide and dexamethasone (CTD) regardless of transplant eligibility in the first line.

4.16. The Subcommittee noted that PTAC in February 2019 had considered carfilzomib for the treatment of relapsed or refractory multiple myeloma and had recommended it be funded with a low priority, subject to Special Authority criteria. The Subcommittee also noted the reasons PTAC had given for its recommendation were that although PTAC

had considered the ENDEAVOR trial data provided good quality evidence and showed PFS and OS improvement in the carfilzomib group, PTAC had considered the potential benefit of carfilzomib to New Zealand patients unclear; and PTAC had considered that although any funded carfilzomib would add another option into the sequence of therapies for MM, given its current dosing schedule it would significantly impact DHB infusion services and could potentially increase inequities in access.

4.17. The Subcommittee also noted that in February 2019 PTAC has also commented with carfilzomib that there were a large number of currently unfunded new treatments for relapsed or refractory multiple myeloma being researched that have uncertain effectiveness and very high cost, especially when used in combination; and that PTAC had supported CaTSoP's view that wider consultation with relevant clinicians on a preferred national treatment algorithm should be undertaken to better understand the clinical priorities for relapsed or refractory multiple myeloma.

4.18. The Subcommittee noted the NCCN (version 3.2018) and ESMO (Moreau et al. Ann Oncol. 2017;28:52-61) guidelines specify many multi-drug combinations in the second-line setting, none of which are currently funded in New Zealand. The Subcommittee noted there would be many options available for improving the funded options in second line, but some have significant infusion requirements. The Subcommittee noted options could be widening access to lenalidomide or funding carfilzomib, daratumumab or ixazomib.

4.19. The Subcommittee noted that carfilzomib is a second-generation irreversible proteasome inhibitor, which (based on the ENDEAVOR trial of twice weekly carfilzomib) is administered as six intravenous infusions per 28-day treatment cycle, and that ENDEAVOR (Dimopoulos et al. Lancet Oncol. 2016;17:27-38; Dimopoulos et al. Lancet Oncol. 2017;18:1327-37) included 929 patients with 1-3 prior lines treatment, reporting a median overall survival (OS) of 47.6 months in the carfilzomib group compared with 40.0 months in the bortezomib group (HR 0.791; 95% CI 0.648 to 0.964) after a median follow-up of 37.5 months in the carfilzomib group and 36.9 months in the bortezomib group.

4.20. The Subcommittee noted the comparator used in the ENDEAVOR study was twice weekly bortezomib, which is likely to cause more neuropathy and have no additional benefit than weekly bortezomib, which is the standard of care in New Zealand. It is therefore likely to overestimate the benefit of carfilzomib in reducing neuropathy in a New Zealand population.

4.21. The Subcommittee also considered treated patients in New Zealand would be older than the median age of 65 years in the study, and nearly all patients would be previously treated with bortezomib and some would have received thalidomide. The Subcommittee considered that the bortezomib comparator was likely superior to the thalidomide-based regimens currently used in New Zealand in second line, but if widened access to bortezomib retreatment was progressed, then this would be an appropriate comparator.

4.22. The Subcommittee considered that limiting the eligible population to those patients currently eligible for lenalidomide in second line who have experienced severe (grade 3 or higher), dose limiting, peripheral neuropathy with bortezomib precluding further treatment would be an option to limit the budget and infusion impacts overall, although it is uncertain if it would be used in preference to oral lenalidomide.

4.23. The Subcommittee noted the results of the subgroup analysis of those in ENDEAVOR with creatinine clearance < 30 mL/min appearing to show less PFS benefit. The

Subcommittee considered that the confidence interval was very large, and that renal impairment can be disease related and improve on treatment. The Subcommittee noted another analysis of the data (Dimopoulos et al. Blood. 2019;133:147-155). The Subcommittee did not consider that renal failure should be an exclusion criterion in the Special Authority criteria.

4.24. The Subcommittee considered there is uncertainly in whether those with refractory disease would benefit to the same extent, but that it would be inappropriate to exclude this group based on the ENDEAVOR subgroup analysis alone.

4.25. The Subcommittee noted median duration of treatment was 48 weeks (interquartile range (IQR) 24·1–88·7) and that this was less than the PFS. The Subcommittee considered the average duration on treatment if funded would likely be close to the 48 weeks of the trial. This difference between treatment duration and PFS was likely due to the high rates of discontinuation due to adverse events and patients choosing to stop, likely due to the high infusion burden, but ongoing disease response despite discontinuation.

4.26. The Subcommittee agreed with PTAC that carfilzomib would add another option into the sequence of therapies rather than displacing or replacing other agents.

4.27. The Subcommittee noted that, in the absence of bortezomib retreatment, most patients that received bortezomib in first line would go on to receive carfilzomib in the second line setting if funded, except those who had contraindications such as congestive heart failure. If bortezomib retreatment was a funded treatment option, the number of patients who would seek treatment with carfilzomib may be lower as some patients may instead receive bortezomib. The Subcommittee noted that although carfilzomib caused less neuropathy, cardiovascular toxicity remained a concern and additional clinical monitoring may be required with a possible requirement for cardiac echocardiograms in some patients.

4.28. The Subcommittee noted that in the ENDEAVOR trial that carfilzomib was given at a dose of 56 mg/m^2 twice weekly x 3 each 28 day cycle, whereas in the ARROW trial (Moreau et al. Lancet Oncol. 2018;19:953-964) a dose of 70 mg/m^2 once weekly x 3 each 28 day cycle was used. The Subcommittee calculated the weekly dosing regimen would result in almost 40% less usage.

4.29. The Subcommittee noted that patients in the ARROW trial were more heavily pretreated and refractory than those in ENDEAVOR, having received at least 2 prior lines of therapy, including bortezomib and an immunomodulatory drug, and demonstrated disease progression on or within 60 days of completion of the last therapy.

4.30. The Subcommittee noted the ARROW comparator was carfilzomib 27 mg/m^2 twice a week, which was lower than the dose used in ENDEAVOR. The Subcommittee considered the ENDEAVOR trial more accurately represented the population proposed for funding in New Zealand.

4.31. The Subcommittee noted the cross-study comparison provided by the supplier, with included an adjustment using propensity score matching. This statistical adjustment for co-variates transformed the median PFS in ARROW from appearing inferior compared with ENDEAVOR to appearing superior. The Subcommittee considered the difference in relative effects sizes to be large and implausible and reflecting likely the large differences between the respective study populations, and that propensity analysis in this setting was thus of poor validity and the adjustment to be inadequately

justified to give confidence that the health benefits gained from carfilzomib 70 mg/m^2 once weekly would be comparable to carfilzomib 56 mg/m^2 twice weekly. The Subcommittee therefore considered that while funded 70 mg/m^2 once weekly could be left as an option for clinicians, it could not be recommended as a mandated approach to limit the dose via Special Authority criteria if the expected benefits were derived from the outcomes in ENDEAVOR. The Subcommittee considered the uptake of any 70 mg/m^2 once weekly dosing option would be low, given this uncertainty of benefit.

4.32. The Subcommittee considered that, based on its limited review of the evidence from ENDEAVOR, there was good quality evidence of improved PFS and OS in a large cohort over a comparator that is likely superior to current treatment in New Zealand. In the context of this and the limited alternative treatment options available in New Zealand, the Subcommittee supported a medium priority recommendation for funding carfilzomib as a second-line treatment for patients with relapsed/refractory multiple myeloma.

Daratumumab updated information

Application

4.33. The Subcommittee reviewed an additional submission from Janssen with further data, which included overall survival, as part of an update to the CASTOR study of daratumumab with bortezomib and dexamethasone for the treatment of relapsed or refractory multiple myeloma.

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

Recommendation

4.35. The Subcommittee **recommended** that daratumumab for the treatment of relapsed or refractory multiple myeloma be listed with a low priority, subject to the following Special Authority criteria:

> Initial application – (relapsed/refractory multiple myeloma) only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has relapsed or refractory multiple myeloma with progressive disease; and
> 2. Daratumumab is to be used as second line treatment; and
> 3. Daratumumab to be administered in combination with bortezomib and dexamethasone.
>
> Renewal application - (relapsed/refractory multiple myeloma) only from a haematologist or any other medical practitioner on the recommendation of a haematologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

4.36. The Subcommittee noted that that although there is evidence of a substantial improvement in PFS from daratumumab use in relapsed or refractory multiple myeloma, based on current information, daratumumab would have a very significant impact on the pharmaceutical budget and DHB infusion services. Both of these were factors in its low priority recommendation.

Discussion

4.37. The Subcommittee noted that in April 2018 and February 2019, CaTSoP and PTAC respectively considered an application for daratumumab for the treatment of relapsed or refractory multiple myeloma. PTAC recommended that the application be deferred pending overall survival data, and CaTSoP had considered that longer-term follow up data were required to confirm the significance of the results.

4.38. The Subcommittee noted Janssen had provided a confidential update of data from CASTOR including OS survival with 47 months follow up.

4.39. The Subcommittee noted that some infusion centres may struggle to deliver initial doses, given the 8-hour initial infusion time which includes intravenous corticosteroid 1 hour prior and then for approximately 7 hours. The second infusion takes 5 hours and subsequent infusions are 4 hours, provided there are no delays due to infusion reactions. The Subcommittee noted limited data on a 90-minute infusion protocol was presented at ASH, the development of a subcutaneous formulation and that splitting the first dose over 2 days (8 mg/kg day 1 and 2) is used by some overseas centres.

