Cancer Treatments Subcommittee of PTAC (CaTSoP) meeting held at PHARMAC on 21 September 2018 (minutes for web publishing)

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Note that this document is not necessarily a complete record of the Cancer Treatments Subcommittee meeting; only the relevant portions of the minutes 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.

These Subcommittee minutes will be reviewed by PTAC at its 21 & 22 February 2019 meeting.

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1. Correspondence and Matters Arising

Ibrutinib for previously untreated CLL

1.1. The Subcommittee noted that PHARMAC had received an abbreviated submission from Janssen for ibrutinib for previously untreated chronic lymphocytic leukaemia (CLL) population who cannot tolerate treatment with either FCR, BR or obinutuzumab, and previously untreated Waldenström's Macroglobulinaemia (WM).

1.2. The Subcommittee noted that PHARMAC had determined there was insufficient capacity on this Subcommittee agenda for discussion in full, and given ibrutinib was not yet funded for other CLL and WM populations with a likely higher health need, PHARMAC sought advice from Subcommittee on the clinical priority to bring this application to CaTSoP for consideration.

1.3. The Subcommittee noted that there was considerable interest amongst haematologists for access to ibrutinib and other currently unfunded agents in CLL, however the Subcommittee considered this application represented a very small number of patients and the currently unmet health need of other CLL populations, such as 17p del CLL and those who relapse within a short duration, is considerably higher.

1.4. The Subcommittee noted that patients with WM had other treatment options including rituximab monotherapy.

1.5. The Subcommittee considered that any Special Authority criteria around intolerance of other agents could present significant fiscal risk and would need to be very specific.

1.6. The Subcommittee considered this population represented a low priority for full evaluation and if would be preferable to consider as a possible widening of access should ibrutinib be funded for other populations.

Azacitidine

1.7. The Subcommittee noted PHARMAC had received expert advice under NPPA for azacitidine for the treatment of therapy related myelodysplastic syndrome / acute myeloid leukaemia which is excluded from the current Special Authority criteria ("The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases"). The Subcommittee noted this was the intent of the Special Authority criteria primarily based on the evidence presented in the AZA-001 study (Fenaux et al. Lancet Oncol. 2009;3:223-32) which excluded these patients.

1.8. The Subcommittee noted that the many of these patients with therapy related disease may be receiving funded treatment under the current restrictions if the primary malignancy was in the patient's distant history. The Subcommittee noted that the specific exclusion in the Special Authority criteria for therapy related MDS would mean most clinicians would not spend time attempting a NPPA application if the chemical injury or prior treatment with chemotherapy and/or radiation for other diseases was more recent, which could lead to some equity concerns if NPPAs were approved.

1.9. The Subcommittee noted that patients with therapy-related MDS/AML may have a worse prognosis than denovo disease as a result of higher prevalence of unfavourable chromosomal changes with higher resistance to standard induction chemotherapy and therefore have very limited treatment options.

1.10. The Subcommittee considered the current expert opinion, based primarily on low quality evidence from multicentre case series, is that there is no reason why patients with therapy-related MDS/AML (blasts <30%) would not benefit to the same extent as those with non-

therapy-related disease. The Subcommittee considered this evidence sufficient considering the rarity of the condition.

1.11. The Subcommittee noted that patient numbers were somewhat uncertain given the secondary nature of the diagnosis is unlikely to be reported in registry figures, although the Subcommittee considered it would likely be less than 10 patients per annum, although that may increase over time with the successful treatment of patients with cancer.

1.12. The Subcommittee considered a reduction in transfusion frequency would be an appropriate measure of benefit. The Subcommittee also considered that repeat bone marrows should not be required for renewal.

1.13. The Subcommittee **recommended** the Special Authority criterion for azacitidine "The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases" be removed, and that the Revised International Prognostic Scoring System (IPSS-R) be included in the initial criteria as an alternative to IPSS.

Osimertinib correspondence

1.14. The Subcommittee noted correspondence from the supplier of osimertinib in response to CaTSoP's April 2018 minute related to this product and additional evidence to support its funding application for osimertinib.

1.15. The Subcommittee noted that at its meeting in April 2018, CaTSoP deferred making a recommendation regarding the funding for osimertinib for locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer second-line after prior EGFR TKI therapy pending publication of longer follow-up including mature survival data from the AURA3 trial.

1.16. The Subcommittee also noted a letter from the Auckland Lung Medical Oncology Team in support of the funding application for osimertinib including details of current management of lung cancer patients in Auckland.

1.17. The Subcommittee considered that the additional evidence provided by the supplier to be of poor quality and insufficient to amend its previous recommendation.

1.18. The Subcommittee reiterated that publication of longer follow-up including mature survival data from the AURA3 trial was awaited.

Caphasol correspondence

1.19. The Subcommittee noted correspondence from the supplier of Caphasol in response to the April 2018 CaTSoP minute regarding consideration of its funding application for calcium phosphate mouthwash (Caphasol Dispersible) for oral mucositis; which it had recommended be declined primarily based on poor quality evidence.

1.20. The Subcommittee considered that the supplier's application appeared to claim that calcium phosphate mouthwash should be used both as prophylaxis and treatment of oral mucositis. However, CaTSoP did not consider prophylaxis necessary and benzydamine solution was currently funded and used as a treatment for oral mucositis.

1.21. The Subcommittee noted that the supplier had referenced supplementary studies to support its application but considered that these were also of poor quality and did not add significantly to the overall poor evidence base for use of calcium phosphate mouthwash for oral mucositis.

2. Lanreotide acetate for gastroenteropancreatic neuroendocrine tumours

Application

2.1. The Subcommittee reviewed a funding application from Ipsen Pty Ltd for lanreotide acetate for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional gastroenteropancreatic neuroendocrine tumours

Recommendation

2.2. The Subcommittee **recommended** that lanreotide acetate for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional gastroenteropancreatic neuroendocrine tumours be funded with a **low** priority, subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with unresectable locally advanced or metastatic non-functional gastroenteropancreatic neuroendocrine tumour; and
> 2. Patient has a World Health Organisation Grade 1 or 2 tumour; and
> 3. Patient has a Ki-67 index of less than 10%; and
> 4. Patient has a WHO performance status of 0-2; and
> 5. Patient has radiologically confirmed disease progression; and
> 6. Treatment is to be administered in 28 day treatment cycles at a maximum of 120 mg per cycle.
> 7. Lanreotide acetate to be discontinued at disease progression.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and the patient is benefiting from treatment.

2.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework

Discussion

2.4. The Subcommittee noted that the incidence of neuroendocrine tumours (NETs) in New Zealand in 2012 was 8.6 per 100,000 population, and that the rate is increasing over time. The Subcommittee noted that 49% of NETs are gastroenteropancreatic in origin.

2.5. The Subcommittee noted that the median age of diagnosis for NETs in New Zealand is 65 years; and that the incidence of NETs is lower in Asian people, and similar in other populations including Māori.

2.6. The Subcommittee noted that the 5-year overall survival (OS) for patients with NETs is 60%, but that survival varies depending on the primary site and grade of the tumour. The Subcommittee noted that the average survival for patients with gastroenteropancreatic NETs (GEP-NETs) is between 9 and 12 years.

2.7. The Subcommittee noted that NETs are classified as functional or non-functional based on the presence or absence of symptoms attributable to hormone hypersecretion and can be further classified based on the degree of cell proliferation and differentiation (Grade 1: well differentiated, Ki67 ≤2%; Grade 2: moderately differentiated, Ki67 3-20%; Grade 3: poorly differentiated, Ki67 >20%).

2.8. The Subcommittee noted that there is often a significant delay in diagnosis for patients with NETs, and consequently 47% of patients have locally advanced or metastatic disease at diagnosis.

2.9. The Subcommittee noted that the applicant had estimated that approximately 50 patients per year would be eligible for treatment for unresectable locally advanced or metastatic, WHO grade 1 or 2, non-functional GEP-NETs. The Subcommittee considered that this was an underestimation, and that approximately 200 patients per year would be eligible for treatment if lanreotide acetate were funded.

2.10. The Subcommittee noted that the initial management approach for patients diagnosed with unresectable locally advanced or metastatic non-functional NETs is watchful waiting. The Subcommittee noted that further treatment is warranted once disease progression occurs.

2.11. The Subcommittee noted that the current funded treatment options available for patients with locally advanced or metastatic NETs in New Zealand include surgery and ablation for debulking, and chemotherapy (e.g. temozolomide, capecitabine). Currently, endocrine therapy with octreotide long-acting release (octreotide LAR) is funded for the control of symptoms of functional-NETs only. The Subcommittee noted that other NET treatment options that are currently unfunded in New Zealand include peptide receptor radionuclide therapy (PRRT) and targeted agents such as sunitinib and everolimus.

2.12. The Subcommittee noted that funding applications have previously been considered for lanreotide acetate, octreotide LAR, sunitinib, temozolomide and PRRT for the treatment of NETs.

2.13. The Subcommittee noted that PTAC had considered a funding application for lanreotide acetate at its meeting in November 2004; and that PTAC recommended funding only if cost-neutral or saving to octreotide LAR for the treatment of acromegaly and functional pancreatic NETs, as these agents were considered to have the same or similar therapeutic effect.

2.14. The Subcommittee noted that the current application requested consideration of lanreotide acetate for the treatment of unresectable locally advanced or metastatic, WHO Grade 1 or 2, non-functional GEP-NETs in patients for whom treatment is warranted, as indicated by radiologically confirmed disease progression, documented clinical progression, or the onset of symptoms associated with the presence of the tumour or tumours (not associated with Carcinoid syndrome).

2.15. The Subcommittee noted that lanreotide acetate is an analogue of somatostatin that acts as a peptide inhibitor of endocrine, neuroendocrine, exocrine, and paracrine functions and has antiproliferative effects.

2.16. The Subcommittee noted that the Medsafe-registered indication relevant to the application for lanreotide acetate is for the treatment of well or moderately differentiated GEP-NETs in adult patients with unresectable locally advanced or metastatic disease. The Subcommittee noted that the recommended dosage for patients with GEP-NETs is 120 mg administered every 28 days for as long as needed for tumour control.

2.17. The Subcommittee noted that the key clinical evidence for the use of lanreotide acetate for the treatment of advanced non-functional GEP-NETs comes from the CLARINET study (Caplin et al. N Engl J Med. 2014;371:224-33) and the CLARINET open-label extension (OLE) study (Caplin et al. Endocr Relat Cancer. 2016;23:191-9).

2.18. The Subcommittee noted that CLARINET was a 96-week, randomized, double-blind, placebo-controlled, phase 3 trial in which 204 patients with advanced, well- or moderately-differentiated, non-functioning, somatostatin receptor-positive, grade 1 or 2 NETs were randomly assigned 1:1 to receive lanreotide 120 mg or placebo by deep subcutaneous injection once every 28 days for a maximum of 24 injections.

2.19. The Subcommittee noted that the median progression-free survival (PFS), the primary endpoint, in the CLARINET trial was not reached in the lanreotide group and was 18.0

months in the placebo group (HR 0.470; 95% CI 0.30, 0.73; *P*<0.001). The Subcommittee noted that the PFS in predefined subgroups generally favoured lanreotide over placebo. The Subcommittee noted that there were no significant between group differences in overall survival or quality of life. The Subcommittee noted Caplin et al (2014) commented that analysis of survival was complicated by crossover and uncertainty over treatments after progression.

2.20. The Subcommittee noted that lanreotide was well tolerated in the CLARINET trial; drug-related adverse events included hyperglycaemia (5% lanreotide group compared with 0% placebo group) and cholelithiasis (10% lanreotide group compared with 3% placebo group).

2.21. The Subcommittee noted that patients in the CLARINET trial who had disease progression while receiving placebo or who had received study drug for 96 weeks and had stable disease were eligible for the single-arm, non-randomised CLARINET OLE study.

2.22. The Subcommittee noted that 88 patients were enrolled in the CLARINET OLE trial: 41 continued on lanreotide (40 stable disease; 1 progressive disease) and 47 patients crossed-over from the placebo arm of CLARINET to receive lanreotide in CLARINET OLE (15 stable disease; 32 progressive disease).