4.40. The Subcommittee noted a high frequency of infusion reactions to the initial doses and considered that infusions may need to be given in the main treatment centres with adequate support to manage infusion site reactions.

4.41. The Subcommittee considered it would be reasonable to list daratumumab based on the strong PFS data and limited OS data available, although considered it should be with a low priority given the high cost and the significant impact on the health system by way of additional infusion requirements.

Correspondence from Myeloma New Zealand

Correspondence

4.42. The Subcommittee noted correspondence from Myeloma New Zealand (NZ) dated 4 April 2019 noting their burden of disease report and limited treatment options at first relapse. Myeloma NZ particularly supported the funding of carfilzomib at first relapse and widened access to lenalidomide for use as maintenance treatment post-autologous stem cell transplant.

Discussion

4.43. The Subcommittee wished to acknowledge and thank Myeloma NZ for the information provided.

4.44. The Subcommittee noted the maintenance treatment results from the open-label, randomised, phase III MRC Myeloma XI clinical trial that randomised 1,917 patients to either lenalidomide maintenance (10 mg orally on days 1–21 of a 28-day cycle) or observation in a 1:1 or 2:1 randomisation ratio depending on time period of randomisation (Jackson et al. Lancet Oncol. 2019;20:57-73).

4.45. The Subcommittee noted that after median follow-up of 31 months, median PFS was 39 months with lenalidomide versus 20 months with observation (HR 0.46 [95% CI: 0.41 to 0.53]; P<0.0001).

4.46. The Subcommittee noted that median OS was not reached in either group and that the reported 3-year OS was 78.6% with lenalidomide versus 75.8% with observation (HR 0.87 [95% CI: 0.73 to 1.05]; P=0.15).

4.47. The Subcommittee noted that the 3-year OS in transplantation-eligible patients was 87.5% with lenalidomide versus 80.2% with observation (HR 0.69 [95% CI: 0.52 to 0.93]; P=0.014), and that the 3-year OS in transplantation-ineligible patients was 66.8% with lenalidomide versus 69.8% with observation (HR 1.02 [95% CI: 0.80 to 1.29]; *P*=0.88).

4.48. The Subcommittee reiterated that, although not within PHARMAC's remit to produce treatment guidelines, there would be value in work on a national preferred algorithm in multiple myeloma, in wider consultation with relevant clinicians, to derive optimal lines and sequencing; and that a group forum may help facilitate some of this discussion, rather than simply seeking written submissions or preferences via a survey. It was suggested that perhaps one expert from each regional cancer centre would be appropriate, and it was noted that management of conflicts of interest would need to be considered. Members also suggested that HSANZ could assist with this work.

Sole supply of immune checkpoint inhibitors for advanced melanoma

Discussion

4.49. The Subcommittee noted that, as discussed in previous records of consideration of pembrolizumab and nivolumab for advanced melanoma, immune checkpoint inhibitor (ICI) agents are considered to provide the same of similar therapeutic benefit in the treatment of advanced melanoma; and are therapeutically equivalent across the different dose regimens (weight based and flat dosing regimens).

4.50. The Subcommittee considered that funding of a single ICI for the treatment of advanced melanoma could be clinically appropriate. The Subcommittee noted that a single funded ICI could result in patients currently on treatment being changed to an alternative ICI.

4.51. The Subcommittee noted that nivolumab has been funded for the treatment of advanced melanoma since July 2016 and pembrolizumab since September 2016. The Subcommittee noted that following the funding of pembrolizumab in this population a number of patients who had been receiving treatment with nivolumab had changed to treatment with pembrolizumab due to the three-weekly administration schedule for pembrolizumab versus two-weekly nivolumab.

4.52. The Subcommittee also noted that the current Special Authority criteria for nivolumab and pembrolizumab for advanced melanoma allow patients to change between these agents due to intolerance within the first 12 weeks of starting treatment.

4.53. The Subcommittee considered that there were currently a significant number of advanced melanoma patients who were responding to and remained on treatment with ICIs beyond 12 months; but that the number of these patients would reduce over time as their disease stopped responding to ICI treatment.

4.54. The Subcommittee considered that, if the current funding criteria were to be amended so that patients had the option to take a treatment holiday (for reasons other than disease progression or toxicity) and recommence at signs of disease progression, patients/clinicians would take advantage of this flexibility in their treatment but in the

absence of this option many patients would likely remain on treatment as long as they could still tolerate it.

4.55. The Subcommittee noted that, whilst there was currently limited data to support retreatment with ICIs following a break for good clinical response, international practice was moving to patients stopping ICI treatment following a good response.

4.56. The Subcommittee considered that there was a similarly a lack of data to inform whether for patients who had had a treatment holiday, whether retreatment would need to be with the same ICI. The Subcommittee considered that, given the class effect of ICIs in advanced melanoma shown by current data, it was likely that response to retreatment would be similar regardless of whether the same or a different ICI were used for retreatment as had been administered previously. The Subcommittee considered that response to retreatment regardless of what ICI is used would be expected to be the same regardless of the length of treatment holiday.

4.57. The Subcommittee also considered that given there was a class effect from ICI in the treatment of advanced melanoma, and as clinicians and patients had already had comfort in changing between ICI due to differences in administration schedules, it would likely be clinically acceptable for patients who are responding to treatment with one agent to be changed to another ICI.

4.58. The Subcommittee considered that there were risks associated with changing ICI treatment for patients who were responding well and that it would be difficult to ascertain whether any subsequent lack of response was due to the change in agent or loss of disease control to ICI more generally.

4.59. The Subcommittee considered that it would be beneficial for analysis to be undertaken of what the current rate of progression of advanced melanoma patients on ICI treatment is so that this could be compared to the progression rate following any change of responding patients to an alternative ICI.

4.60. The Subcommittee considered that, given the potential risks of changing ICIs, that the duration of any sole supply arrangement for ICIs for advanced melanoma should aim to be of a length that patients would not change ICI treatment multiple times.

4.61. The Subcommittee considered that, if only one ICI were to be funded for the treatment of advanced melanoma, an appropriate timeframe to allow patients to transition to an alternative ICI would be 3 to 6 months to allow for education and any changes in protocol.

5. Pembrolizumab for the adjuvant treatment of resected stage III melanoma

Application

5.1. The Subcommittee considered the funding of pembrolizumab for the adjuvant treatment of resected stage III melanoma.

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

Recommendation

5.3. The Subcommittee **recommended** that the application for pembrolizumab for the adjuvant treatment of resected stage III melanoma be deferred, pending further data to support the benefit of use of pembrolizumab in this setting.

5.4. The Subcommittee considered that the data currently available for the benefit of adjuvant pembrolizumab for the treatment of resected stage III melanoma was insufficient to inform a funding decision at this time.

Background

5.5. The Subcommittee noted that an application from Merck Sharpe and Dohme (MSD) for pembrolizumab for the adjuvant treatment of resected stage III melanoma was reviewed by PTAC in August 2019 and that PTAC recommended it be deferred pending further data to support the benefit of pembrolizumab in this setting.

5.6. The Subcommittee noted that In August 2019 PTAC had requested advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the health need of this population, current surveillance requirements, and the interpretation of evidence for health benefit specifically regarding: the impact of immune checkpoint inhibitors on the melanoma treatment landscape and given this the utility and validity of recurrence-free survival (RFS) as a surrogate for overall survival (OS) in patients with resected stage III melanoma; the likelihood of overall survival (OS) data from Keynote-054 and other immune checkpoint inhibitor studies and interpretation of its clinical significance; consideration of class effect, optimal timing or sequencing of PD-1 inhibitor therapy in stage III and/or stage IV melanoma; patient number estimates; and appropriate proposed Special Authority criteria including response assessment requirements.

Discussion

RFS as a surrogate outcome measure

5.7. The Subcommittee noted that PTAC had considered recurrence-free survival (RFS) as a surrogate outcome for overall survival (OS), and noted that PTAC had reviewed the results of a meta-analysis that included a total of about 5000 patients with stage II or III melanoma from 11 studies comparing interferon to observation, and 1 study of interferon compared to vaccination (Suciu et al. J Natl Cancer Inst. 2018; 110. Doi: 10.1093/jnci/djx133). The Subcommittee noted that PTAC had:

- noted that the authors predicted that a hazard ratio of 0.77 or less for RFS would predict a benefit in OS, and PTAC had considered that there is a statistical link between the probability of RFS and OS, although its external validity was unclear.
- considered that all studies used in the meta-analysis (published in 2010 to 2013) would have recruited participants before immunotherapy was widely used and therefore did not reflect current melanoma treatment paradigms, which presented challenges for validating this prediction.
- considered that there was currently insufficient survival data to inform assessments of whether RFS is an appropriate surrogate outcome for OS in resected stage III melanoma, but given data collection from Keynote-054 was ongoing, that OS data would likely be available ahead of sufficient data to assess RFS as a surrogate.

5.8. The Subcommittee considered that the best available evidence for RFS as a surrogate outcome for OS in patients with resected stage III melanoma was the meta-analysis by Suciu et al (described in 1.5, above). Members considered it unclear whether RFS in resected stage III melanoma is due to a biological response to any therapy, or if it is due to a response to a particular therapy. The Subcommittee considered that the meta-analysis data was derived from studies which did not utilise immunotherapy, therefore the applicability of this evidence is limited.

5.9. The Subcommittee considered that the impact on the relative validity of data for RFS in this population from the use of immune checkpoint inhibitors as standard of care was unclear, however, some evidence suggests that RFS is correlated to OS in patients treated with ipilimumab for resected stage III melanoma (Eggermont et al. Eur J Cancer. 2019;119:1-10).

Evidence

5.10. The Subcommittee noted that PTAC had reviewed the pivotal trial evidence for the use of adjuvant pembrolizumab for the treatment of resected stage III melanoma, which comes from the randomised (1:1), phase III, double-blind, placebo-controlled Keynote-054 clinical trial that investigated pembrolizumab (200 mg) compared to placebo every 3 weeks for up to 1 year in 1,019 patients with completely resected high-risk stage III melanoma (Eggermont et al. N Engl J Med. 2018;378:1789-1801; Eggermont et al. Eur J Cancer. 2019: 116;148-57). The Subcommittee noted that:

- PTAC noted that the Keynote-054 trial used AJCC 7th Edition tumour staging, included a large proportion of patients with stage IIIA disease, stratified patients by tumour stage and geographic location, and required patients to have had a complete lymph node dissection (lymphadenectomy).

- PTAC members considered that the trial had certainty of staging due to complete lymphadenectomies and pathological staging with AJCC 7th Edition, compared to future trials which would be more reliant on radiological staging with use of AJCC 8th Edition.

- PTAC considered the trial inclusion and exclusion criteria were relevant to New Zealand patients, except that fewer New Zealand patients may now have complete lymph node dissections as standard of care.

5.11. The Subcommittee noted that the Keynote-054 clinical trial demonstrates RFS at 12 months of 75.4% with pembrolizumab compared to 61.0% with placebo (HR 0.57, 98.4% CI: 0.43 to 0.74, *P*<0.001), and RFS at 18 months of 71.4% (95% CI: 66.8 to 75.4) with pembrolizumab compared to 53.2% (95% CI: 47.9 to 58.2) with placebo (*P* value not reported) (Eggermont et al. N Engl J Med. 2018;378:1789-1801). The Subcommittee noted that the currently published results of the Keynote-054 trial had median follow-up of 15 months, that median RFS was not reached and that there currently appeared to be no data available for OS or quality of life. The Subcommittee considered that PTAC's assessment of the Keynote-054 clinical trial data regarding adjuvant pembrolizumab for resected stage III melanoma was accurate.

5.12. Members noted that a network meta-analysis had been performed to indirectly compare the efficacy of pembrolizumab compared to competing regimens for the adjuvant treatment of stage III melanoma, however, the meta-analysis did not include nivolumab (Lorenzi et al. J Drug Assess. 2019;8:135-45).

5.13. Members considered that no other relevant additional data (eg from Keynote-054 or other immune checkpoint inhibitor studies) had been published or presented during the period of time that had elapsed since PTAC reviewed this application.

5.14. The Subcommittee considered that long-term data for RFS is required to assess the potential benefit of adjuvant pembrolizumab for resected stage III melanoma, and that 3-year follow-up data would likely be available from the Keynote-054 clinical trial within the next year and 5 year follow-up data would likely be available in the next few years. The Subcommittee considered that it would be reasonable to expect OS data results from the Keynote-054 clinical trial, to be published in future.

5.15. Members noted that OS for patients with stage III melanoma who received adjuvant ipilimumab compared with placebo has been reported to plateau over time and considered that the hazard ratios were stable over the latter 5 to 7 years of follow-up (Eggermont et al. Eur J Cancer. 2019;119:1-10; Eggermont et al. J Clin Oncol. 2019;15(suppl) Abstract Nr 2512). Members considered it was possible that pembrolizumab responses could follow a similar pattern, however this would not be known until further longer-term data was available.

5.16. The Subcommittee considered that, if further data from the Keynote-054 trial shows only a few months difference in RFS, this may not be a clinically meaningful difference given asymptomatic patients have good RFS and the majority (~80%) of patients with resected stage III melanoma who do not receive adjuvant treatment do not relapse.

5.17. The Subcommittee considered that based on currently available evidence, the below Special Authority criteria for adjuvant treatment were appropriate including response assessment requirements, and noted that the requirement to initiate treatment within 13 weeks of surgical resection is derived from the Keynote-054 clinical trial:

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

5.18. The Subcommittee considered that there was limited data available to inform an assessment of the value of surveillance in patients with resected stage III melanoma. Members noted a study of 668 patients with melanoma in Germany reported that the majority of recurrences were not found during routine follow-up and the authors indicated that the utility of routine follow-up was limited (Livingstone et al. Eur J Cancer. 2015; 51:653-67). Members noted that a review of 7 international guidelines for melanoma surveillance found no consensus on follow-up or imaging (Trotter et al. J

Clin Aesthet Dermatol. 2013; 6:18-26). Members considered that studies of lymph node dissections included 3-monthly ultrasound sonography, however, use of this surveillance may not be relevant due to the change in practice for lymph node dissection.

5.19. The Subcommittee considered that there is variation in current practice regarding response assessments and surveillance (including the type and frequency of assessments) for patients with stage III melanoma in New Zealand, however, a clinical examination of the skin at 3-monthly intervals would be the expected standard care comparator, in accordance with the Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (The Cancer Council Australia and Australian Cancer Network, Sydney and New Zealand Guidelines Group, Wellington [2008]).

5.20. The Subcommittee considered that the current evidence for nivolumab and pembrolizumab suggests there may be a class effect of immune checkpoint inhibitors in the adjuvant treatment of stage III melanoma, and noted that there appears to be consistency between the available RFS data for pembrolizumab and the more mature RFS data for nivolumab (up to 3-year follow-up) recently presented from the CheckMate-238 trial comparing adjuvant nivolumab with ipilimumab in 906 patients with completely resected high-risk stage III melanoma (Weber et al. Ann Oncol. 2019;30(suppl_5): Abstract Nr 1310O). The Subcommittee considered that the CheckMate-238 trial population was very similar to, but had slightly more advanced disease than, the Keynote-054 trial population.

5.21. The Subcommittee considered that given the data currently available evidence for use of immune checkpoint inhibitors, it was unclear what the optimal timing or sequencing of these agents in stage III and/or stage IV melanoma should be. The Subcommittee considered that there would likely be data available in the near future regarding retreatment with immune checkpoint inhibitors in patients with stage III/IV melanoma and response rates to subsequent treatment, which would help to inform consideration of sequencing and optimal timing for use of these agents.

5.22. The Subcommittee considered that it was difficult to estimate the number of melanoma patients with resected stage III melanoma, who may seek treatment with pembrolizumab as there are limitations to staging data and uncertainties due to the variation in staging classification.

5.23. The Subcommittee considered that the application should be reviewed by CaTSoP once longer-term data was available, including data for 3-year RFS. The Subcommittee considered that data regarding retreatment with immune checkpoint inhibitors would also be needed to inform further consideration of use of these agents in the treatment of melanoma.

6. Rituximab biosimilar discussion

Application

6.1. The Subcommittee reviewed an application from Sandoz New Zealand (a Novartis division) for Riximyo, a biosimilar of rituximab for use in multiple funded indications.

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

Recommendations

6.3. The Subcommittee considered there is no evidence to suggest any differences in the health benefits or risks between reference and biosimilar rituximab, and recommended it was clinically acceptable for Riximyo to be listed and be the only available rituximab product for all funded indications, if the cost saving is worthwhile, and supply is secured.

6.4. The Subcommittee **recommended** PHARMAC should consider widening access to rituximab as part of the biosimilar transition, which should include a review of commonly approved rituximab NPPA applications.

Discussion

6.5. The Subcommittee noted this discussion was to seek advice on the clinical evidence and implementation considerations following a recent competitive process for the supply of rituximab. This process sought bids for the exclusive supply of rituximab for all funded indications except rheumatoid arthritis (which remains protected by patents).

6.6. The Subcommittee noted that rituximab is chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is a glycosylated IgGI kappa immunoglobulin containing murine light- and heavy- chain variable region sequences (Fab domain) and human constant region sequences (Fc domain).

6.7. The Subcommittee noted approximately 1000 patients received rituximab for a cancer indication in in 2018, with 750 initial approvals for Non-Hodgkin lymphoma (in its various forms) and 80 initial approvals for Chronic Lymphocytic Leukaemia. The Subcommittee noted PHARMAC had estimated approximately 850 patients receive rituximab for a non-cancer indication.

6.8. The Subcommittee noted maintenance therapy for CD20+ low grade or follicular B-cell Non-Hodgkin lymphoma following induction with first-line systemic chemotherapy had been considered previously and was currently ranked on PHARMACs Options for Investment list. The Subcommittee noted widening of access was being actively considered. The Subcommittee noted rituximab Named Patient Pharmaceutical Assessment (NPPA) applications are common for a range of uses and it would be worthwhile to review recent applications and widen access if possible to reduce the administration burden on clinicians.

6.9. The Subcommittee noted Riximyo has been developed in a stepwise approach according the European guidelines (CHMP) guidelines for demonstrating biosimilarity compared with the reference product Mabthera. These European guidelines have been adopted by Medsafe in New Zealand. The Subcommittee noted Riximyo is Medsafe approved for the treatment of all indications currently approved for Mabthera.

6.10. The Subcommittee noted a non-clinical study which demonstrates in a wide variety of tests, using an extensive array of routine analytical and extended characterisation methods, that the physiochemical and functional comparability between the biosimilar (GP2013) and the reference rituximab are highly similar in higher outer structure, post translational modifications and size variant. The extensive functional characterisation package indicated that Riximyo has the same biological properties as the reference rituximab (Visser et al. BioDrugs. 2013;5:495-507).