2.23. The Subcommittee noted that the median PFS, the primary endpoint, in CLARINET OLE for all patients was 32.8 months (95% CI 30.9, 68.0) and the median PFS for patients who had progressed on placebo during the CLARINET trial was 14.0 months (95% CI 10.1, not reached).

2.24. The Subcommittee considered that 96% of patients enrolled in the CLARINET trial did not have disease progression at baseline, and that these participants represented a more indolent disease group than patients with progressive disease (the requested population). The Subcommittee considered that this meant that the PFS benefit observed with lanreotide treatment in CLARINET and the total CLARINET OLE population likely overestimates the magnitude of benefit that would be expected for patients with progressive disease.

2.25. The Subcommittee considered that the 32 patients in CLARINET OLE who had progressed on placebo during the CLARINET trial more accurately reflects the patient group requested: patients with radiologically confirmed disease progression and patients with documented clinical progress. The Subcommittee noted that the applicant also requested funding for a symptomatic population but considered that efficacy in this patient group was not supported by the trial evidence.

2.26. The Subcommittee considered that while the majority of the evidence for the efficacy of lanreotide acetate is in patients who do not have progressive disease, it is patients with progressive disease who have a higher health need and are more likely to benefit from the antiproliferative effect of lanreotide acetate than patients who do not have progressive disease.

2.27. The Subcommittee considered that there is an unmet need for funded treatment options for patients with unresectable locally advanced or metastatic, WHO grade 1-2, non-functional GEP-NETs, and that while overall the evidence is relatively poor, the results of the CLARINET OLE trial indicate that lanreotide acetate does provide a health benefit in these patients. The Subcommittee considered that this benefit is likely due to disease stabilisation, as lanreotide acetate is unlikely to cause significant disease regression, as can occur with chemotherapy agents.

2.28. The Subcommittee noted that PTAC and CaTSoP had previously reviewed an application for octreotide LAR for the treatment of non-functional small intestinal NETs and CaTSoP had declined the application based on the low-to-moderate level of evidence which did

not indicate an overall survival gain or quality of life improvement (PTAC minutes – Feb 2013; CaTSoP minutes – Mar 2013); however, the Subcommittee considered that octreotide LAR and lanreotide acetate have similar mechanisms of action, and that while the trial data for both octreotide LAR and lanreotide had quality issues, there was likely a similar level of benefit from these agents. The Subcommittee therefore considered that the sum of the evidence for octreotide LAR and lanreotide acetate support the use of somatostatin analogues for the treatment of non-functional NETs, and that the Subcommittee would therefore be supportive of widening access to octreotide LAR if cost-effectiveness analysis favoured this agent over lanreotide acetate.

2.29. The Subcommittee considered that PHARMAC should undertake economic assessment of both octreotide LAR and lanreotide acetate for patients with non-functional NETs, ensuring that the impact these treatments would have on the sector due to the different routes of administration is considered (octreotide LAR is administered by intramuscular injection by a health care professional; lanreotide acetate is administered subcutaneously and so could be self-administered by patients).

2.30. The Subcommittee noted that, if lanreotide acetate and PRRT were funded, the appropriate treatment paradigm would likely be for lanreotide acetate to be used as first-line treatment and PRRT as second-line treatment for unresectable locally advanced or metastatic non-functional GEP-NETs, unless there was a particularly heavy burden of disease.

3. Venetoclax for Chronic Lymphocytic Leukaemia

Application

3.1. The Subcommittee reviewed two supplier applications for venetoclax for the treatment chronic lymphocytic leukaemia (CLL). These applications were for the indications of relapsed or refractory CLL with 17p deletion and relapsed or refractory CLL with no other suitable treatment options.

3.2. The Subcommittee reviewed additional data provided by the supplier in May 2018 that included longer follow-up data from the clinical trials considered by PTAC at its February 2018 meeting.

3.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework

Recommendation

3.4. The Subcommittee **recommended** that venetoclax for the treatment of patients with chronic lymphocytic leukaemia and 17p deletion or TP53 mutations be funded with a high priority subject to the following Special Authority criteria:

> Venetoclax – Retail Pharmacy - Specialist
>
> Special Authority for Subsidy
> Initial application (17p deletion or TP53 mutation CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Either:
> 1.1. Patient has treatment naïve CLL; or
> 1.2. Patient has previously treated CLL with relapsed disease; and
> 2. There is documentation confirming that patient has 17p deletion by FISH testing or TP53 mutation by sequencing; and
> 3. Patient has an ECOG performance status of 0-2.
>
> Renewal application (17p deletion or TP53 mutation CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL).

3.5. The Subcommittee **recommended** that venetoclax for the treatment of relapsed chronic lymphocytic leukaemia (within 12 months of prior therapy) be funded with a high priority subject to the following Special Authority criteria:

Venetoclax – Retail Pharmacy – Specialist

Initial application (relapsed CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has CLL that has been previously treated with at least two cycles of an anti-CD20 treatment; and
2. Patient disease has relapsed within 12 months of previous treatment; and
3. Patient has an ECOG performance status of 0-2.

Renewal application (relapsed CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL).

3.6. The Subcommittee **recommended** that venetoclax for the treatment of relapsed chronic lymphocytic leukaemia (12-36 months of prior therapy) be funded with a medium priority subject to the following Special Authority criteria:

Venetoclax – Retail Pharmacy – Specialist

Initial application (relapsed CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has CLL that has been previously treated with at least two cycles of an anti-CD20 treatment; and
2. Patient disease has relapsed between 12 and 36 months of previous treatment; and
3. Patient has an ECOG performance status of 0-2.

Renewal application (relapsed CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL).

Discussion

3.7. The Subcommittee noted that the currently funded treatment options for CLL in New Zealand are more limited than those available internationally (Hallek. Am J Hematol. 2017;92:946-965; Eichhorst et al. Ann Oncol. 2015;26:v78-84; Wierda et al. J Natl Compr Canc Netw. 2017;15:293-311).

3.8. The Subcommittee noted the suitability of venetoclax given oral once-daily dosing.

3.9. The Subcommittee noted that in patients with a high tumour burden (likely to be in the vicinity of 10-20% of patients with CLL) the first two doses of venetoclax should be administered as a hospital inpatient due to the risk of tumour lysis syndrome seen in early clinical trials. The Subcommittee noted that venetoclax toxicity was predominantly haematological, and considered it generally manageable.

3.10. The Subcommittee noted international registry data suggesting a recent considerable drop in the rates of allogenic stem cell transplant for CLL, possibly due in part to the

introduction of newer targeted agents for the treatment of CLL. The Subcommittee noted allogenic transplant for CLL is rare in New Zealand (less than 10 per annum), but it is possible that newer agents may delay or replace the need some allogenic transplants in eligible patients. The Subcommittee noted that Māori may be less likely to have an available allogenic donor.

17p del CLL

3.11. The Subcommittee noted that patients with CLL and a 17p deletion or TP53 mutations have fewer currently funded treatment options and have a worse prognosis and poorer response to chemoimmunotherapy compared to CLL patients without these genetic mutations. The Subcommittee noted these mutations are present in 3-8% of patients with CLL at diagnosis and up to 30% in patients with relapsed/refractory disease.

3.12. The Subcommittee noted that testing for 17p deletion or TP53 mutations is routinely performed at diagnosis but may not routinely be repeated at relapse in all centres, especially as a positive result may limit treatment options. The Subcommittee considered that testing at relapse would become routine (possibly on multiple occasions) if a targeted treatment were available for this population.

3.13. The Subcommittee noted the single-arm Phase II M13-982 trial of venetoclax in patients with relapsed or refractory chronic lymphocytic leukaemia with 17p deletion, including a recent update published since the PTAC consideration (Stilgenbauer et al. Lancet Oncol. 2016;17:768-78; Stilgenbauer et al. J Clin Oncol. 2018;36:1973-1980). The Subcommittee noted the treatment was venetoclax monotherapy (after dose ramp up phase and protocol for tumor lysis syndrome management) until disease progression. The Subcommittee noted median follow-up of 26.6 months, with an estimated 24-month PFS of 54% (95% CI, 45% to 62%) and OS of 73% (95% CI, 65% to 79%).

3.14. The Subcommittee noted no trials are planned for venetoclax monotherapy in newly diagnosed patients with TP53 mutations or 17p deletion. The Subcommittee noted the CLL14 Phase III trial assessing the use of venetoclax in combination with obinutuzumab in front-line CLL for a fixed treatment duration of 12 months, which will include some patients with TP53 mutations and 17p deletions, is due for completion in 2019.

3.15. The Subcommittee considered the M13-982 trial population was similar in terms of their baseline characteristics to the RESONATE-17 trial for ibrutinib in the 17p deletion population, including age and the median number of prior lines of treatment (two) in those with relapsed/refractory disease (O'Brien et al. Lancet Oncol 2016;17:1409-18). The Subcommittee noted a recent publication combining the results from three ibrutinib trials in the 17p deletion population (Jones et al. Br J Haematol. 2018;182:504-512). The Subcommittee noted median follow-up of 28 months, with an estimated 24-month PFS of 65% (95% CI, 58% to 71%) and OS of 77% (95% CI, 71% to 82%).

3.16. The Subcommittee noted that main international comparator for the use of venetoclax in R/R 17p CLL patients is ibrutinib. As ibrutinib is not currently funded in New Zealand, the appropriate comparator would likely be an allogenic transplant for eligible patients, chemotherapy (FC or CHOP) in fit patients and best supportive care or chlorambucil for patients considered to be unfit. The Subcommittee noted that only a minority of patients in this group would be fit enough to receive an allogenic transplant.

3.17. The Subcommittee noted correspondence from haematologists who suggested that it would be reasonable to use venetoclax monotherapy in newly diagnosed patients with TP53 mutations or 17p deletion, given the few effective funded treatment options at present. The Subcommittee considered this to a be a reasonable approach given the small number of patients included in the venetoclax and ibrutinib trials appeared to gain a similar response from targeted treatment upon diagnosis compared with those receiving the agents at relapse.

3.18. The Subcommittee considered the latest publication (Stilgenbauer et al. 2018) addressed PTACs concern about data maturity for venetoclax compared to ibrutinib in the 17p deletion population. The Subcommittee considered there was sufficient evidence to consider them to have the same or similar evidence of heath benefit in this high health need setting.

Refractory/Relapsed (R/R) CLL

3.19. The Subcommittee noted that patients with refractory CLL or an early relapse after frontline chemoimmunotherapy have a worse prognosis compared to those with a longer duration of disease remission. This was particularly so in those who relapse within 12 months as their expected survval is very short, but also applied to those who relapsed within 36 months (Tam et al. Blood. 2014;124:3059-64). The Subcommittee also considered that patients who do not have 17p deletion or TP53 mutations, but who have a relapse within 24-36 months have an unmet health need similar to that of those patients who do have these mutations. The Subcommittee noted PTAC's previous recommendation for the 17p deletion or TP53 mutation doesn't currently apply to this group with early relapse.

3.20. The Subcommittee noted the applicants suggested group for relapsed or refractory CLL "with no other suitable treatment options" would likely represent the vast majority of patients who had an early relapse given the treatments currently funded for this group.

3.21. The Subcommittee noted the Phase II M14-032 trial of venetoclax in heavily pre-treated patients with relapsed/refractory CLL after ibrutinib (Jones et al. Lancet Oncol. 2018;19:65-75) or idelalisib (Coutre et al. Blood. 2018;131:1704-1711) have both been published since the PTAC consideration. The Subcommittee noted the idelalisib cohort added 36 additional patients to the ibrutinib cohort of 91.

3.22. The Subcommittee considered the response rates in these trials (ORR, 65%-67%) appeared high given pre-treatment with novel agents, a median of five prior lines of therapy (range 1-15) in the ibrutinib cohort and three prior lines of therapy (range 1-11) in the idelalisib cohort, and high rates of 17p deletion (47% and 22% in the ibrutinib and idelalisib cohorts respectively). The Subcommittee noted median PFS was not yet reached after 14 months, but the Kaplan-Meier estimates indicated a median time to progression of 24.7 months. The Subcommittee noted a poster update from ASCO June 2018, which included a small amount of additional follow-up (17.3 months vs 14 months in Jones et al. 2018), and supported the estimated median time to progression of 24.7 months.

3.23. The Subcommittee noted that there is some evidence that venetoclax can provide deep responses, including Minimal Residual Disease (MRD) negativity, possibly at higher rates than ibrutinib. The Subcommittee noted that although MRD has been linked to progression-free survival, it currently remains unclear whether higher rates of MRD-negativity results in an improvement in overall survival in CLL.

3.24. The Subcommittee noted that two years fixed duration therapy may be a possibility and that the recently published Murano study (Seymour et al. N Engl J Med. 2018;378:1107-1120) of 389 patients was useful in demonstrating the efficacy of venetoclax in those with relapsed or refractory CLL. The Subcommittee noted this randomised, open-label phase III study compared two years of venetoclax plus six months of rituximab versus bendamustine plus rituximab for 6 months (bendamustine-rituximab group). The Subcommittee noted the promising PFS data in the venetoclax-rituximab group (median not reached) compared to the median time to progression of 17 months in the bendamustine-rituximab group. The Subcommittee noted 24-month rates of PFS were 84.9% and 36.3%, respectively. The Subcommittee noted the benefit of venetoclax across all subgroups, including those with 17p deletion.

3.25. The Subcommittee noted another publication for ibrutinib in this population has been published since last consideration (Brown et al. Leukemia. 2018;32:83-91) which has a median follow up of 19 months (14 months in prior publication). The Subcommittee noted the median PFS was not reached in the ibrutinib arm with 74% of those randomized to ibrutinib remaining progression free at 24 months.

3.26. The Subcommittee noted that internationally venetoclax is most commonly used as a salvage treatment following ibrutinib (consistent with the Jones et al. 2018 publication) given the later development; however, if venetoclax is funded prior to ibrutinib, the majority of the New Zealand population will be ibrutinib-naïve. The Subcommittee considered in this scenario there is a possibility of improved outcomes compared to the published trial evidence as New Zealand patients would have received fewer lines of pre-treatment and patients may receive treatment earlier, so they may be fitter and have less advanced disease than those treated in the trials.

3.27. The Subcommittee noted its recommendations for venetoclax were made in the absence of ibrutinib funding, and as such the very early relapse group (within 12 months of prior treatment) was given a higher priority based primarily on the high unmet health need in that population.

3.28. The Subcommittee considered that, if venetoclax were funded, the Special Authority criteria for venetoclax would need to require at least 2 cycles of prior anti-CD20 containing chemotherapy to ensure it is targeted to a truly relapsed/refractory population.

4. Brentuximab vedotin and pembrolizumab for the treatment of Hodgkin's lymphoma

Application

4.1. The Subcommittee, at the request of PTAC, reviewed the evidence for the use of brentuximab vedotin for the treatment of Hodgkin's lymphoma.

4.2. The Subcommittee also reviewed an application from Merck Sharp and Dohme to fund pembrolizumab for the treatment of relapsed/refractory Hodgkin's lymphoma after two or more lines of chemotherapy for patients who are either ineligible for, or relapsed following, an autologous stem cell transplant.

4.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework

Recommendation

4.4. The Subcommittee **recommended** that brentuximab vedotin for the treatment CD30-positive Hodgkin's lymphoma which has relapsed after two or more lines of chemotherapy for patients who are ineligible for autologous stem cell transplant, and for the treatment of relapsed/refractory CD30-positive Hodgkin's lymphoma for patients who have already had an autologous stem cell transplant, be funded with a high priority subject to the following Special Authority criteria:

> BRENTUXIMAB VEDOTIN – PCT only – Specialist
> **Special Authority for Subsidy**
> **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:
> 4. Either:
> 4.1. Both:
> 4.1.1. Patient has relapsed/refractory CD30-positive Hodgkin's lymphoma after two or more lines of chemotherapy; and
> 4.1.2. Patient is ineligible for autologous stem cell transplant; or
> 4.2. Both:
> 4.2.1. Patient has relapsed/refractory CD30-positive Hodgkin's lymphoma; and
> 4.2.2. Patient has previously undergone autologous stem cell transplant; and

5. Patient has not previously received funded brentuximab vedotin; and
6. Response to brentuximab vedotin treatment is to be reviewed after a maximum of 6 treatment cycles.
7. Brentuximab vedotin to be administered at doses no greater than 1.8 mg/kg every 3 weeks.

Renewal application (relapsed/refractory Hodgkin's lymphoma) - 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:

2. Patient has achieved a partial or complete response to brentuximab vedotin after 6 treatment cycles; and
3. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment; and
4. Patient is to receive a maximum of 16 total cycles of brentuximab vedotin treatment.

4.5. The Subcommittee **recommended** that brentuximab vedotin for the second line treatment of CD30-positive systemic anaplastic large-cell lymphoma be funded with a medium priority subject to the following Special Authority criteria:

BRENTUXIMAB VEDOTIN – PCT only – Specialist
Special Authority for Subsidy
Initial application (anaplastic large cell 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:

1. Patient has relapsed/refractory CD30-positive systemic anaplastic large cell lymphoma; and
2. Patient has an ECOG performance status of 0-1; and
3. Patient has not previously received brentuximab vedotin; and
4. Response to brentuximab vedotin treatment is to be reviewed after a maximum of 6 treatment cycles.
5. Brentuximab vedotin to be administered at doses no greater than 1.8 mg/kg every 3 weeks.

Renewal application (anaplastic large cell lymphoma) - 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:

1. Patient has achieved a partial or complete response to brentuximab vedotin after 6 treatment cycles; and
2. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment; and
3. Patient is to receive a maximum of 16 total cycles of brentuximab vedotin treatment.

4.6. The Subcommittee **recommended** that the application for pembrolizumab for the treatment of relapsed/refractory Hodgkin's lymphoma after two or more lines of chemotherapy for patients who are either ineligible for, or relapsed following, an autologous stem cell transplant, be deferred until additional data are available.

Discussion

4.7. In May 2018, the Pharmaceutical and Therapeutics Advisory Committee (PTAC) reviewed an application from Merck Sharp and Dohme for the use of pembrolizumab for the treatment of patients with Hodgkin's lymphoma who have relapsed after two lines of chemotherapy and were either ineligible for, or relapsed following, an autologous stem cell transplant (auto-SCT). As part of the discussion regarding this application, the PTAC noted that the standard of care internationally is brentuximab vedotin, which was previously considered by the PTAC in August 2016. The PTAC also noted that there is evidence suggesting nivolumab may be effective for the treatment of relapsed/refractory classical Hodgkin's lymphoma. The PTAC therefore requested that the application for pembrolizumab for the treatment of Hodgkin's lymphoma be reviewed by CaTSoP in conjunction with a review of the updated evidence for brentuximab vedotin and the evidence for the use of nivolumab for the treatment of Hodgkin's lymphoma.

4.8. The Subcommittee noted that approximately 100 patients are diagnosed with Hodgkin's lymphoma each year in New Zealand, and that there is a bimodal incidence with a peak at young adulthood and a peak in older patients. The Subcommittee noted that the incidence of Hodgkin's lymphoma is similar in Māori and non-Māori.

4.9. The Subcommittee considered that approximately 80% of patients with Hodgkin's lymphoma are cured with first-line therapy, which consists of multiagent conventional chemotherapy, radiotherapy, or both. The Subcommittee considered that second-line therapy consists of salvage-chemotherapy and, if eligible, subsequent auto-SCT, which is curative in half of all relapsed patients.

4.10. The Subcommittee considered that approximately 10 patients with Hodgkin's lymphoma would relapse after auto-SCT per year in New Zealand. Some of these individuals may be eligible for allogenic stem cell transplant, which is curative in approximately 50% of patients; however, half of these patients treated with allogeneic stem cell transplant will have ongoing complications, 25% are likely to experience an inadequate response, and there is 25% transplant-related mortality.

4.11. Patients who are ineligible for auto-SCT, and those who progress after auto-SCT and are ineligible for allogenic stem cell transplant, would be considered incurable within the current New Zealand treatment paradigm.

Brentuximab vedotin - background

4.12. The Subcommittee noted that brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to the microtubule disrupting agent monomethyl auristatin E. The Subcommittee noted that CD30 is expressed by malignant cells of Hodgkin's lymphoma and some T cell lymphomas.

4.13. The Subcommittee noted that brentuximab vedotin is administered as an intravenous infusion once every three weeks. The Subcommittee considered that brentuximab vedotin would be administered in the day ward, and patients would receive up to 16 infusions.

4.14. The Subcommittee noted that the most common treatment-related adverse events occurring with brentuximab vedotin are peripheral sensory neuropathy, nausea, fatigue, neutropenia, and diarrhoea; but that the agent is generally associated with a low incidence of Grade 3-4 AEs.

4.15. The Subcommittee noted that brentuximab vedotin is not currently registered for use in New Zealand.

Brentuximab vedotin – relapsed/refractory Hodgkin's lymphoma after auto-SCT

4.16. The Subcommittee noted that the key evidence for the use of brentuximab vedotin as a single agent for patients with Hodgkin's lymphoma who have relapsed following auto-SCT comes from an open-label phase 2 trial in which 102 patients received 1.8 mg/kg brentuximab vedotin once every 3 weeks for up to 16 cycles (Chen et al. Blood. 2016;128:1562-6). The Subcommittee noted that the 5-year follow-up results identified a median overall survival (OS) of 41 months and a median progression-free survival (PFS) of 9.3 months. The Subcommittee noted that 33% of patients achieved a complete response (CR), and that the 5-year PFS rate in this group was 52%. The Subcommittee noted that, of the 13 patients who had achieved a CR and remained in follow-up, 9 had received no further cancer treatment and may be cured.

4.17. The Subcommittee noted that there is no clinical trial data available comparing brentuximab vedotin to an alternative active treatment that is available to patients in New Zealand with Hodgkin's lymphoma who have relapsed following auto-SCT.

4.18. The Subcommittee noted the results of a retrospective real-world analysis of 87 patients with Hodgkin's lymphoma who had relapsed following auto-SCT (Bair et al. Am J Hematol. 2017;92:879-884). The Subcommittee noted that the median OS was not reached for patients who received brentuximab vedotin compared with 19.0 months for patients who did not receive brentuximab vedotin (median follow-up 71.9 months).

4.19. The Subcommittee considered that if brentuximab vedotin were funded for the treatment of relapsed/refractory Hodgkin's lymphoma, a larger number of patients may be fit enough to undergo allo-SCT, and that this has the potential to be a significant cost to the health sector.

Brentuximab vedotin – relapsed/refractory Hodgkin's lymphoma ineligible for auto-SCT

4.20. The Subcommittee noted that treatment for patients with relapsed/refractory Hodgkin's lymphoma who are ineligible for auto-SCT is considered palliative. The Subcommittee noted that the currently available treatment options include radiotherapy, gemcitabine, and other conventional chemotherapies. The Subcommittee noted that the most commonly used chemotherapy combination is ICE (ifosfamide, carboplatin, etoposide), which provides a complete response rate of approximately 20%.

4.21. The Subcommittee noted that there are no randomised controlled trials comparing the use of brentuximab vedotin with currently available regimens for patients with relapsed/refractory Hodgkin's lymphoma who are ineligible for auto-SCT, but that brentuximab vedotin is registered internationally for this indication on the basis of efficacy in multiply relapsed patients.

4.22. The Subcommittee noted the results of a retrospective, real-world, chart-review study that included 136 patients with relapsed/refractory Hodgkin's lymphoma who were ineligible for auto-SCT and received brentuximab vedotin for progressive disease (Bröckelmann et al. Eur J Haematol. 2017;99:553-558). The Subcommittee noted that, in this study, single-agent brentuximab vedotin yielded an overall response rate of 74%, a PFS of 15.1 months, and an OS of 17.8 months. The Subcommittee noted that the responses were not significantly different to the duration of previous responses, and peripheral neuropathy was seen in 9.6% of patients.

4.23. The Subcommittee noted the results of a phase 1/2, single-arm, open-label clinical trial that evaluated the combination of brentuximab vedotin and bendamustine as a first salvage regimen in 31 patients with relapsed/refractory Hodgkin's lymphoma (LaCasce et al. Blood. 2018;132:40-48). The Subcommittee noted that the complete response rate was 73.6% after a median of 2 cycles with manageable toxicity. The Subcommittee also noted that the estimated 2-year PFS rate in patients who received subsequent auto-SCT or continued brentuximab vedotin monotherapy was similar (69.8% compared with 62.6%). The Subcommittee considered that the evidence provided by this study was not adequate to consider widening the current Special Authority criteria for bendamustine to include Hodgkin's lymphoma.