6.11. The Subcommittee noted a randomised, double-blind study to demonstrate pharmacokinetic and pharmacodynamic equivalence of Riximyo and reference rituximab as well as non-inferior efficacy, safety and immunogenicity in adults with active rheumatoid arthritis refractory or intolerant to conventional DMARDS and at least one TNF inhibitor (Smolen et al. Ann Rheum Dis. 2017;76:1598-1602).

6.12. The Subcommittee noted a randomised, double-blind study to demonstrate comparability in overall response with Riximyo and reference rituximab combined with cyclophosphamide, vincristine, and prednisone (R-CVP) in previously untreated follicular lymphoma (Jurczak et al. Lancet Haematol. 2017;4:e350-e361).

6.13. The Subcommittee noted a randomised, double-blind study to demonstrate comparability in clinical safety after switching from a reference biologic to biosimilar rituximab (Riximyo) in rheumatoid arthritis (Tony et al. Arthritis Care Res (Hoboken). 2019;71:88-94).

6.14. The Subcommittee considered the above clinical studies were all randomised double-blind trials clearly demonstrating biosimilarity of Riximyo (also called GP2013 and Rixathon) with reference rituximab. The Subcommittee noted all measures of efficacy and adverse events appear indistinguishable. The Subcommittee considered there is no reason to believe, given the physiochemical and functional comparability, that there be any clinical risk with changing to biosimilar rituximab.

6.15. The Subcommittee noted market share data for rituximab in selected EU markets and that uptake of rituximab biosimilars, including Riximyo (branded as Rixathon in Europe) has been substantial. The Subcommittee noted confidential data provided by Sandoz on the global usage and estimated cumulative patient exposure to the Riximyo brand since June 2017.

6.16. The Subcommittee considered the comparability of Riximyo and Mabthera has been sufficiently demonstrated with regard to physicochemical characteristics, pharmacology, efficacy and safety outcomes. The clinical evidence for comparability is of good quality and supports the use of Riximyo for all funded indications.

6.17. The Subcommittee considered there is no evidence to suggest any differences in the health benefits or risks obtainable with the Riximyo and Mabthera brands of rituximab and concluded it would be clinically acceptable were Riximyo the only available rituximab product (sole supply) for all indications, provided cost savings were worthwhile and supply secured.

6.18. The Subcommittee noted that concerns about a change from Mabthera to a biosimilar might arise in patients and/or physicians where the patient has shown a beneficial response to the Mabthera brand. The Subcommittee considered that while there may be a nocebo effect, reassurance will be provided by the virtually identical characteristics of these drugs and the above convincing studies by Smolen et al. and Jurzcak et al. and the fact that the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA) and other medicines regulators have comprehensively assessed the evidence and accepted this biosimilar product.

6.19. The Subcommittee noted the supplier is proposing a comprehensive engagement programme, which involves scientific and educational presentations at tertiary and secondary hospitals in the 3 months pre-launch and 4 months post-launch. The Subcommittee considered that as this is a substitution medicine, with no additional benefits or side effects, that most prescribing physicians will not be especially concerned. The Subcommittee considered it would be preferable to have a clinician or

independent educational group provide the education to those clinicians who are interested.

7. Trastuzumab review and biosimilar discussion

Application

7.1. The Subcommittee reviewed an application from Celltrion Healthcare New Zealand Limited for CT-P6, a biosimilar trastuzumab, for use in multiple indications (early breast cancer, metastatic breast cancer, and gastric cancer).

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

Recommendation

7.3. The Subcommittee considered that there is no evidence to suggest any differences in the health benefits or risks between reference and biosimilar trastuzumab, and **recommended** it was clinically acceptable for a biosimilar trastuzumab, such as CT-P6, to be listed and be the only available trastuzumab product for all funded indications, if the cost saving is worthwhile and supply is secured.

7.4. The Subcommittee supported a competitive process and **recommended** that PHARMAC bring any other biosimilar trastuzumab options to CaTSoP, when available in future, for review. The Subcommittee noted that there is sufficient evidence of biosimilarity to reference trastuzumab (Herceptin) and considered that interchangeability or switch data should be reviewed if available in future.

Discussion

7.5. The Subcommittee noted that in August 2019, PTAC reviewed an application for CT-P6, a biosimilar trastuzumab, for use in multiple indications (early breast cancer, metastatic breast cancer, and gastric cancer).

7.6. The Subcommittee noted that PTAC recommended that PHARMAC could progress a competitive procurement process for trastuzumab and considered that a managed change to a single trastuzumab biosimilar product, such as CT-P6, would be clinically acceptable for the treatment of HER2-positive early breast cancer and HER2-positive metastatic breast cancer.

7.7. The Subcommittee noted that PTAC requested the Cancer Treatment Subcommittee of PTAC (CaTSoP) provide PHARMAC any advice on implementation issues.

7.8. The Subcommittee noted that CT-P6 is a humanised monoclonal antibody that selectively binds with high affinity to HER2, that trastuzumab products have been shown to inhibit proliferation and mediate antibody-dependent cellular toxicity in tumour cells that overexpress HER2, and that in vitro analysis has confirmed that CT-P6 functions in a manner similar to reference trastuzumab (Herceptin) (Jeong et al. Expert Opin Biol Ther. 2019;19:1085-95).

7.9. The Subcommittee noted that the application for CT-P6 (Herzuma) requested funding for trastuzumab for the treatment of early breast cancer, metastatic breast cancer, and gastric cancer, subject to patent expiry. The Subcommittee also noted that PTAC considered that, in the absence of new evidence relevant to gastric cancer, the

application for CT-P6 would be considered only for HER2-positive early and metastatic breast cancers.

7.10. The Subcommittee noted that the intravenous preparation of the trastuzumab reference product has been listed on the Pharmaceutical Schedule since 2005 and is currently funded in New Zealand for HER2-positive early and metastatic breast cancer. Members considered that patients who receive neoadjuvant treatment for breast cancer are a relatively homogenous group, however, patients with metastatic breast cancer are a heterogenous group whose drug resistance mechanisms may have been altered by prior anticancer treatment regimens.

7.11. The Subcommittee noted that CT-P6 has been approved by the EMA for use in the European Union, by the FDA for use in the United States, and by Medsafe for use in New Zealand for all the indications of the reference trastuzumab product. The Subcommittee noted that the Medsafe approval for CT-P6 includes use in combination with a taxane for patients who have not received chemotherapy for metastatic disease. Members also considered vinorelbine in combination was a suitable and effective alternative to combine with a taxane, as occurs with reference trastuzumab (although use of reference trastuzumab or CT-P6 in combination with vinorelbine is not Medsafe-approved for this indication).

7.12. The Subcommittee noted that biosimilars are rigorously investigated for risks of reactions and to assess immunogenicity. The Subcommittee noted that investigation of pharmacokinetics (PK), pharmacodynamics (PD), antidrug antibodies, safety and efficacy are required to assess clinical efficacy in appropriate populations and to establish biosimilarity with the reference product.

7.13. The Subcommittee considered the non-clinical evidence was comprehensive and supported biosimilarity between CT-P6 and reference trastuzumab:

7.14. The Subcommittee noted data from a 3-way similarity study with an extensive comparative analysis of primary, secondary and tertiary structure, glycan profiles and of post-translational modifications, and considered that the molecular characteristics of CT-P6 demonstrated no significant differences between the biosimilar and reference trastuzumab (Lee et al. MAbs. 2018;10:547-71).

7.15. Members noted that non-clinical PD data for CT-P6 demonstrated very similar blocking of HER2 cleavage and subsequent HER-2 down-regulation compared with reference trastuzumab (Herzuma Assessment report. European Medicines Agency [EMA], 2017).

7.16. The Subcommittee considered that the safety data from the phase I clinical trials in healthy subjects were similar and presented no concerns.

7.17. The Subcommittee noted the results of the phase III, randomised, double-blind, active-controlled, CT-P6 3.2 equivalence trial which investigated 8 cycles of neoadjuvant CT-P6 or reference trastuzumab (with neoadjuvant chemotherapy), then surgery, followed by adjuvant CT-P6 or reference trastuzumab for a total of 1 year of treatment in 549 women with stage I-IIIa operable HER2-positive breast cancer (Stebbing et al. Lancet Oncol. 2017;18:917-28).

7.18. The Subcommittee considered that the CT-P6 3.2 trial patient characteristics were well balanced between groups, that patients had good baseline left ventricular ejection fraction (LVEF) and that staging was slightly higher in the CT-P6 arm. The

Subcommittee considered that these factors were not sufficient to impact the clinical trial outcomes.

7.19. The Subcommittee noted that the primary outcome of the CT-P6 3.2 trial was pathological complete response (pCR) after surgery, and that this excluded ductal carcinoma in situ (DCIS). The Subcommittee noted that after 19.5 months of follow up the pCR rate was 46.8% with CT-P6 compared to 50.4% with reference trastuzumab. The Subcommittee noted that the pCR with CT-P6 was within the prespecified equivalence margin of ±15% from the expected pCR of 54%, therefore demonstrating equivalence according to this definition.

7.20. The Subcommittee noted the safety data from the CT-P6 3.2 trial was broadly similar between CT-P6 and reference trastuzumab. The Subcommittee considered that there were similar frequencies of treatment-emergent adverse events in each group, and comparable immunogenicity with no differences in the frequency of infusion reactions or anti-drug antibodies. The Subcommittee noted that there were no significant differences in LVEF change.