Brentuximab vedotin – relapsed/refractory Hodgkin's lymphoma after allo-SCT

4.24. The Subcommittee noted that the prognosis for patients who have relapsed/refractory Hodgkin's lymphoma who have subsequently relapsed following allogeneic stem cell transplant (allo-SCT) is poor. The Subcommittee noted that there are no randomised clinical trials investigating the use of brentuximab vedotin in this indication.

4.25. The Subcommittee noted the results of a cohort study that reported on the safety and efficacy of brentuximab vedotin in 25 heavily pre-treated patients with Hodgkin's lymphoma who had relapsed more than 100 days after allo-SCT (Gopal et al. Blood 2012;120:560-8). The Subcommittee noted that the overall response rate was 50% and the complete response rate was 38%. The Subcommittee noted that the median time to response was 8.1 weeks, the median PFS was 7.8 months, and the median OS was not reached. The Subcommittee noted that peripheral sensory neuropathy was reported in 48% of patients, and cytomegalovirus was detected in 5 patients.

Brentuximab vedotin – relapsed/refractory anaplastic large-cell lymphoma

4.26. The Subcommittee considered that approximately 15 patients per year would be expected to be diagnosed with anaplastic large-cell lymphoma (ALCL) in New Zealand.

4.27. The Subcommittee considered that first-line treatment for patients with ALCL is systemic multiagent chemotherapy, with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) the standard first-line regimen. The Subcommittee considered that approximately 50% of patients will relapse following frontline therapy and will progress to salvage chemotherapy and auto-SCT (if appropriate). The Subcommittee considered that these patients have a poor prognosis, with a 5-year OS of no more than 50%.

4.28. The Subcommittee noted that there are no randomised controlled trials comparing brentuximab vedotin with currently available regimens for patients with relapsed/refractory ALCL.

4.29. The Subcommittee noted the 5-year results of a single-arm, open-label, pivotal phase 2 study that evaluated the safety and efficacy of brentuximab vedotin monotherapy in 58 patients with relapsed/refractory ALCL (Pro et al. Blood. 2017;130:2709-2717). The Subcommittee noted that after a median-follow up of 71.4 months, the complete response rate was 66%, the median OS was not reached, and the median PFS was not reached. The Subcommittee noted that the 5-year OS for the group of patients who underwent subsequent consolidative stem cell transplant was 75%. The Subcommittee noted that 57% of patients reported peripheral neuropathy, the majority (91%) of whom experienced resolution or improvement.

4.30. The Subcommittee noted that the response rates reported with the use of brentuximab vedotin for relapsed/refractory ALCL appear to be higher compared with other drugs that have recently been approved for use in other peripheral T cell lymphomas (e.g. pralatrexate, romidepsin).

Pembrolizumab

4.31. The Subcommittee noted that pembrolizumab is an anti–PD-1 monoclonal antibody that is administered as an intravenous infusion once every three weeks. The Subcommittee considered that pembrolizumab would be administered in the day ward.

4.32. The Subcommittee noted that PD-1 ligands are upregulated on Reed-Sternberg cells as a consequence of chromosome 9p24.1 amplification, and therefore Hodgkin's lymphoma is a good candidate for treatment with immune checkpoint inhibitors such as pembrolizumab and nivolumab.

4.33. The Subcommittee noted that pembrolizumab is registered in New Zealand for the treatment of patients with refractory classical Hodgkin's lymphoma who have relapsed after 3 or more prior lines of therapy.

4.34. The Subcommittee noted that the majority of the evidence to date regarding the use of pembrolizumab for the treatment of Hodgkin's lymphoma is following treatment with brentuximab vedotin.

4.35. The Subcommittee noted that the primary evidence for the use of pembrolizumab for the treatment of relapsed/refractory Hodgkin's lymphoma comes from the single-arm, phase 2 Keynote-087 trial (Chen et al. J Clin Oncol. 2017;35:2125-2132). The Subcommittee noted that this trial included 210 patients divided into three cohorts on the basis of disease progression and treatments received: after auto-SCT and subsequent brentuximab vedotin, after salvage chemotherapy and brentuximab vedotin (thus ineligible for auto-SCT due to chemoresistant disease), and after auto-SCT without subsequent brentuximab vedotin. The Subcommittee considered that 35 patients in the latter group had not received brentuximab vedotin at any time, and that these are the patients relevant to the current New Zealand population. The Subcommittee noted that the overall response rate in these patients was 71% and the complete response rate was 14%. The

Subcommittee considered that these results were similar to the response rates observed with brentuximab vedotin, although the follow-up is too short to determine whether this response is as durable. The Subcommittee further noted that the response rates were similar between the cohorts, irrespective of prior treatment regimen.

4.36. The Subcommittee noted that the incidence of grade 3-4 adverse events in KEYNOTE-087 was low; infusion-related reactions were observed in 28.6% of patients.

4.37. The Subcommittee noted that there are no data available regarding the use of pembrolizumab for the treatment of relapsed/refractory Hodgkin's lymphoma following two or more cycles of standard chemotherapy in patients who are ineligible for auto-SCT who have not received previous brentuximab vedotin. The Subcommittee noted that the patients with relapsed/refractory Hodgkin's lymphoma who were ineligible for auto-SCT in both the KEYNOTE-087 trial and the phase1b KEYNOTE-013 trial had all received prior brentuximab vedotin.

4.38. The Subcommittee noted the results of the phase 2, open-label CheckMate 205 trial which investigated the efficacy of nivolumab, another anti–PD-1 monoclonal antibody, for the treatment relapsed/refractory Hodgkin's lymphoma after auto-SCT (Armand et a. J Clin Oncol. 2018;36:1428-1439). The Subcommittee noted that the trial included 60 patients who were brentuximab vedotin-naïve patient, and that the overall response rate in this population was 65% and the complete response rate was 29%.

4.39. The Subcommittee noted that the data regarding the use of nivolumab is more mature than the pembrolizumab data, with a median follow-up of 18 months in the CheckMate 205 trial compared with 10 months in the KEYNOTE-087 trial.

General discussion

4.40. The Subcommittee considered that there is more data available regarding the efficacy of brentuximab vedotin for the treatment of relapsed/refractory Hodgkin's lymphoma than there is for the use of checkpoint inhibitors in this indication.

4.41. The Subcommittee considered that it is unclear if patients with relapsed/refractory Hodgkin's lymphoma would continue to receive benefit from treatment with brentuximab vedotin beyond 16 cycles. The Subcommittee therefore considered that, if brentuximab vedotin were to be funded, retreatment would not be permitted.

4.42. The Subcommittee considered that the risk of developing graft versus host disease may be higher with checkpoint inhibitors, and therefore patients who receive these agents may be less likely to undergo allo-SCT.

4.43. The Subcommittee considered that the vast majority of data available to date regarding the use of checkpoint inhibitors for the treatment of relapsed/refractory Hodgkin's lymphoma is in patients who have previously received brentuximab vedotin and are therefore not relevant to the current population of Hodgkin's lymphoma patients in New Zealand. The Subcommittee considered it remained unclear whether responses to immune checkpoint inhibitors are better in patients pre-treated with brentuximab vedotin.

4.44. The Subcommittee noted the phase 3 KEYNOTE-204 trial, which will investigate the efficacy and safety of pembrolizumab compared with brentuximab vedotin in patients with relapsed/refractory Hodgkin's lymphoma, is currently underway, and that this trial is likely to provide evidence more relevant to patients with Hodgkin's lymphoma in New Zealand.

5. Breast Cancer Treatments Review

Application

5.1. The Subcommittee noted a discussion paper from PHARMAC staff regarding the current breast cancer treatment landscape, treatments for breast cancer currently under consideration for funding, and an overview of pipeline products in development for the treatment of breast cancer which may be considered by PHARMAC in future.

Discussion

5.2. The Subcommittee noted that breast cancer is the most commonly diagnosed cancer and leading cause of cancer-related death among women in New Zealand.

5.3. The Subcommittee noted that the incidence of breast cancer is higher in Māori women than non-Māori (incidence rate 130.2 per 100,000 population vs 94.6 per 100,000 per population), and there are significant ethnic disparities in survival (Māori and Pacifica women having poorer outcomes than other ethnic groups).

5.4. The Subcommittee considered that the reason for this disparity was not necessarily due to differences in biology but could also be attributed to a differential timing of presentation and whether treatment was administered appropriately, some of which was due to socio-economic barriers.

5.5. The Subcommittee noted that there are various histologic and molecular subtypes of breast cancer that differ in microscopic appearance and biologic behaviour. The Subcommittee noted that these factors are used to guide treatment decisions.

5.6. The Subcommittee noted that many pharmaceutical treatments were targeted to subpopulations of breast cancer patients defined by molecular phenotype which are predictive of response. The Subcommittee noted that there were a number of testing platforms available which could help to identify patients who would respond to treatments and therefore could help to inform treatment decisions. The Subcommittee considered that testing could have a significant impact on DHBs and that there was currently limited capacity for this in DHBs. However, as the field developed it would be likely that further analysis would be needed by the health sector to balance the cost of testing with the potential for pharmaceutical and service savings from identifying patients most likely to benefit and those who would not.

6. Fulvestrant for locally advanced or metastatic breast cancer

Application

6.1. The Subcommittee reviewed the funding of fulvestrant for the treatment of locally advanced or metastatic breast cancer in light of updated information.

6.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework

Recommendation

6.3. The Subcommittee **recommended** that the funding of fulvestrant as a second-or third line treatment of locally advanced or metastatic breast cancer be funded with a medium priority subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 6 months.
>
> 1. Patient has oestrogen-receptor positive locally advanced or metastatic breast cancer; and
> 2. Patient has disease progression following prior treatment with an aromatase inhibitor or tamoxifen for their locally advanced or metastatic disease; and
> 3. Patient is amenorrhoeic for 12 months or greater, either naturally or induced, with endocrine levels consistent with a postmenopausal state; and
> 4. Treatment to be given at a dose of 500 mg monthly following loading doses; and

5. Treatment to be discontinued at disease progression.

Renewal application only from a medical oncologist or relevant specialist on the recommendation of a medical oncologist. Approvals valid for 6 months.

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

6.4. The Subcommittee **recommended** that the funding of fulvestrant as a first-line treatment of locally advanced or metastatic breast cancer be declined.

Discussion

6.5. The Subcommittee noted that funding of fulvestrant for post-menopausal women with locally advanced or metastatic breast cancer who have failed two lines of previous endocrine therapy was considered by PTAC in 2006 and CaTSoP in 2008.

6.6. The Subcommittee noted that in 2006 PTAC had recommended funding with low priority pending CaTSoP advice and noted that PTAC had considered that:

- The available clinical data demonstrates fulvestrant has a similar therapeutic benefit to anastrazole for patients who have had prior tamoxifen
- The evidence did not demonstrate efficacy of fulvestrant after failure of both tamoxifen and aromatase inhibitors,
- Sequencing of endocrine therapies was a critical issue in the management of advanced breast cancer and the place and dosing regimen of fulvestrant was unclear.
- Despite the lack of evidence of efficacy following failure of two endocrine treatments, a third-line position for funding would be reasonable given prognosis and comparison of the monthly cost of aromatase inhibitors at the time.

6.7. The Subcommittee noted that the cost of aromatase inhibitors had reduced significantly since PTACs consideration of fulvestrant in 2006.

6.8. The Subcommittee noted that in 2008 CaTSoP had recommended that funding of fulvestrant be declined and had noted that while, overall the evidence demonstrated fulvestrant in the third-line setting could stabilise disease in approximately 30% of patients for 5-6 months which could delay the start of chemotherapy; there was no evidence that delaying the start of chemotherapy would extend life, save money or reduce toxicity as suggested by the applicant.

6.9. The Subcommittee noted that since previous consideration of fulvestrant by PTAC and CaTSoP there was additional published evidence available regarding the use of fulvestrant in the treatment of advanced breast cancer.

6.10. The Subcommittee noted that the Breast Cancer Aotearoa Coalition had submitted an application requesting consideration of funding for fulvestrant as a first and later line treatment for oestrogen receptor (ER) positive advanced breast cancer.

6.11. The Subcommittee noted that previous PTAC and CaTSoP consideration of fulvestrant, and it's now lapsed Medsafe registration, were for a dose regimen of 250 mg monthly, whereas the internationally used dose is 500mg monthly based on the more recently published data from the CONFIRM and FALCON studies.

Evidence

6.12. The Subcommittee noted that the primary evidence for the use of fulvestrant 500mg monthly in the treatment of advanced breast cancer comes from the CONFIRM study (Leo

et al JCO 2010;28:4594-600); a randomised double-blind, parallel group Phase III study of fulvestrant 500 mg monthly (n=362) compared with 250 mg monthly (n=374) in postmenopausal locally advanced or metastatic ER-positive breast cancer.

6.13. The Subcommittee noted eligibility criteria included relapse on adjuvant endocrine therapy or within 1 year from completion of adjuvant endocrine therapy; and for de novo patients or those relapsed more than 1 year from completion of adjuvant endocrine therapy, previous treatment with either an anti-oestrogen or an aromatase inhibitor as first-line therapy was required. Members noted that patients were excluded if they had received more than one chemotherapy or endocrine therapy for advanced disease.

6.14. The Subcommittee noted that CONFIRM protocol was for treatment to be continued until disease progression, subsequent lines of therapy at investigators discretion and no crossover between treatment arms was allowed at the time of disease progression.

6.15. The Subcommittee noted that the last endocrine therapy before fulvestrant was an aromatase inhibitor for 42.5% of patients and an anti-oestrogen for the remaining 57.5% of patients.

6.16. The Subcommittee noted that median progression free-survival (PFS), the primary endpoint, was 6.5 months and 5.5 months in the 500-mg and 250-mg dose arms respectively (HR=0.80, 95% CI 0.68-0.94; P=0.006).

6.17. The Subcommittee noted that final overall survival (OS) analysis (Leo et al. JNCI 2014;160:djt337) reported after 75.3% of patients had died, median OS was 26.4 months in the 500-mg arm vs 22.3 months in the 250-mg arm (HR=0.81, nominal P=0.02).

6.18. The Subcommittee noted median durations of exposure to fulvestrant were 174 days (range, 10 to 1,441 days) and 145 days (range, 7 to 1,387 days) in the 500- and 250-mg groups, respectively; and no substantial difference in incidence and severity of adverse events or quality of life was seen between the two treatment arms.

6.19. The Subcommittee noted the double-blind registration trial in 221 Chinese women with the same indication as CONFIRM participants (Zhang et al. Oncotarget 2016:7;57301-9) reported a median PFS of 8.0 months in the 500-mg arm and 4.0 months in the 250-mg arm (HR=0.75l 95% CI 0.54-1.03; P=0.078).

6.20. The Subcommittee noted the primary evidence of the use of fulvestrant compared to an aromatase inhibitor is from the FALCON study (Robertson et al. Lancet 2016;388:2997-3005); a randomised double-blind phase III study of fulvestrant 500 mg monthly (n=230) versus anastrozole 1 mg daily (n=232) in ER-positive and/or progesterone receptor-positive locally advanced or metastatic breast cancer, endocrine therapy naïve patients.

6.21. The Subcommittee noted that median PFS, the primary endpoint, was 16.6 months in the fulvestrant arm and 13.8 months in the anastrazole arm (HR 0.797; 95% CI 0.637-0.999; P=0.0486).

6.22. The Subcommittee also noted the open-label randomised Phase II FIRST trial (Ellis et al JCO 2015;33:3781-7) comparing fulvestrant 500 mg monthly with anastrozole 1 mg daily in 205 postmenopausal women with ER-positive locally advanced or metastatic breast cancer who had not received any previous systemic therapy for advanced disease. The Subcommittee noted that median OS was reported as 54.1 months v 48.4 months, respectively (HR 0.70, 95% CI 0.50-0.98; P=0.04).

6.23. The Subcommittee noted that in FIRST, previous endocrine therapy had been received by 29 (28.4%) of the patients treated with fulvestrant 500 mg and 23 (22.3%) of the anastrozole-treated patients. The Subcommittee noted that only 3 of these 52 had received aromatase inhibitors previously (2 in the anastrozole arm and 1 in the fulvestrant arm) and that the remainder had received adjuvant tamoxifen.

6.24. The Subcommittee considered that there was good evidence to support that fulvestrant 500 mg monthly as a single agent delays the time to progression for patients with ER-positive advanced breast cancer, however it is unclear whether this would prevent any subsequent lines of therapy in this population and the evidence for an overall survival benefit is limited.

6.25. The Subcommittee considered that fulvestrant does not have the same risk of venous thromboembolism as tamoxifen, however required two intramuscular injections per dose. The Subcommittee considered that, given the potential administrative difficulties, there would likely be a clinical preference for oral agents as first-line treatment.

6.26. The Subcommittee considered that based on currently available evidence patients most likely to benefit from treatment with fulvestrant are postmenopausal women with ER-positive advanced breast cancer who have received a good response to prior aromatase inhibitor treatment.

6.27. The Subcommittee considered that there remained a lack of data regarding optimal sequencing of endocrine treatments for ER-positive advanced breast cancer. However, members considered that there appeared not to be cross-resistance with tamoxifen indicating it would be appropriate to use fulvestrant in any sequence with tamoxifen.

6.28. Members considered that it would not be appropriate to amend current New Zealand practice to use fulvestrant in a first-line setting given the likely cost-differential between fulvestrant and aromatase inhibitors/tamoxifen. However, considered that if pricing were comparable this should be reviewed.

7. Pertuzumab for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer

Application

7.1. The Subcommittee reviewed a funding application from Roche Products (New Zealand) Ltd for pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast 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 **recommended** that the application for the funding of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer be **declined** based on insufficient evidence available at this time.

Discussion

7.4. The Subcommittee noted that the standard treatment approach for early breast cancer is surgery followed by systemic therapy with or without radiotherapy. The Subcommittee noted that adjuvant treatments are selected on the basis of the findings from surgery, with an aim to target metastatic microscopic disease.

7.5. The Subcommittee noted that neoadjuvant therapy can be administered before surgery with an aim to reduce tumour size prior to resection. The Subcommittee noted that neoadjuvant therapy for breast cancer may involve chemotherapy, hormonal therapy, and/or targeted therapy.

7.6. The Subcommittee considered that the benefits associated with the use of neoadjuvant therapy include avoiding delays in treatment due to surgical complications (e.g. infection), providing an opportunity to observe response and modify therapy early, and as a means of identifying new and active drugs; however, the Subcommittee considered that the evidence available to date does not demonstrate that neoadjuvant therapy provides an overall survival advantage, although it does allow more patients to undergo breast conserving surgery rather than mastectomy.

7.7. The Subcommittee considered that high pathological complete response rates observed in patients with HER2-positive breast cancer and triple-negative breast cancer treated with neoadjuvant therapy is what drove interest in the use of neoadjuvant treatments in breast cancer (Cortazar et al. Lancet. 2014;384:164-72).

7.8. The Subcommittee noted that patients with locally advanced HER2-positive disease have a significant health need, as these are aggressive, rapidly growing tumours with a poor prognosis if untreated.

7.9. The Subcommittee noted that the 5-year breast cancer-specific survival in patients with HER2-positive stage I-III disease with treatment is currently between 80%–92%, depending on hormone receptor positivity (Lawrenson et al. NZMJ. 2018;131:51-60).

7.10. The Subcommittee considered that between 50 and 70 patients with HER2-positive disease would be offered neoadjuvant therapy in New Zealand each year; however, this would likely increase with time given trends for increasing neoadjuvant treatment. Members considered that the patients most likely to be offered neoadjuvant therapy include those who have locally advanced breast cancer where surgery may not achieve adequate margins, patients who have locally advanced breast cancer who would generally be considered for mastectomy but have a preference for breast conserving surgery, and patients with HER2-positive or triple negative breast cancer who have tumours greater than 2 cm in size.

7.11. The Subcommittee noted that pathological complete response has been proposed as an early surrogate marker for predicting survival outcome for patients with breast cancer; and that various definitions and outcomes were reported across different trials. The Subcommittee noted the findings of the CTNeoBC pooled analysis which identified that patients who have eradication of all invasive tumour from the breast and are node-negative at definitive surgery (tpCR) have improved survival (Cortazar et al. Lancet. 2014;384:164-72).

7.12. The Subcommittee noted that the absolute amount of improvement in the tpCR rate required to affect long-term outcomes was not established in the CTNeoBC analysis, and that only 1,989 patients with HER2-positive disease were included. The Subcommittee considered that, with the evidence currently available, the absolute survival benefits associated with differences in tpCR rates cannot be defined.

7.13. The Subcommittee noted that pertuzumab is a HER2-targeted monoclonal antibody that is registered in New Zealand for use in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of inflammatory or locally advanced HER2-positive early breast cancer, in combination with trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high risk of recurrence, and in combination with trastuzumab and docetaxel for the treatment of HER2-positive metastatic breast cancer for patients who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease. The Subcommittee noted that pertuzumab was currently funded for use in this metastatic setting.

7.14. The Subcommittee noted that the recommended initial dose of pertuzumab in all settings is 840 mg administered as an intravenous infusion over 60 minutes, followed by doses of 420 mg administered as intravenous infusions over 30–60 minutes once every three weeks for a total of 4 cycles.

7.15. The Subcommittee noted that the key evidence for the use of pertuzumab for the treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer comes from the open-label, randomised, Phase 2 NeoSphere trial (Gianni et al. Lancet Oncol. 2012;13:25-32).

7.16. The Subcommittee noted that NeoSphere was a proof-of-concept study which investigated the activity of the combination of pertuzumab and/or trastuzumab with docetaxel and the combination of pertuzumab and trastuzumab without chemotherapy in the neoadjuvant setting in 417 treatment-naïve patients with locally advanced, inflammatory, or early HER2-positive breast cancer. The Subcommittee noted that patients received four cycles of neoadjuvant therapy, followed by surgery and adjuvant chemotherapy.

7.17. The Subcommittee noted that the primary endpoint in the NeoSphere study was pathological complete response in the breast, defined as the absence of invasive disease in the breast (bpCR), with tpCR included as a secondary endpoint. The Subcommittee considered that tpCR had a stronger association with outcome than bpCR.

7.18. The Subcommittee noted that, at the time of the primary analysis, the tpCR rate (a secondary outcome) was 21.5% in patients who received trastuzumab plus docetaxel; 39.3% in patients who received pertuzumab, trastuzumab, and docetaxel; 11.2% in patients who received pertuzumab plus trastuzumab; and 17.7% in patients who received pertuzumab plus docetaxel. The Subcommittee noted that the tpCR rate was lower in patients with hormone receptor-positive disease, and that the majority of patients in all treatment groups achieved a clinical response (67.6%–88.1%).

7.19. The Subcommittee noted that there were no unexpected grade 3 or higher toxicities reported in the NeoSphere trial, and that the mean maximum decrease in left ventricular ejection fraction measurement was low at 4%–5%.

7.20. The Subcommittee noted the authors of the NeoSphere publication state that: “The phase 2 design and the small sample size of our study will prevent future analyses of outcome in the overall population and in subsets; thus, the study will not contribute to clarification of the actual predictive role of pathological complete response according to hormone receptor status.”.

7.21. The Subcommittee noted the 5-year analysis of the NeoSphere trial, which identified 5-year progression free survival (PFS) rates of 81% in patients who received trastuzumab plus docetaxel; 86% in patients who received pertuzumab, trastuzumab, and docetaxel; 73% in patients who received pertuzumab plus trastuzumab; and 73% in patients who received pertuzumab plus docetaxel (Gianni et al. Lancet Oncol. 2016;17:791-800). The Subcommittee noted that subgroup analysis comparing patients who received trastuzumab plus docetaxel with patients who received pertuzumab, trastuzumab, and docetaxel did not reach statistical significance.

7.22. The Subcommittee noted the exploratory subgroup analyses of PFS according to tpCR in the 5-year follow-up of NeoSphere. The Subcommittee noted that the 5-year PFS rate was 85% in patients with tpCR and 76% in patients with no tpCR (HR 0.54; 95% CI 0.29, 1.00), with a trend in all treatment groups towards improved outcomes in patients who achieved tpCR. The Subcommittee considered that the difference between the treatment arms was relatively small and that the overall trend could be attributed to the difference in survival between patients with hormone receptor-negative and positive disease, as observed in previous studies.