7.21. Members considered the possibility of an interaction between pertuzumab and biosimilar trastuzumab, which bind to different subdomains of the HER2 receptor and therefore do not directly interact. Members considered that as CT-P6 binds to the same epitope on subdomain IV of the HER2 receptor as reference trastuzumab, it is unlikely there would be an interaction between CT-P6 and pertuzumab which binds to subdomain II. Members considered CT-P6 would provide the same benefit that would be expected as for reference trastuzumab.

7.22. The Subcommittee considered that the efficacy and safety data supported the biosimilarity of CT-P6 compared with reference trastuzumab.

7.23. The Subcommittee considered that a change to a biosimilar trastuzumab as a result of a competitive procurement process would be unlikely to have any impact on health benefits or risks for patients who would receive treatment with reference trastuzumab, due to comprehensive testing already being done to assess risks and benefits. The Subcommittee considered that it was clinically acceptable for a biosimilar trastuzumab to be listed and be the only available trastuzumab product for all funded indications if the cost saving is worthwhile and supply is secured. The Subcommittee supported a competitive process and recommended that PHARMAC bring any other biosimilar trastuzumab options that are proposed for funding to CaTSoP, when available in future, for review.

7.24. The Subcommittee considered that the evidence for biosimilarity of CT-P6 and reference trastuzumab demonstrated that similarity was established. The Subcommittee considered that interchangeability (for which there are different regulatory definitions used in Europe and the USA) still remained unconfirmed and that there is limited real-world data regarding switching from one trastuzumab product to another, or multiple changes between trastuzumab products over time. The Subcommittee considered that interchangeability data would be desirable and should be reviewed in future, if such data becomes available.

7.25. The Subcommittee considered that they had no concerns and did not identify any specific risks associated with changing existing patients who have commenced on a treatment course of reference trastuzumab to biosimilar trastuzumab, whether these were patients with early breast cancer who would receive a 9 week or 12 month course, or patients with metastatic breast cancer who would be treated until disease progression. The Subcommittee considered that, for patients who were responding

well to reference trastuzumab and then change to biosimilar trastuzumab, it may be difficult to ascertain whether any subsequent loss of response was due to the change or due to natural progression of the disease. Members noted that any change would be closely managed and supported by treating clinicians and hospital pharmacists.

7.26. The Subcommittee noted a 6-month transition period has been proposed by PHARMAC. The Subcommittee considered that it would be clinically acceptable to change trastuzumab products during a patient's treatment course if they have more than 6 months' Herceptin treatment remaining. The Subcommittee noted that during the transition period, Herceptin would remain funded as per Special Authority current criteria and that patients with less than 6 months' Herceptin treatment remaining would not be required to transition.

7.27. The Subcommittee considered that it would be important to establish confidence for prescribers and other groups regarding biosimilar trastuzumab in order to support implementation of a biosimilar. The Subcommittee considered that the minor batch-to-batch variation of reference trastuzumab in 2019 compared with trastuzumab in 2015 was relevant for comparative purposes, and similar data may be helpful for clinician education. Members considered it would also be useful to have patient outcome data available to support and assess the impact of any change.

8. Obinutuzumab for relapsed/refractory Non-Hodgkin lymphoma and treatment naïve follicular lymphoma

Application

8.1. The Subcommittee considered the following applications from Roche Products (New Zealand) Ltd:

- obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with indolent non-Hodgkin lymphoma (NHL) who relapsed after, or are refractory to, a rituximab-containing regimen, and

- obinutuzumab for the first-line induction and maintenance treatment of adult patients with follicular lymphoma (FL).

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

Recommendation

8.3. The Subcommittee **recommended** that obinutuzumab in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with indolent non-Hodgkin lymphoma (NHL) who relapsed after, or are refractory to, a rituximab-containing regimen, be funded with a medium priority.

8.4. The Subcommittee made this recommendation due to the unmet need of this small patient group, the highly relevant clinical trial evidence (to New Zealand patients) and the evidence for a difference in PFS, a clear difference in OS (despite immature data) and reasonable toxicity profile associated with obinutuzumab.

8.5. The Subcommittee recommended the following new Special Authority criteria for obinutuzumab for the treatment of the above recommended patient group:

Initial application (indolent, low grade lymphomas) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. Patient has an indolent low grade lymphoma; and
2. Patient is refractory to any previous regimen containing rituximab; and
3. Patient has an ECOG performance status of 0-2; and
4. Patient has been previously treated with no more than four chemotherapy regimens; and
5. Obinutuzumab to be administered at a maximum dose of 1000 mg in combination with bendamustine at a maximum dose of 90 mg/m2 for a maximum of 6 cycles; and

Renewal application (indolent, low grade lymphomas) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 24 months for applications meeting the following criteria:

1. Patient has no evidence of disease progression following obinutuzumab induction therapy; and
2. Obinutuzumab to be administered at a maximum of 1000 mg every 2 months for a maximum of 2 years; and
3. Obinutuzumab to be discontinued at disease progression.

Note: 'Indolent, low-grade lymphomas' includes follicular, mantle, marginal zone and lymphoplasmacytic/Waldenstrom macroglobulinaemia. Rituximab-refractory is defined as failure to respond to, or progression during, any previous rituximab-containing regimen (monotherapy or combined with chemotherapy), or progression within 6 months of the last rituximab dose, in the induction or maintenance treatment settings. Response to first-line systemic chemotherapy in combination with obinutuzumab needs to be assessed 2-4 weeks after the last treatment course. Maintenance therapy should commence at 8 weeks after completion of the first-line systemic treatment.

8.6. The Subcommittee recommended the following change to the Special Authority criteria for bendamustine in both initial and renewal (additional text in **bold**):

*Bendamustine is to be administered as a monotherapy **or in combination with obinutuzumab** for a maximum of 6 cycles in rituximab refractory patients*

8.7. The Subcommittee **recommended** that obinutuzumab for the first-line induction and maintenance treatment of adult patients with follicular lymphoma (FL) be deferred.

8.8. The Subcommittee decided that in order to consider this application sufficiently it would need to see mature PFS and safety data for this patient group from the GALLIUM trial (unlikely to be available for at least a few years), and considered OS data was unlikely to be forthcoming in this patient group.

General discussion

8.9. The Subcommittee noted that treatment of indolent non-Hodgkin lymphoma (NHL), including follicular lymphoma (FL), in New Zealand consists of multiple treatment lines using rituximab in combination with chemotherapy (predominantly bendamustine-rituximab for first line therapy), with stem cell transplant in appropriate cases at later relapse. The Subcommittee noted that funding restrictions for rituximab or bendamustine retreatment require rituximab- or bendamustine-treatment free intervals of 12-months. The Subcommittee noted that approximately 14% of patients with NHL will experience rituximab-refractory disease or relapse within six months of rituximab treatment.

8.10. The Subcommittee noted that rituximab maintenance therapy for FL is not currently funded in New Zealand, but that an application for rituximab maintenance therapy for CD20+ low-grade or follicular B-cell NHL received a medium priority recommendation from CaTSoP in April 2018. The Subcommittee considered that funded rituximab maintenance would not change the health need of patients who ultimately become rituximab-refractory.

8.11. The Subcommittee considered that treatment of indolent non-Hodgkin lymphoma in the third line and later is challenging, especially for rapidly relapsing disease, that most patients with NHL eventually relapse, and that antibody treatments (eg rituximab) offer more benefit if used in combination with chemotherapy.

8.12. The Subcommittee noted that obinutuzumab, like rituximab, is an anti-CD20 monoclonal antibody but that obinutuzumab has a broader mechanism of action and uses a direct pathway to cause malignant cell death.

8.13. The Subcommittee noted that obinutuzumab is Medsafe-approved for first-line treatment of patients with FL (in combination with chemotherapy followed by maintenance) and for patients with indolent NHL who did not respond to, or who progressed during/within 6 months of prior rituximab (in combination with bendamustine followed by maintenance).

Obinutuzumab for relapsed/refractory indolent NHL

8.14. The Subcommittee noted that in August 2018 the application for indolent NHL was reviewed by PTAC, which recommended funding with a low priority, and noted the reasons PTAC had given for its recommendation were what PTAC considered evidence of improved PFS, uncertain evidence of an OS benefit, and no significant difference in safety or HRQoL. The Subcommittee also noted that PTAC had requested advice from CaTSoP regarding the need for another agent in NHL and the potential impact of increasing infusion requirements due to maintenance therapy.

8.15. The Subcommittee considered that the applicant's patient number estimate (N = 36) was reasonable and the estimate by PHARMAC staff (N = 9, based on bendamustine use in rituximab-refractory patients) was too low, but that bendamustine may be contraindicated in patients who are heavily pre-treated, of advanced age, or have co-morbidities. The Subcommittee considered that the small group of patients with relapsed/refractory indolent NHL have an unmet health need and that uptake of obinutuzumab plus bendamustine could be low due to patient characteristics.

8.16. The Subcommittee noted that the primary evidence for the efficacy of obinutuzumab in combination with bendamustine for rituximab-refractory indolent NHL comes from the phase 3 GADOLIN trial; an open-label, randomised (1:1), multicentre trial that investigated the efficacy and safety of induction therapy with obinutuzumab plus bendamustine followed by obinutuzumab maintenance therapy, compared with bendamustine monotherapy induction therapy, in 413 patients with rituximab-refractory indolent NHL (Sehn et al. Lancet Oncol. 2016;17:1081-93; Cheson et al. J Clin Oncol. 2018;36:2259-66).

8.17. The Subcommittee considered that limitations of the GADOLIN trial design and patient group characteristics would have biased the results; specifically, different doses of bendamustine (120 mg as monotherapy; 90 mg with obinutuzumab), use of bendamustine monotherapy as a comparator and without maintenance (patients more likely to progress than with obinutuzumab plus bendamustine), imbalances in the proportion of patients refractory to prior rituximab monotherapy (18.6% in the obinutuzumab plus bendamustine group and 23.0% in the monotherapy group in the intention-to-treat population, and in 15.2% and 24.6%, respectively, of patients with FL), and broad definitions of rituximab-refractory (applying to prior rituximab monotherapy and rituximab-containing combination chemotherapy regimens). The Subcommittee considered that rituximab monotherapy is seldom used in New Zealand, as patients may respond to rituximab with chemotherapy.

8.18. The Subcommittee noted the UK National Institute for Health and Care Excellence (NICE) technology appraisal of obinutuzumab plus bendamustine had reported limitations in estimates of overall survival (OS) which favoured the intervention (Rafia et al. Pharmacoeconomics. 2018;36:1143-51).

8.19. The Subcommittee noted that the median progression-free survival (PFS) in the GADOLIN trial was 25.8 months with obinutuzumab plus bendamustine compared to 14.1 months with bendamustine monotherapy (HR 0.57; 95% CI 0.44 to 0.73; P<0.001). The Subcommittee noted that median OS was not reached for either group, where the Kaplan Meir survival differences were statistically significant (HR 0.67; 95% CI 0.47-0.96; P=0.0269) and considered that a reasonable number of survival events had occurred. The Subcommittee noted that the PFS and OS results were consistent in the FL patient subgroups (Cheson et al. J Clin Oncol. 2018;36:2259-66).

8.20. The Subcommittee considered that obinutuzumab had a reasonable safety profile, that adverse events (AEs) were similar between the treatment groups, and that the higher proportion of treatment withdrawals due to AEs with bendamustine monotherapy may be due to poor tolerance of the larger bendamustine dose in this group.

8.21. The Subcommittee considered that GADOLIN demonstrated a PFS benefit and an apparent OS effect, despite the published data not being fully mature and the limitations of the trial.

8.22. The Subcommittee considered that the clinical trial evidence from the GADOLIN trial was highly relevant to New Zealand patients with indolent NHL, because the trial control arm used bendamustine monotherapy as would be the case in New Zealand for rituximab-refractory patients where a rituximab treatment-free interval of 12 months or more is required for renewal of rituximab on relapse.

8.23. The Subcommittee considered that the infusion resource required to administer obinutuzumab maintenance every 2 months for 2 years or until disease progression was small, that a small number of patients would receive this treatment, and that obinutuzumab maintenance would require similar infusion resources to maintenance rituximab (if funded), however, obinutuzumab may be more challenging to administer than rituximab. The Subcommittee considered that uptake of this regimen might be quite low.

Obinutuzumab for first-line treatment of FL

8.24. The Subcommittee noted that in August 2018 the application for FL was reviewed by PTAC, which recommended the application be deferred pending further data, and that PTAC considered it should be funded only if cost-neutral to rituximab maintenance. The Subcommittee noted the reasons PTAC had given for its recommendation were what PTAC considered evidence of improved PFS but no evidence of quality of life benefit and no clear evidence of OS benefit with obinutuzumab compared with rituximab. The Subcommittee also noted that PTAC had requested advice from CaTSoP regarding the long-term safety data of obinutuzumab and the likely efficacy of retreatment with obinutuzumab or rituximab.

8.25. The Subcommittee considered that the patient number estimates by the applicant (N = 119) and PHARMAC staff (N = 88) were reasonable estimates of the number of newly diagnosed patients with FL, although they could be slightly overestimated.

8.26. The Subcommittee noted that the primary evidence for the efficacy of obinutuzumab induction and maintenance therapy for the first-line treatment of FL derives from the GALLIUM trial; an open-label, phase 3, randomised (1:1) trial that investigated the

efficacy and safety of obinutuzumab plus chemotherapy induction therapy compared with rituximab plus chemotherapy followed by maintenance with the same antibody in 1202 patients with previously untreated FL (Marcus et al. N Engl J Med. 2017;377:1331-44; Hiddemann et al. J Clin Oncol. 2018;36:2395-404).

8.27. The Subcommittee considered that the GALLIUM trial was of good quality, where it included patients with up to grade 3a disease, used the GELF tumour burden criteria for treatment eligibility, had a standard rituximab treatment schedule, and had a good balance of patients between treatment groups. The Subcommittee noted that three chemotherapy regimens were allowed: bendamustine (used in 57.1% of patients), CHOP (33.1%) and CVP (9.8%).

8.28. The Subcommittee noted that after a median follow-up of 41 months, the 3-year investigator-assessed PFS rate in the GALLIUM trial was 82% in the obinutuzumab group compared with 75% in the rituximab group (HR 0.68; 95% CI 0.54 to 0.87; P=0.0016), and that results of PFS as assessed by independent review committee were similar. Members considered that the PFS results by chemotherapy regimen were consistent. The Subcommittee noted that the 3-year OS rate was 94% in the obinutuzumab group compared with 92% in the rituximab group (HR 0.82; 95% CI 0.54 to 1.22; P=0.32) (Hiddemann et al. J Clin Oncol. 2018;36:2395-404).

8.29. The Subcommittee noted that secondary malignancy occurred in 5% of patients receiving bendamustine, more infections were reported in patients receiving bendamustine (20-26%) than other regimens (12-20%), and higher rates of grade 3-5 cytopenias were reported in patients receiving CHOP than with other regimens. The Subcommittee considered these safety signals were small, but that longer-term data is needed to evaluate their clinical significance.

8.30. The Subcommittee noted that in patients older than 70 years that a higher proportion of fatal events occurred prior to starting new anticancer therapy with bendamustine (13%) compared with CHOP (2%) or CVP (4%), and considered this was a concern due to patients likely being older at the time of their diagnosis with FL.

8.31. The Subcommittee considered that the difference in PFS between groups was small and that the GALLIUM trial data was too immature to conclude whether obinutuzumab would be preferred over rituximab for induction and maintenance treatment for FL. The Subcommittee requested that it see mature efficacy and safety data, once available, although it considered these data unlikely to be available for at least a few years. The Subcommittee considered that OS data was unlikely to be produced as it is challenging to obtain this in FL, due to confounding from crossovers with subsequent multiple lines of therapy.

8.32. The Subcommittee noted that there is no available data for retreatment using either obinutuzumab or rituximab after obinutuzumab in the first-line setting, and considered that the efficacy and safety of retreatment with obinutuzumab or rituximab is currently unknown. The Subcommittee considered that long-term safety and efficacy data are lacking in FL and there is a small signal for increased infections and secondary malignancy that requires additional follow up to determine if this is a concern.

9. CDK4/6 inhibitors for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer

Application

9.1. The Subcommittee reviewed the funding of CDK4/6 inhibitors for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

9.2. The Subcommittee considered applications from Novartis New Zealand Limited for the use of ribociclib (Kisqali):

- in combination with fulvestrant for the second-line treatment of HR-positive, HER2-negative locally advanced breast cancer who have failed previous endocrine therapy.

- in combination with an aromatase inhibitor as a first-line treatment for HR-positive, HER2-negative locally advanced breast cancer.

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

Recommendation

9.4. The Subcommittee **recommended** that ribociclib in combination with an aromatase inhibitor as a first-line treatment of HR-positive, HER2-negative locally advanced breast cancer who have failed previous endocrine therapy be funded with high priority subject to the same Special Authority criteria as previously recommended for palbociclib in this setting.

9.5. The Subcommittee **recommended** that ribociclib in combination with fulvestrant for the second-line treatment of HR-positive, HER2-negative locally advanced breast cancer who have failed previous endocrine therapy be funded with high priority subject to the same Special Authority criteria as previously recommended for palbociclib in this setting.

9.6. The Subcommittee reiterated its previous recommendations that palbociclib as a first-line treatment in combination with an aromatase inhibitor and in combination with fulvestrant as a second line treatment of HR-positive HER2-negative locally advanced breast cancer be funded with medium priority subject to the same Special Authority criteria as previously recommended.

9.7. The Subcommittee noted the different priority assigned to ribociclib and palbociclib was primarily due to differences in the quality of data currently available for these agents.

9.8. The Subcommittee considered that based on currently available data there was a class effect from CDK4/6 inhibitors in the treatment of HR-positive HER2-negative locally advanced breast cancer and **recommended** funding for patients to receive one line of treatment with a CDK4/6 inhibitor in either a first or second-line setting with high priority.

9.9. The Subcommittee reiterated its previous recommendation that the following Special Authority criteria be applied to funding of CDK4/6 inhibitors (note combined first-line and second-line criteria are shown below):

Special Authority for Subsidy – Retail Pharmacy

Initial application - only from a medical oncologist or any other medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has unresectable locally advanced or metastatic breast cancer; and
2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
3. Patient has an ECOG performance score of 0-2; and
4. Either:
   4.1. Patient's disease has relapsed or progressed during prior endocrine therapy; or
   4.2. Both:
      4.2.1. Patient has not received prior systemic treatment for metastatic disease; and
      4.2.2. Patient has been amenorrhoeic for 12 months or greater, either naturally or induced, with endocrine levels consistent with a postmenopausal state.
5. [CDK4/6 inhibitor] must be used in combination with an endocrine partner.