7.23. The Subcommittee considered that the results observed in the NeoSphere study can only be considered descriptive, as the study was not powered to detect a statistical difference in 5-year PFS or disease-free survival rates as evidenced by all confidence intervals crossing zero.

7.24. The Committee noted that additional evidence for the use of pertuzumab for the treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer comes from the open-label, randomised, Phase 2 TRYPHAENA trial (Schneeweiss et al. Ann Oncol. 2013;24:2278-84).

7.25. The Subcommittee noted that the TRYPHAENA trial was primarily designed to evaluate the tolerability, and particularly cardiac safety, of neoadjuvant trastuzumab and pertuzumab in combination with anthracycline- or carboplatin-based neoadjuvant systemic chemotherapy in 225 patients with HER2-positive primary breast cancer.

7.26. The Subcommittee noted that the cardiac profile observed in TRYPHAENA was similar to that observed in the NeoSphere trial, and that the combination of trastuzumab and pertuzumab was generally well tolerated regardless of the chemotherapy regimen used.

7.27. The Subcommittee noted that the tpCR rate in TRYPHAENA was between 45% and 52% in the treatment groups, but that this was a secondary endpoint.

7.28. The Subcommittee noted the authors of the TRYPHAENA publication stated: “The study was not intended to evaluate superiority of any arm, and all three arms were experimental. Therefore, comparison of toxic effect and response rates with a control arm is not possible which limits the interpretation of the study.”.

7.29. The Subcommittee considered that the patient population in TRYPHAENA was small and that the study was exploratory in nature. The Subcommittee therefore considered that the results of TRYPHAENA were of limited value in assessing the benefits associated with the use of neoadjuvant pertuzumab.

7.30. The Subcommittee also noted the results of the Phase 3 APHINITY trial, which investigated the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy as adjuvant therapy in patients with HER2-positive, operable breast cancer (von Minckwitz et al. NEJM 2017;377:122-31). The Subcommittee noted that the 3-year rate of invasive-disease-free survival was 94.1% for patients in the pertuzumab group compared with 93.2% for patients in the placebo group (HR 0.81; 95% CI 0.66, 1.00; *P*=0.045). The Subcommittee considered that while the difference in the 3-year rate of invasive-disease-free survival was significant due to the size of the study population, the benefits demonstrated were much smaller than expected from the results of the CLEOPATRA study, which had shown marked benefits when pertuzumab was used in metastatic disease.

7.31. The Subcommittee considered that although the tpCR rates observed in the NeoSphere and TRYPHAENA trials suggested that there may be a benefit when pertuzumab was used as a neoadjuvant treatment in combination with trastuzumab and chemotherapy, neither NeoSphere nor TRYPHAENA were designed to definitively demonstrate a survival benefit. The Subcommittee considered the magnitude of benefit, if any, from pertuzumab as a neoadjuvant treatment was highly uncertain based on currently available evidence.

7.32. The Subcommittee considered that the strength and quality of evidence available at this time was weak and is not sufficient to recommend the use of pertuzumab as a neoadjuvant treatment of HER2-positive locally advanced, inflammatory, or high-risk early stage breast cancer. The Subcommittee noted that if funding of pertuzumab in this setting was to be reconsidered, it should be supported by additional evidence powered to detect a PFS and OS benefit.

8. Pertuzumab for patients with previously treated HER-2 positive metastatic breast cancer

Application

8.1. The Subcommittee reviewed the funding of pertuzumab in HER-2 positive metastatic breast cancer patients whose metastatic disease has been previously treated with trastuzumab in light of additional published evidence.

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 pertuzumab in combination with trastuzumab be funded with low priority as a second-line treatment for patients who have progressed on or after previous treatment with trastuzumab for their metastatic disease and not had any other lines of treatment since stopping trastuzumab subject to the following Special Authority criteria (additions to the current criteria shown in bold, deletions in strikethrough):

> Initial application – (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
> 2. Either:
> 2.1. Patient is chemotherapy treatment naïve; or
> 2.2. Patient has not received prior treatment for their metastatic disease and has had a treatment free interval of at least 12 months between prior (neo)adjuvant chemotherapy treatment and diagnosis of metastatic breast cancer; ~~and~~ **or**
> 2.3. **Both:**
> 2.3.1. **Patient has had disease progression on or after prior treatment with trastuzumab for their metastatic disease; and**
> 2.3.2. **Patient has had no treatment for their metastatic disease since stopping trastuzumab; and**
> 3. The patient has good performance status (ECOG grade 0-1);
> 4. Pertuzumab to be administered in combination with trastuzumab;
> 5. Pertuzumab maximum first dose of 840 mg, followed by maximum of 420 mg every 3 weeks; and
> 6. Pertuzumab to be discontinued at disease progression.
>
> Renewal application - (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> Both:
> 1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including ISH or other current technology); and
> 2. The cancer has not progressed at any time point during the previous 12 months whilst on pertuzumab and trastuzumab.

8.4. The Subcommittee **recommended** that funding of pertuzumab for patients previously treated with trastuzumab in all other metastatic breast cancer settings be declined.

8.5. The Subcommittee **recommended** that the Special Authority criteria for trastuzumab for metastatic breast cancer be amended to allow its second-line use only in combination with pertuzumab for patients who have progressed on or after previous treatment with trastuzumab for their metastatic disease and not had any other lines of treatment since stopping trastuzumab subject to the following Special Authority criteria (additions to the current criteria shown in bold, deletions in strikethrough):

Initial application - (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
Any of the following:

1. All of the following:
   - 1.1 The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
   - 1.2 The patient has not previously received lapatinib treatment for HER-2 positive metastatic breast cancer; and
   - 1.3 Trastuzumab not to be given in combination with lapatinib; and
   - 1.4 Trastuzumab to be discontinued at disease progression; or

2. All of the following:
   - 2.1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
   - 2.2 The patient started lapatinib treatment for metastatic breast cancer but discontinued lapatinib within 3 months of starting treatment due to intolerance; and
   - 2.3 The cancer did not progress whilst on lapatinib; and
   - 2.4 Trastuzumab not to be given in combination with lapatinib; and
   - 2.5 Trastuzumab to be discontinued at disease progression; or

3. All of the following:
   - 3.1 The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
   - 3.2 Either:
     - 3.1.1 Patient is chemotherapy treatment naïve; or
     - 3.1.2 Patient has not received prior treatment for their metastatic disease and has had a treatment free interval of at least 12 months between prior (neo)adjuvant chemotherapy treatment and diagnosis of metastatic breast cancer; ~~and~~ or
     - 3.2.3 Both:
       - 3.2.3.1 Patient has had disease progression on or after prior treatment with trastuzumab for their metastatic disease; and
       - 3.2.3.2 Patient has had no treatment for their metastatic disease since stopping trastuzumab; and
   - 3.3 The patient has good performance status (ECOG grade 0-1); and
   - 3.4 Trastuzumab to be administered in combination with pertuzumab; and
   - 3.5 Trastuzumab to be discontinued at disease progression.

Renewal- (metastatic breast cancer) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ (including FISH or other current technology); and
2. The cancer has not progressed at any time point during the previous 12 months whilst on trastuzumab; and
3. Trastuzumab not to be given in combination with lapatinib; and
4. Trastuzumab to be discontinued at disease progression.

Discussion

8.6. The Subcommittee noted that pertuzumab has been funded since 1 January 2017 for the first-line treatment of patients with HER-2 positive metastatic breast cancer subject to certain Special Authority criteria being met.

8.7. The Subcommittee noted that during consultation on the proposal to list pertuzumab, although responders were generally supportive, issues were raised with the Special Authority criteria particularly regarding extending funded access to pertuzumab for patients whose metastatic disease has been previously treated with trastuzumab.

8.8. The Subcommittee noted that trastuzumab pre-treated patients, whether they are currently on treatment or have had previous treatment for their metastatic disease but are currently off treatment, are not able to access funded pertuzumab as they are excluded from the current Special Authority criteria.

8.9. The Subcommittee noted that currently funded treatment for HER-2 positive metastatic breast cancer patients without access to pertuzumab is first-line trastuzumab, in combination with cytotoxic chemotherapy initially, until disease progression.

8.10. The Subcommittee considered that trastuzumab pre-treated patients represent a different clinical setting to the patient group for which clinical advice has been previously received from PTAC and CaTSoP and was proposed for funding in 2017, and also differ from the Medsafe registered indication which is '*in combination with trastuzumab and docetaxel for patients with HER2-positive metastatic breast cancer who have not received prior anti-HER2 therapy or chemotherapy for their metastatic disease*'.

8.11. The Subcommittee noted that the current Special Authority criteria for pertuzumab were recommended by PTAC and CaTSoP based on the eligibility criteria for the Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study (Baselga et al. NEJM. 2012;366:109-19; Swain et al. Lancet Oncology 2013;14:461-71) which investigated combination therapy of pertuzumab plus trastuzumab with docetaxel for first-line treatment of HER2-positive metastatic breast cancer.

8.12. The Subcommittee noted that in February 2017 PTAC had considered the funding of pertuzumab for patients with previously treated HER-2 positive metastatic breast cancer and all available evidence at the time and had deferred making a recommendation pending publication of further evidence to support its use in these settings.

8.13. The Subcommittee noted that since PTAC's consideration in February 2017 the PHEREXA study had been published in full and the final overall survival (OS) analysis of the PHEREXA study had been presented at the 2018 ASCO meeting in poster form.

8.14. The Subcommittee noted that PHEREXA was a phase III study of trastuzumab + capecitabine with (n=228) or without (n=224) pertuzumab for patients who received a prior taxane and progressed during/after one line of trastuzumab-based therapy in the HER2-positive metastatic breast cancer setting. (Urruticoechea et al. 2017;35:3030-8). The Subcommittee noted that eligibility criteria included disease progression during or after first-line trastuzumab-based therapy for metastatic breast cancer (trastuzumab was required to have been part of the last prior-treatment regimen and adjuvant trastuzumab was permitted); and exclusion criteria included prior capecitabine or pertuzumab.

8.15. The Subcommittee noted that statistical analysis in Urruticoechea et al. 2017 indicated the planned sample size was approximately 450 patients which was expected to provide 75% power to detect a 33% increase in median progression-free survival (PFS); and a hierarchical testing procedure was used to control for type 1 error in multiple statistical tests allowing for formal interpretation of primary and secondary endpoints. The Subcommittee noted that 446 patients were randomized to the safety population as 6 patients from the intention to treat arm without pertuzumab did not receive any treatment.

8.16. The Subcommittee noted that around 40% of patients in PHEREXA had received more than 12 months of response to trastuzumab in the first-line setting, and that three quarters of patients had received treatment with trastuzumab for metastatic disease only. The Subcommittee noted that the median treatment free interval of PHEREXA participants was 6.18 months in the study arm and 10.49 months in the control arm.

8.17. The Subcommittee noted that the final pre-specified analysis of secondary endpoints reported at ASCO 2018 (Urruticoechea et al. 2018 ASCO poster) were as follows:

- Median time on study, including post-treatment follow-up, was 23.2 months in the control arm and 33.0 months in the pertuzumab arm.
- Final analysis of OS was 28.1 months in the control arm vs 37.2 months in the pertuzumab arm (HR 0.76, 95% CI 0.60–0.98), a 9.1 month difference; However, this was not statistically significant due to hierarchical testing.
- Investigator-assessed PFS was 9.0 months in the control arm vs 11.8 months in pertuzumab arm (HR 0.83, 95% CI 0.68–1.02), a 2.8 month difference.

8.18. The Subcommittee noted that Urruticoechea et al. 2018 noted that the sponsor decided to end the study early, close to the time of planned final OS analysis, given the primary endpoint (independent review facility–assessed PFS) was not met and concluded that the final analysis of OS was consistent with the interim OS analysis and no new safety signals were observed.

8.19. The Subcommittee also noted the supportive evidence from the Cleopatra Crossover population (Herold et al. J Adv Pract Oncol 2016:7:839) and the Phase II population published in 2010 by Baselga et al. (JCO 2010;28:1138-44).

8.20. The Subcommittee noted a joint letter of support from Breast Cancer Aotearoa Coalition and the Breast Cancer Foundation NZ for the funding of pertuzumab for all patients who have progressed during or after first-line trastuzumab in the metastatic setting which noted the Urruticoechea et al. 2018 presentation at ASCO.