Renewal application - only from a medical oncologist or any other medical practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:
1. [CDK4/6 inhibitor] must be used in combination with an endocrine partner; and
2. No evidence of progressive disease; and
3. The treatment remains appropriate and the patient is benefitting from treatment.

Discussion

9.10. The Subcommittee noted that there are currently three CDK4/6 inhibitors marketed internationally (abemaciclib, palbociclib and ribociclib), each with slightly different dosing schedules, inhibiting CDK4/6 at slightly different concentrations, and each with slightly differing reports of adverse events. However, the Subcommittee considered that currently available evidence indicates there is a class effect from use of these agents in the treatment of HR-positive HER2-negative locally advanced breast cancer.

9.11. The Subcommittee noted that three funding applications for two CDK4/6 inhibitor agents (palbociclib and ribociclib) had been previously considered by both PTAC and CaTSoP, however both committees had previously considered the totality of data for the class of agents that was available at the time.

9.12. The Subcommittee noted the following summary of previous consideration and recommendations regarding funding applications for CDK4/6 inhibitors for HR-positive, HER2-negative locally advanced breast cancer:

		CaTSoP	**PTAC**
Chemical			
Palbociclib	first-line	Medium (September 2018)	Low (May 2019)
	second-line	Medium (April 2019)	Medium (May 2019)
Ribociclib	first-line	Application not previously considered by CaTSoP	Low (May 2019)
	second-line	Application not previously considered by CaTSoP.	Application not previously considered by PTAC.
Class			
	first-line	High priority (April 2019)	

CDK4/6 inhibitors	second-line	High priority in patients with hormone-sensitive disease (April 2019)	Class effect associated with CDK4/6 inhibitors for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer subject to the criteria recommended by CaTSoP. No priority given. (May 2019).
		Medium priority for all second-line patients (April 2019)	

9.13. The Subcommittee noted that a fourth application, for ribociclib as a second-line treatment, had been received subsequent to PTAC's consideration of CDK4/6 inhibitors in May 2019 and that to date no funding application for abemaciclib had been received.

Ribociclib applications

9.14. The Subcommittee noted the primary evidence from ribociclib in the treatment of HR-positive HER2-negative locally advanced breast cancer comes from three studies – MONALEESA 2, MONALEESA 3 and MONALEESA 7.

9.15. The Subcommittee noted that MONALEESA-2 is a phase 3 randomized, double-blind, placebo-controlled trial of first-line ribociclib plus letrozole compared with placebo plus letrozole in 668 postmenopausal women with HR-positive, HER2-negative advanced breast cancer (Hortobagyi et al. Ann Oncol. 2018;29:1541-7).

9.16. The Subcommittee noted that patients received ribociclib in 28-day treatment cycles (600 mg/day; 3-weeks-on/1-week-off) until disease progression, unacceptable toxicity, death, or discontinuation for any other reason; and that treatment crossover was not permitted.

9.17. The primary end point was locally assessed PFS, per RECIST v1.1 and considered that as compared to centrally assessed endpoints, this could introduce inconsistency to the data. The Subcommittee noted that at a median follow-up of 26.4 months, the median PFS was 25.3 months in the palbociclib arm compared with 16.0 month in the placebo/letrozole arm (HR 0.568; 95% CI 0.457 to 0.704; log-rank P = 9.63 x 10-8).

9.18. The Subcommittee noted that the key secondary end point was OS however OS data remained immature, with 50 deaths in the ribociclib arm and 66 in the placebo arm (HR 0.746, 95% CI 0.517 – 1.078).

9.19. The Subcommittee noted that the most frequent all-cause grade 3/4 AEs (≥15% in either arm; ribociclib plus letrozole versus placebo plus letrozole) were neutropenia and leukopenia.

9.20. The Subcommittee noted that overall, 192 patients (57.5%) in the ribociclib plus letrozole arm had at least one ribociclib/placebo dose reduction versus 26 (7.9%) in the placebo plus letrozole arm; most patients required a single dose reduction [115 (34.4%) versus 20 (6.1%), respectively].

9.21. The Subcommittee considered that quality of life data from MONALEESA-2 indicated that this was not diluted with use of ribociclib over time and the lower pain scores with ribociclib would be clinically meaningful for patients.

9.22. The Subcommittee noted that MONALEESA-7 is a phase 3, randomised, double-blind, placebo-controlled trial of ribociclib plus endocrine therapy compared with placebo and endocrine therapy in 672 pre or perimenopausal women with HR-positive, HER2-negative advanced breast cancer who had not previously received a CDK4/6 inhibitor (Tripathy et al. Lancet Oncol. 2018;19:904-15).

9.23. The Subcommittee noted that eligibility criteria included locoregionally recurrent or metastatic disease not amenable to curative therapy (eg not candidates for curative surgery or radiotherapy), up to one previous line of chemotherapy for advanced disease, and no previous treatment with a CDK4/6 inhibitor.

9.24. The Subcommittee noted that that patients could receive either tamoxifen (36%) or a nonsteroidal aromatase inhibitor (64%) as endocrine therapy all with goserelin. The Subcommittee noted treatment crossover was not permitted and considered this was a similar study design to MONALEESA-2.

9.25. The Subcommittee noted that the primary endpoint was investigator-assessed progression-free survival and at a median follow-up of 19.2 months, that the median PFS was 23.8 months in the ribociclib arm compared with 13.0 months in the placebo/endocrine therapy arm (HR 0.55; 95% CI 0.44 to 0.69; P<0.0001).

9.26. The Subcommittee noted that median progression-free survival per the central assessment of the independent masked review cohort (n=267) was not reached (95% CI 19·9 months–not reached) among the 133 patients assessed in the ribociclib group and 11·1 months (7·4–16·9) in the 134 patients assessed in the placebo group (HR 0·43, 95% CI 0·29–0·63).

9.27. The Subcommittee noted that overall survival results were not mature at the time of this analysis, with 89 deaths recorded in total at data cut-off (43 [13%] in the ribociclib group and 46 [14%] in the placebo group); and that the study remains masked for further follow-up of overall survival.

9.28. The Subcommittee noted that MONALEESA-3 is a phase III, double-blind, placebo-controlled trial of ribociclib plus fulvestrant compared with placebo plus fulvestrant in 484 postmenopausal women with HR-positive, HER2-negative advanced (metastatic or locoregionally recurrent disease not amenable to curative treatment) breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy (Slamon et al. J Clin Oncol. 2018;36:2465-72). The Subcommittee considered this was a similar trial design to MONALEESA-2 and-7 except for the 2:1 randomisation.

9.29. The Subcommittee noted that exclusion criteria included prior treatment with chemotherapy for advanced disease, fulvestrant, or a CDK4/6 inhibitor.

9.30. The Subcommittee noted that at a median follow-up of 20.4 months, that the median PFS was 20.5 months in the ribociclib arm compared with 12.8 months in the placebo/fulvestrant arm (HR 0.593; 95% CI 0.480 to 0.732; P<0.001). The Subcommittee noted that the median PFS in patients who were treatment-naïve in this trial was not reached in the ribociclib arm compared with 18.3 months in the placebo/fulvestrant arm.

9.31. The Subcommittee noted that the OS data were reported as immature by Slamon et al 2018, with a total of 70 deaths (14.5%) were observed in the ribociclib arm versus 50 (20.7%) in the placebo arm.

9.32. The Subcommittee noted that Novartis had provided unpublished data from a second OS interim analysis at a median follow-up of 39.4 months, which includes 275 deaths (78% of the total 351 events). The Subcommittee noted that the estimated hazard ratio from this second OS interim analysis was 0.724 (95% CI: 0.568, 0.924; p-value 0.00455). The Subcommittee noted that the p-value threshold to claim significance = 0.01129 and therefore OS was considered to be statistically significant despite median OS having been not reached (NR) in the ribociclib arm and was 40.0 months (95% CI: 37.0, NE) in the placebo arm. The Subcommittee noted that median OS in the treatment-naïve (first-line) subgroup was NR vs 45.1 months (HR, 0.700 [95% CI, 0.479-1.021]) and in the second-line subgroup was 40.2 vs 32.5 months (HR, 0.730 [95% CI, 0.530-1.004]). The Subcommittee noted that this OS data was presented at ESMO 2019 and that as per protocol, these OS results will be considered final.

9.33. The Subcommittee considered that all three MONALEESA studies have shown an OS benefit from use of ribociclib for the treatment of HR-positive HER2-negative advanced breast cancer.

Advice requested by PTAC

9.34. The Subcommittee noted that in August 2019 PTAC had recognised that there were some differences in the records of PTAC and CaTSoP's consideration of the funding applications for these agents (likely based on the different but complementary expertise, experience, and perspectives each committee brought to its consideration under the Factors for Consideration). The Subcommittee noted that PTAC considered it would be useful that CaTSoP clarify its advice about CDK4/6 inhibitors so that PTAC could further consider its priorities and recommendations for this class of agents.

9.35. The Subcommittee noted that in particular PTAC asked if CaTSoP could provide a more detailed evidence review and discussion about:

- Why the health need of a second-line population was rated higher than the first-line setting, but that the recorded recommendation was that funding of CDK4/6 inhibitors as a class was a lower priority for use in second-line than in first-line.
- More details about CaTSoP's interpretation of the evidence for differences in outcomes such as for overall survival (OS), progression-free survival (PFS), and quality of life in both first- or second-line settings for late breast cancers.
- More details about CaTSoP's assessment the OS benefit, its magnitude, and precision, for the different treatment settings, and the evidence used for this advice.
- in the context of CDK4/6 inhibitors, advice on: the strength and quality of available evidence for the use of surrogate outcomes specifically for locally advanced or metastatic breast cancers, particularly those that are HR-positive and/or HER2-negative, and thus the applicability of such outcomes data in this setting.

9.36. The Subcommittee considered that previously treated (second-line) patients were considered to have a higher health need than those in the first-line population as they would be more symptomatic and have likely to exhaust their endocrine options more quickly. However, the Subcommittee considered that in April 2019 the relative funding priority for all second-line patients was considered to be slightly lower than that in the first-line setting due to the quality of evidence and likely higher absolute level of benefit in terms of PFS and OS in a first-line setting. Although, members noted that this does

not include those second-line patients with hormone sensitive disease where the data in this subgroup is considered to be stronger than in a general second-line population.

9.37. The Subcommittee considered that the updated survival data for ribociclib from MONALEESA-3 and MONALEESA-7 reinforced the signal of a class effect from use of CDK4/6 inhibitors in the treatment of HR-positive HER2-negative advanced breast cancer.

9.38. The Subcommittee considered that benefit from use of CDK4/6 inhibitor has been demonstrated across both first and second-line populations. The Subcommittee considered that the differences in trial results is likely to have been driven by heterogeneity of the trial populations, such as the number of patients with endocrine-sensitive disease or ESR-1 mutation rates, although this was based on expert opinion and not supported by any current data.

9.39. The Subcommittee considered that a benefit from CDK4/6 inhibitors is reported in both first-line post-menopausal patients and first-line pre-menopausal patients treated with ovarian suppression with the strength of evidence best for those who receive aromatase inhibitor and goserelin. The Subcommittee considered that patients with hormone-sensitive disease appear to get the most benefit from use of a CDK4/6 inhibitor in a second-line setting; and that the durability of response for the overall second-line population is likely to be slightly shorter than when used in a first-line HR-positive HER2-negative advanced breast cancer population.

9.40. The Subcommittee considered that of the various trials for use of the three CDK4/6 inhibitor agents with currently published evidence, the ribociclib trials were of highest quality due to their clinical trial design, which meant that OS could be demonstrated, whereas the survival data from the palbociclib and abemaciclib trials were compromised by the crossover design.

9.41. The Subcommittee considered that there is good quality evidence that CDK4/6 inhibitors provide a PFS of around 10 to 12 months and around a 30% improvement in OS (in a disease setting where it is difficult to demonstrate OS gain) both of which were clinically meaningful for patients with HR-positive HER2-negative advanced breast cancer.

9.42. The Subcommittee considered that while improving OS is considered the most important therapeutic goal in advanced breast cancer, it has been difficult to demonstrate an OS advantage in clinical trials in advanced breast cancer populations and particularly in a first-line setting. The Subcommittee considered this is both because powering studies to show OS requires very large patient numbers and also because heterogeneous populations with long post progression survival, crossover and heterogeneous post study therapy as well as the evolving treatment standards for these patients all impact on study outcomes.

9.43. The Subcommittee noted that it had considered some of the issues and challenges related to clinical trial design, surrogate outcomes and critical appraisal at its meeting in July 2019.

9.44. The Subcommittee considered that in advanced breast cancer there is evidence to support the use of surrogate measure, such as PFS, for OS including a number of systematic reviews across a variety of advanced breast cancer patient populations.

9.45. The Subcommittee acknowledged that the quality of these reviews was variable (the number of trials included in these reviews and the number of patients in the trials

included differed, some reviews use all lines of therapy whereas some restrict to first or second line) almost all of these reviews addressed the issue of PFS as a surrogate measure for OS in metastatic disease.

9.46. The Subcommittee noted that some reviews did not show any correlation between PFS and OS while other showed a modest correlation (square correlation statistic ranged from 0.1-0.57), however considered that the more tightly the population was defined the better the correlation became for example HR-positive, HER2-negative disease in premenopausal women.

9.47. The Subcommittee also noted a study of mBC patients and oncology care providers (nurses and oncologists) in the US aimed at evaluating by the value of OS, PFS, and other treatment attributes in treatment decision by surveys designed to assess preferences for OS/PFS and stable disease and the timing thereof, preferences for level of evidence and toxicity rates as well as willingness to pay for specific treatment attributes (MacEwan et al MDM Policy Pract. 2019; 4: 2381468319855386).

General comments

9.48. The Subcommittee noted that on 1 September 2019, PHARMAC issued a Request for Proposals for the supply of a CDK4/CDK6 inhibitor for the treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer; and that this process was seeking commercial bids from the suppliers of these medicines for use as both first and second-line treatment for patients who meet the Special Authority criteria detailed in the RFP document (as recommended by CaTSoP in April 2019). The Subcommittee considered it would be a preferred outcome for both first and second-line populations to be funded as a result of this competitive process.

10. Pembrolizumab for Hodgkin lymphoma

Application

10.1. The Subcommittee reviewed an application for pembrolizumab for the treatment of classical Hodgkin lymphoma (HL). The indication sought was in a narrower population than previously considered by PTAC and CaTSoP. Specifically, pembrolizumab was sought as a 'bridge to transplant' for the treatment for relapsed and refractory HL for individuals eligible for autologous or allogeneic stem cell transplantation, with 'refractory or relapsed' defined as:

- refractory to a second or subsequent line of chemotherapy; or
- relapsed after at least three lines of therapy.

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

Recommendation

10.3. The Subcommittee **recommended** that pembrolizumab be funded as a bridge to transplant for the treatment for relapsed and refractory HL in individuals eligible for autologous or allogeneic stem cell transplantation who are refractory to a second or subsequent line of chemotherapy or have relapsed after at least three lines of therapy, with a medium priority.

10.4. The Subcommittee recommended that pembrolizumab be funded in this setting based on the high health need in a small population, the limited treatment duration and the

evidence of high response rates with pembrolizumab regardless of line of therapy, which may assist in getting patients to potentially curative stem cell transplants.

10.5. The Subcommittee recommended the following new Special Authority criteria for the above recommended patient group:

Special Authority for Subsidy– PCT only – Specialist
Initial application (relapsed/refractory Hodgkin's lymphoma) - 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. Either:
   1.1. Patient has Hodgkin lymphoma refractory to a second or subsequent line of chemotherapy; or
   1.2. Patient has Hodgkin lymphoma that has relapsed following three prior lines of therapy; and
2. If a sufficient response is obtained, the patient would be otherwise eligible for a planned autologous or allogeneic stem cell transplantation; and
3. Response to pembrolizumab is to be reviewed after 12 weeks (3 doses).
4. Pembrolizumab to be administered at doses no greater than 200 mg once every 3 weeks up to maximum of 18 weeks (6 doses).

Discussion

10.6. The Subcommittee noted that in September 2018 it had considered an application for pembrolizumab for the treatment of refractory/relapsed HL after two or more lines of chemotherapy for patients who were either ineligible for, or had relapsed following, an autologous stem cell transplant. The Subcommittee recommended that the application be deferred until additional data were available.

10.7. The Subcommittee noted the current treatment paradigm for HL in New Zealand, where approximately 100 patients are diagnosed each year and approximately 80% are effectively cured with first line chemotherapy treatment.

10.8. The Subcommittee estimated that approximately 20 patients would relapse, and 16 of these would be fit enough for second-line treatment. Eight patients might be refractory to second-line therapy and would receive pembrolizumab, and eight might respond sufficiently to second-line therapy to proceed to autologous stem cell transplant. Half of those receiving pembrolizumab would respond and also get to autologous stem cell transplant. Of those 12 receiving an autologous stem cell transplant, 50% would expect to be cured but six might progress after autologous stem cell transplant and be considered for a third-line therapy.

10.9. Of the six patients receiving third-line chemotherapy, the Subcommittee estimated two to four patients may be treated with pembrolizumab, with a view to proceeding to allotransplant, with the remaining two responding to third-line chemotherapy and proceeding directly to allotransplant.

10.10. The Subcommittee noted that a maximum of 18 weeks or six doses was requested, which the Subcommittee considered appropriate.

10.11. The Subcommittee noted that the primary evidence for the use of pembrolizumab for the treatment of relapsed/refractory Hodgkin lymphoma comes from the previously considered single-arm, phase 2 Keynote-087 trial (Chen et al. J Clin Oncol. 2017;35:2125-32). The Subcommittee noted a high overall response rate of 57% in patients refractory to all previous lines of therapy, and 72% overall response (complete response rate 31%, partial response rate 41%) in those who hadn't received brentuximab vedotin. The Subcommittee noted this study population aligned with the New Zealand population and was less heavily treated than the majority of patients in Keynote 87 who had been treated with brentuximab vedotin. The Subcommittee noted

response rates did not vary according to the extent of previous therapy (<3 vs ≥ 3 lines of therapy).

10.12. The Subcommittee noted auto-SCT following a response to induction therapy is strongly associated with improved survival in HL (Moskowitz et al. Blood. 2012;119:1665-70) and is thus the standard of care in NZ and internationally.

10.13. The Subcommittee noted a potential historical comparator could be from the CALGB 59804 trial of salvage regimens in relapsed Hodgkin's lymphoma (Bartlett et al. Ann Oncol. 2007;18:1071-9).