8.21. The Subcommittee considered that based on PHEREXA data it appeared there was no significant difference in PFS between the trial arms even with data maturity; median OS was similar, albeit slightly shorter, to that reported in the CLEOPATRA study where an OS difference was observed; and that there remains a non-significant difference in OS due to hierarchical testing.

8.22. The Subcommittee considered that there was limited evidence for the use of pertuzumab in pre-treated patients and that there would likely not be any additional randomised controlled trial data given the use of pertuzumab internationally as standard of care.

8.23. The Subcommittee considered that there remained a lack of evidence to support the addition of pertuzumab to the treatment regimen of metastatic breast cancer patients currently receiving trastuzumab.

8.24. The Subcommittee considered the currently available evidence did support a response to pertuzumab in combination with trastuzumab for metastatic breast cancer patients whose disease has progressed on or after trastuzumab. The Subcommittee considered the magnitude of benefit of pertuzumab in combination with trastuzumab in this setting remained uncertain and was likely less durable than in a first-line setting, however if the survival from PHEREXA were realised this would be clinically meaningful.

8.25. The Subcommittee noted that the evidence was restricted to patients who had received trastuzumab as their most recent prior metastatic treatment, and there was no evidence to support the use of pertuzumab and trastuzumab for patients who had received additional lines of treatments since discontinuation of trastuzumab treatment.

8.26. The Subcommittee considered that there would be a defined patient population of long-term trastuzumab responders in these clinical circumstances which would likely be around 100 patients.

8.27. The Subcommittee considered that there was a relatively high cost associated with these treatments.

8.28. The Subcommittee considered that use of pertuzumab as a second-line treatment for metastatic breast cancer could only be supported when used in combination with trastuzumab and that this would require amendment to the current access criteria for trastuzumab.

8.29. The Subcommittee noted that the second-line use of trastuzumab alone as retreatment and treatment beyond progression in patients with HER-2 positive metastatic breast cancer who have progressed on trastuzumab had been previously considered by CaTSoP in November 2010 and PTAC in February 2011. The Subcommittee noted that this use of trastuzumab had been recommended for decline because it was considered inappropriate (and not cost-effective) and treatment with trastuzumab should be discontinued at the time of tumour progression and further applications should be declined.

9. Palbociclib as initial endocrine therapy for the treatment of hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer

Application

9.1. The Subcommittee reviewed a funding application from Pfizer New Zealand Ltd for palbociclib to be used in combination with an aromatase inhibitor as initial endocrine therapy for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer.

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

Recommendation

9.3. The Subcommittee **recommended** that palbociclib for use in combination with an aromatase inhibitor as initial endocrine therapy for the treatment of hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer be funded with a **medium** priority subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has inoperable 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. Patient has not received prior systemic treatment for metastatic disease; and
> 5. Palbociclib must be used in combination with a non-steroidal aromatase inhibitor; and
> 6. Patient has been amenorrhoeic for 12 months or greater, either naturally or induced, with endocrine levels consistent with a postmenopausal state.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Palbociclib must be used in combination with a non-steroidal aromatase inhibitor; and
> 2. No evidence of progressive disease; and
> 3. The treatment remains appropriate and the patient is benefitting from treatment.

Discussion

9.4. The Subcommittee noted that approximately 3000 women are diagnosed with breast cancer each year in New Zealand, that an unknown proportion will progress from localized to advanced disease, and that approximately 20% of patients will have locally advanced or metastatic disease at diagnosis. The Subcommittee considered that approximately

55%–65% of patients with advanced disease will have hormone receptor (HR)-positive, HER2-negative disease.

9.5. The Subcommittee considered that estimating the number of patients who would be eligible for treatment for HR-positive, HER2-negative locally advanced or metastatic breast cancer per year in New Zealand was difficult; but considered that the applicant's estimate of approximately 550 eligible patients per year was likely high.

9.6. The Subcommittee considered that if eligibility criteria did not specifically exclude it, it was likely that the approximately 20%–25% of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who are premenopausal/perimenopausal would undergo ovarian suppression to fit eligibility criteria as 'postmenopausal'.

9.7. The Subcommittee noted the results of an observational study of 815 patients with metastatic breast cancer in the Netherlands that identified a median survival of 24.8 months for patients with HR-positive/HER2-negative metastatic breast cancer, compared with 34.4 months for HR-positive/HER2-positive disease, 19.8 months for HR-negative/HER2-positive disease, and 8.8 months for triple-negative disease (Lobbezoo et al. Breast Cancer Res Treat. 2013;141:507-14).

9.8. The Subcommittee considered that the currently funded first-line treatments for advanced HR-positive/HER2-negative breast cancer include aromatase inhibitors or tamoxifen.

9.9. The Subcommittee considered that the uptake of palbociclib, if funded, would likely be high as endocrine therapies are the only currently funded agents for patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer. Furthermore, the Subcommittee considered that in the first few years of listing there were would likely be a significant number of prevalent patients seeking treatment due to the long duration of survival with hormonal agents.

9.10. The Subcommittee noted that palbociclib is a reversible inhibitor of the cyclic-dependent kinases (CDK) 4 and 6, which are critical components of the cell-cycle regulatory machinery. The Subcommittee noted that CDK4/6 inhibitors reduce cellular proliferation by blocking progression through the G1 phase of the cell cycle, promoting transient, and possibly permanent, proliferative arrest.

9.11. The Subcommittee noted that palbociclib is approved for the treatment of HR-positive/HER2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor, and in combination with fulvestrant in women who have received prior endocrine therapy.

9.12. The Subcommittee noted that the application submitted by the supplier was for consideration of funding for palbociclib as an initial (first-line) endocrine agent only and did not appear to include its use in combination with fulvestrant as a second-line endocrine agent.

9.13. The Subcommittee noted that the recommended dose of palbociclib is 125 mg once daily for 21 consecutive days followed by 7 days off treatment, and that treatment should be continued as long as the patient is deriving clinical benefit from therapy.

9.14. The Subcommittee noted that the applicant identified two clinical trials that provide the key evidence for palbociclib for the treatment of HR-positive/HER2-negative advanced breast cancer: the phase 2 PALOMA-1 trial and the phase 3 PALOMA-2 trial.

9.15. The Subcommittee noted the open-label, randomized, phase 2 PALOMA-1 trial which investigated the safety and efficacy of palbociclib in combination with letrozole compared with letrozole alone as first-line treatment in 165 postmenopausal women with HR-positive/HER2-negative advanced breast cancer (Finn et al. Lancet Oncol. 2015;16:25-35).

9.16. The Subcommittee noted the study design and patient demographics of the PALOMA-1 trial and identified that 12% of patients had received prior treatment with anastrozole or letrozole.

9.17. The Subcommittee noted that in the PALOMA-1 trial, after a median follow-up of 29.6 months in the palbociclib plus letrozole arm and 27.9 months in the letrozole alone arm, that the median progression-free survival (PFS; primary endpoint) was 20.2 months and 10.2 months in the treatment groups, respectively (HR 0.488; 95% CI 0.319, 0.748; *P*=0.004). The Subcommittee noted that the objective response rates were 43% in the palbociclib plus letrozole arm compared with 33% in the letrozole alone arm (*P*=0.13), and that the clinical benefit rate was 81% compared with 58% (*P*=0.0009), respectively. The Subcommittee noted that the median duration of response for patients who achieved a complete or partial response was 20.3 months in the palbociclib plus letrozole arm compared with 11.1 months in the letrozole alone arm.

9.18. The Subcommittee noted the median overall survival (OS) at the time of the primary analysis of the PALOMA-1 trial was 37.5 months in the palbociclib plus letrozole arm compared with 33.2 months in the letrozole alone arm (HR 0.813, 95% CI 0.492, 1.345; *P*=0.42).

9.19. The Subcommittee noted that the rates of anaemia, nausea, arthralgia, and alopecia in PALOMA-1 were higher in the palbociclib plus letrozole arm compared with the letrozole alone arm. The Subcommittee noted that 33% of patients in the palbociclib plus letrozole arm had dose interruptions due to an adverse event compared with 4% of patients in the letrozole alone arm, and that 40% of patients receiving palbociclib plus letrozole had a dose reduction. The Subcommittee noted that 13% of patients in the palbociclib plus letrozole arm discontinued treatment due to an adverse event compared with 2% of patients in the letrozole alone arm.

9.20. The Subcommittee also noted the updated analysis of PALOMA-1 published in abstract form, which identified a median OS of 37.5 months in the palbociclib plus letrozole arm compared with 34.5 months in the letrozole alone arm (HR 0.897; 95% CI 0.623, 1.294; *P*=0.281) (Finn et al. J Clin Oncol. 2017;35:1001-1001).

9.21. The Subcommittee noted that there were no statistically significant differences in pain severity or pain interference scores between the two treatment arms in PALOMA-1 (Bell et al. Curr Med Res Opin. 2016;35:959-65).

9.22. The Subcommittee noted that a PFS benefit in patients who received palbociclib plus letrozole was observed across the majority of subgroups (Finn et al. Breast Cancer Res. 2016;18:67).

9.23. The Subcommittee noted the double-blind, randomized, placebo-controlled, phase 3 PALOMA-2 trial, which investigated the efficacy and safety of palbociclib plus letrozole compared with placebo plus letrozole in 666 postmenopausal women with oestrogen receptor-positive, HER2-negative advanced breast cancer who had not received prior systemic treatment for advanced disease (Finn et al N Engl J Med. 2016;375:1925-1936).

9.24. The Subcommittee noted the study design and patient demographics of the PALOMA-2 trial. The Subcommittee noted that 49% of patients had visceral disease at baseline, 48% of patients had received prior chemotherapy, and 21% of patients had received prior treatment with anastrozole or letrozole.

9.25. The Subcommittee noted that, after a median follow-up of 23 months, that the median investigator-assessed PFS (primary endpoint), in the PALOMA-2 trial was 24.8 months in the palbociclib arm compared with 14.5 months in the placebo arm (HR 0.58; 95% CI 0.46, 0.72; *P*<0.001). The Subcommittee noted that the objective response rates were 55.3% in the palbociclib arm compared with 44.4% in the placebo arm (OR 1.55; 95% CI 1.05, 2.28; *P*=0.03), and that the clinical benefit rate was 84.3% compared with 70.8% (OR

2.23; 95% CI, 1.39, 3.56; *P*<0.001), respectively. The Subcommittee noted that the median duration of response for patients who achieved a complete or partial response was 22.5 months in the palbociclib arm compared with 16.8 months in the placebo arm. The Subcommittee noted that the OS data were immature at the time of the primary analysis.

9.26. The Subcommittee noted that the rates of anaemia, haematological adverse events, alopecia, diarrhoea, and stomatitis in PALOMA-2 were higher in the palbociclib arm compared with the placebo arm. The Subcommittee noted that any grade neutropenia was reported for 79.5% of patients in the palbociclib arm, but that grade 3 or 4 febrile neutropenia was reported in only 1.8% of patients. The Subcommittee noted that 36.0% of patients in the palbociclib arm had dose reductions compared with 1.4% in the placebo arm, and that 9.4% of patients in the palbociclib arm discontinued due to adverse events compared with 1.4% of patients in the placebo arm.

9.27. The Subcommittee considered that, if palbociclib were funded, this would likely result in additional hospital visits related to toxicity and additional blood tests for neutropenia may also be required; in the absence of significant toxicity and neutropenia, patients would likely undergo regular follow-ups every 6-months.

9.28. The Subcommittee noted the quality-of-life (QoL) results of PALOMA-2, which identified that the addition of palbociclib to letrozole delayed deterioration in health-related QoL (Rugo et al. Ann Oncol. 2018;29:888-894).

9.29. The Subcommittee noted the open-label, randomised, phase 2 TREnd trial which investigated the clinical activity of palbociclib in combination with endocrine therapy or palbociclib alone in 115 postmenopausal women with HR-positive/HER2-negative advanced breast cancer who have progressed on previous endocrine therapy (Malorni et al. J Clin Oncol. 2017;35:1002-1002). The Subcommittee noted that the median PFS was 10.8 months in patients receiving palbociclib plus endocrine therapy compared with 6.5 months in patients receiving palbociclib alone. The Subcommittee considered that this indicates that palbociclib may have clinical activity in patients who have previously received endocrine therapy; however, these results are exploratory at this stage.

9.30. The Subcommittee noted the double-blind, randomised, phase 3 PALOMA-3 trial, which investigated the efficacy of palbociclib in combination with fulvestrant compared with placebo plus fulvestrant in 521 women with HR-positive/HER2-negative breast cancer who had relapsed during prior endocrine therapy (Turner et al. N Engl J Med. 2015;373:209-219). The Subcommittee noted that the patient population included premenopausal/perimenopausal and postmenopausal women, and that the former received goserelin for the duration of the study.

9.31. The Subcommittee considered that the results of the PALOMA-3 trial demonstrated that palbociclib combined with fulvestrant appeared to provide a PFS benefit compared with fulvestrant alone in patients who had received prior endocrine therapy. The Subcommittee noted that overall survival data were immature at the time of interim analysis. The Subcommittee considered that based on currently available evidence it appeared there was a lower level of benefit from use of palbociclib in a second-line setting as compared to as a first-line endocrine therapy.

9.32. The Subcommittee noted the double-blind, randomized, phase 3 MONALEESA-7 trial, which investigated the efficacy and safety of ribociclib plus endocrine therapy in premenopausal women with advanced HR-positive breast cancer (Tripathy et al. Lancet Oncol. 2018;19:904-915). The Subcommittee noted that ribociclib is another CDK4/6 inhibitor, and that the results of MONALEESA supported that ribociclib plus endocrine therapy improved PFS compared with placebo plus endocrine therapy.

9.33. The Subcommittee noted that there were other CDK4/6 inhibitors in late-stage development and considered that, based on the currently available evidence, there

appeared to be a class effect in terms of similar response rates and improved PFS from CDK4/6 inhibitors in HR-positive breast cancer. The Subcommittee noted it was interested to review further CDK4/6 data as it became available.

9.34. The Subcommittee noted that survival data for all agents under development appeared not to be powered for OS; however, the Subcommittee considered that PFS is an adequate endpoint in this population, and noted the findings of a recent report published by The National Cancer Institute Breast Cancer Steering Committee which identified that PFS is the preferred endpoint for trials investigating first- or second-line treatment for HR-positive/HER2-negative breast cancer. (Seidman et al. J Clin Oncol. 2018;JCO1800242).

9.35. The Subcommittee noted that the eligibility criteria for PALOMA 2 required women to be postmenopausal, defined by having undergone prior bilateral oophorectomy, spontaneous cessation of menses for 12 consecutive months or more, or having follicle-stimulating hormone and oestradiol levels in postmenopausal ranges without an alternative cause. The Subcommittee noted that this excluded patients rendered postmenopausal through the use of luteinizing-hormone-release hormone (LHRH) agonists. The Subcommittee considered that these patients also have the potential to benefit from treatment with palbociclib in combination with an aromatase inhibitor and considered that the evidence provided by the PALOMA-3 trial (which included pre/perimenopausal patients receiving goserelin) supports this. The Subcommittee considered that patients rendered postmenopausal through the use of LHRH agonists should be included in the Special Authority criteria based on extrapolation of the PALOMA-3 data. Members considered that an additional 10-15% of patients may undergo this type of hormonal manipulation with LHRH agonists to access palbociclib, however given the demographics of the breast cancer population this would likely be limited to only younger patients with high risk disease.

9.36. The Subcommittee considered that the results of the PALOMA-3 trial, which investigated the efficacy of palbociclib in combination with fulvestrant in the second-line, were promising however, considered the data is currently immature and should be reviewed once mature published data becomes available. The Subcommittee considered that, while fulvestrant was not currently funded in New Zealand, if fulvestrant were to be Medsafe approved and both agents were listed on the Schedule, that the Special Authority criteria for palbociclib should be reconsidered.

9.37. The Subcommittee considered that the cost-effectiveness of palbociclib was adversely affected by the relatively high price being sought by the supplier.

9.38. The Subcommittee considered that overall there was reasonable evidence of a modest effect from the use of palbociclib in combination with a non-steroidal aromatase inhibitor as a first-line treatment for postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

10. Trastuzumab emtansine for HER-2 positive metastatic breast cancer after prior trastuzumab and a taxane treatment

Recommendation

10.1. The Subcommittee **recommended** that trastuzumab emtansine be funded with medium priority for the treatment of HER-2 positive metastatic breast cancer patients who have received prior treatment with trastuzumab and a taxane, separately or in combination, subject to the following Special Authority criteria:

> TRASTUZUMAB EMTANSINE- Special Authority for Subsidy – PCT only
> Initial - only from a relevant specialist or medical practitioner or on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
>
> All of the following:

1. Patient has metastatic breast cancer expressing HER-2 IHC 3+ or ISH+ including FISH or other current technology); and
2. Patient has previously received trastuzumab and a taxane, separately or in combination; and
3. Either
    3.1. The patient has received prior therapy for metastatic disease*; or
    3.2. The patient developed disease recurrence during, or within six months of completing adjuvant therapy*; and
4. Patient has not received prior treatment with pertuzumab; and
5. Patient has a good performance status (ECOG 0-1); and
6. Patient has left ventricular ejection fraction of 50% or more; and
7. Patient does not have symptomatic brain metastases; and
8. Treatment to be discontinued at disease progression.

Renewal – only from a relevant specialist or medical practitioner or on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:
1. The cancer has not progressed at any time point during the previous approval period whilst on trastuzumab emtansine; and
2. Treatment to be discontinued at disease progression.

Note: Prior or adjuvant therapy includes anthracycline, other chemotherapy, biological drugs other than trastuzumab, or endocrine therapy.

10.2. The Subcommittee **recommended** that trastuzumab emtansine for the treatment of HER-2 positive metastatic breast cancer patients who have previously received trastuzumab in combination with pertuzumab be deferred pending further evidence to support its use in this setting.

Discussion

10.3. The Subcommittee noted that In November 2017 PTAC considered the application for trastuzumab emtansine and recommended it be funded with low priority for the second-line treatment of patients with HER-2 positive metastatic breast cancer (mBC) who have previously received trastuzumab and a taxane, separately or in combination.

10.4. The Subcommittee noted that PTAC had also recommended that the application be referred to the Cancer Treatments Subcommittee for advice regarding the likely benefit for patients previously treated with pertuzumab, impact on quality of life, appropriate place and sequence in New Zealand treatment settings, estimated patient numbers, and proposed access criteria.

10.5. The Subcommittee noted that PTAC considered there was reasonable evidence, although only from open-label studies, of some survival benefit in those patients previously treated with trastuzumab in the first-line setting. However, PTAC had noted there was little evidence that supported its use in a pertuzumab/trastuzumab pre-treated mBC population.

10.6. The Subcommittee noted that the health need of patients with HER-2 positive mBC was well described in the November 2017 PTAC minute.

10.7. The Committee noted that trastuzumab emtansine is a HER2-targeted antibody-drug conjugate that contains trastuzumab linked to microtubule inhibitory DM1 (together referred to as TDM1). The Committee noted that the mechanism of action includes trastuzumab binding of the HER-2 receptor, internalisation, and degradation which releases DM1 leading to cell death.

10.8. The Committee noted that the primary evidence for the use of trastuzumab emtansine for the treatment of HER-2 positive mBC was from two open-label, phase 3 studies: TH3RESA and EMILIA; and three phase 2 studies TDM4374g, TDM4258g, and JO22997.

10.9. The Subcommittee noted the TH3RESA study (Krop et al. Lancet Oncol 2017;18:743-54) was a study of trastuzumab emtansine (n=404) vs treatment of physicians choice (including chemotherapy, HER-2 directed therapy, and hormonal therapy, n=198) in patients with HER2-positive advanced breast cancer previously treated with both trastuzumab and lapatinib (advanced setting) and a taxane (any setting) and with progression on two or more HER2-directed regimens in the advanced setting.

10.10. The Subcommittee considered that as patients in the TH3RESA study had received at least two prior regimens of HER-2 directed therapy, with a median of 4 prior lines of therapy, this population was of limited relevance to a New Zealand setting.

10.11. The Subcommittee noted that after a median follow-up of 30.5 months, median overall survival (OS) was 22·7 months [95% CI 19·4-27·5] in the trastuzumab emtansine arm vs 15·8 months [13·5-18·7] in the physician's choice arm; hazard ratio 0·68 [95% CI 0·54-0·85]; p=0·0007). The Subcommittee considered a 6.9 month difference would be clinically significant, and that the magnitude of benefit may be substantially higher given the high (47%) crossover to the trastuzumab emtansine arm after progression on standard physicians choice chemotherapy.

10.12. The Subcommittee noted that the median duration of treatment with trastuzumab emtansine was 5.3 months and that no significant adverse events were reported. The Subcommittee noted that quality of life data for patients on TH3RESA favoured trastuzumab emtasine over the physician's choice chemotherapy and seemed durable.

10.13. The Subcommittee noted the pivotal evidence comes from the EMILIA study (Dieras et al Lancet Oncol 2017;18:732-42); a study of trastuzumab emtansine (3.6 mg/kg intravenously every 3 weeks) compared with capecitabine (1000 mg/m² self-administered orally twice daily on days 1–14 on each 21-day cycle) plus lapatinib (1250 mg orally once daily on days 1–21) in 991 men and women aged 18 years of older with HER-2 positive unresectable, locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane.

10.14. The Subcommittee noted that exclusion criteria included grade 3 or worse peripheral neuropathy, symptomatic CNS metastases, previous treatment with trastuzumab emtansine, lapatinib, or capecitabine, or hormonal therapy in the 7 days before randomisation or non-hormonal anticancer, biological, or investigational treatment in the 21 days before randomisation. The Subcommittee considered the population in EMILIA was of more relevance to a New Zealand setting given patients had received only prior treatment with trastuzumab and a taxane.

10.15. The Subcommittee noted that the protocol for EMILIA was amended to allow patients in the control arm to crossover, if they met the original study eligibility criteria for treatment with trastuzumab emtansine, after the efficacy boundary for OS was crossed. The Subcommittee noted that patients in the trastuzumab emtansine arm were not allowed to crossover but could receive control study treatment as post-progression therapy.

10.16. The Subcommittee noted that the Dieras et al 2017 publication reported final results at a median follow-up of 41.9 months (IQR 34.6-50.7) in the control group and 47.8 months (IQR41.9-55.5) in the trastuzumab emtansine group. The Subcommittee noted that median OS in the ITT population was 25.9 months (95% CI 22.7–28.3) in the control group vs. 29.9 months (95% CI 26.3–34.1) in the trastuzumab emtansine group (hazard ratio 0.75, 95% CI 0.64–0.88).

10.17. The Subcommittee noted that 136 (27%) of 496 patients crossed over from control to trastuzumab emtansine after the second interim OS analysis (median follow-up duration

24.1 months [IQR 19.5–26.1]) and subsequent protocol amendment; and that median OS in the control group censored at crossover was 24.9 months (95% CI 0.59-0.82).

10.18. The Subcommittee considered that the 4.0 month survival difference was statistically significant and demonstrated despite, a high level of crossover and further lines of treatment beyond study; which created uncertainty regarding the exact magnitude of benefit patients would receive (i.e it may be larger) but supported the strength of the data.

10.19. The Subcommittee noted that PTAC had queried that the reason for exclusion of 10% of patients in THERESA and EMILIA, however CaTSoP considered that the protocols described in publications detailed a reasonable and appropriate approach to screening inclusion and exclusion.

10.20. The Subcommittee considered that there was only very limited weak and poor quality evidence to support the use of trastuzumab emtansine in a previously pertuzumab pretreated population.

10.21. The Subcommittee considered that overall there was insufficient data to support the use of trastuzumab emtansine in a pertuzumab pretreated population and although there may be a biological rationale for it use in this setting this was not well discussed in the literature.

10.22. The Subcommittee considered that while there were quality issues with the currently available evidence it did support the use of trastuzumab emtansine for the treatment of patients who had received prior treatment with trastuzumab and a taxane without pertuzumab and that for patients who did respond to treatment the benefit would likely be similar to that observed in EMILIA and therefore clinically meaningful.

10.23. The Subcommittee considered that as there was a diminishing pool of around 100 patients with these clinical circumstances given that all newly diagnosed mBC patients would be treated with pertuzumab in a first line setting.