PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 20 & 21 August 2020 via Videoconference

Present:

PTAC members:
Mark Weatherall (Chair)
Marius Rademaker (Deputy Chair)
Alan Fraser
Brian Anderson
Bruce King
Elizabeth Dennett
Giles Newton Howes
Jane Thomas
Jennifer Martin
Lisa Stamp
Matthew Strother
Rhiannon Braund
Sean Hanna
Simon Wynn Thomas
Stephen Munn
Tim Stokes

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Chair

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1. The role of PTAC, PTAC Subcommittees and meeting records

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

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

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

1.4. PTAC and PTAC Subcommittees have complementary roles, expertise, experience, and perspectives. PTAC may therefore, at times, make recommendations that differ from PTAC Subcommittees', including the priority assigned to recommendations, when considering the same evidence. Likewise, PTAC Subcommittees may, at times, make recommendations that differ from PTAC's, or from other PTAC Subcommittees', when considering the same evidence.

PHARMAC considers the recommendations provided by both PTAC and PTAC Subcommittees when assessing applications.

2. Cancer Treatment Subcommittee Record

2.1. The Committee noted the record of the Cancer Treatments Subcommittee of PTAC (CaTSoP) held on 3 July 2020.

2.2. The Committee reported no new conflicts of interest with regard to this agenda item.

2.3. In regards to item 4, and consideration of azacitidine access widening:

2.3.1. The Committee noted that in 2010, PTAC and CaTSoP had considered the application for azacitidine for intermediate-2 or high risk Myelodysplastic Syndromes (MDS), Chronic Myelomonocytic Leukaemia (CMML) or Acute Myeloid Leukaemia (AML) and **recommended** that it be funded with a low priority. The Committee noted that azacitidine has been funded for MDS, CMML and AML subject to Special Authority criteria since 2014.

2.3.2. The Committee noted that the use of azacitidine has become the standard of care internationally for both therapy related MDS and AML for patients with a blast count above 30% and that generally other agents are added on to azacitidine for the treatment of this patient group.

2.3.3. The Committee acknowledged the Subcommittee's discussion regarding the widening of access to azacitidine for the treatment of patients with therapy-related MDS/AML, and noted the Subcommittee's recommendation to widen such access with a high priority. The Committee noted that Māori have an increased prevalence and risk of AML compared with New Zealand Europeans.

2.3.4. The Committee noted the Subcommittee's consideration that patients with therapy-related MDS/AML were excluded from the clinical trials for azacitidine and that this contributed to the lack of evidence in this population.

2.3.5. The Committee considered there to be significant uncertainty regarding the strength and quality of evidence present to support a benefit of treatment with azacitidine in patients with therapy-related MDS/AML. Given this, the Committee

considered it was uncertain what had led to the high priority recommendation from the Subcommittee for the use of azacitidine in this population.

2.3.6. The Committee acknowledged the Subcommittee's discussion regarding the widening of access to azacitidine for the treatment for patients with a blast count above 30% and noted the Subcommittee's recommendation to widen such access with a high priority.

2.3.7. The Committee noted the evidence cited in the record to support a benefit of azacitidine treatment for patients with a blast count above 30% and a reduction in transfusion requirements. The Committee considered there to be significant uncertainty regarding the survival benefit and quality of life improvement that could be obtained from treatment with azacitidine for this population.

2.4. In regards to item 5, and consideration of gemtuzumab ozogamicin and midostaurin for acute myeloid leukaemia:

2.4.1. The Committee noted that Māori have an increased prevalence and risk of AML compared to New Zealand Caucasians.

2.4.2. The Committee noted the Subcommittee's recommendation to fund gemtuzumab-ozogamicin with a high priority and acknowledged CaTSoP's discussion of gemtuzumab-ozogamicin for the treatment of patients with favourable and intermediate cytogenetic risk AML.

2.4.3. The Committee noted the results of the ALFA-0701 trial (Lambert et al. Haematologica. 2019;104:113-9) and the Hills et al. meta analysis (Hills et al. Lancet Oncol. 2014;15:986-96) which indicated an event free survival improvement for gemtuzumab-ozogamicin compared with standard chemotherapy for the treatment of patients with intermediate or favourable cytogenetic risk AML. The Committee considered there to be uncertainty regarding the overall survival and health related quality of life benefit for gemtuzumab-ozogamicin compared with standard chemotherapy in this population.

2.4.4. The Committee noted the Subcommittee's recommendation to fund midostaurin with a high priority and acknowledged CaTSoP's discussion of midostaurin for the treatment of patients with FLT3 mutation positive AML

2.4.5. The Committee noted the results of the RATIFY trial (Stone et al. N Engl J Med. 2017;377:454-64) which indicated an event free survival improvement for midostaurin compared with standard chemotherapy for the treatment of patients with FLT3 mutation positive AML. The Committee considered there to be uncertainty regarding the overall survival and health related quality of life benefit for midostaurin compared to the standard chemotherapy for the treatment of FLT3 mutation positive AML.

2.4.6. The Committee considered that based on the available evidence that there was a greater survival benefit for midostaurin than that of gemtuzumab-ozogamicin. However, the Committee noted the higher relative priority consideration by CaTSoP for gemtuzumab-ozogamicin compared to midostaurin on the basis that gemtuzumab ozogamicin would result in benefits for a wider population of patients with AML.

2.5. In regards to item 6, and consideration of atezolizumab for the treatment of first-line non-small cell lung cancer (NSCLC) as monotherapy and combination therapy:

2.5.1. The Committee noted that application for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of NSCLC had been previously considered by CaTSoP in April 2019 and recommended for decline noting that the currently available evidence was insufficient to support a positive recommendation for the specific combination regimens at that time.

2.5.2. The Committee noted that additional information had been provided by the supplier including additional data from a number of trials including the Impower150 trial and a recent expert review of the first-line atezolizumab combination regimen (Reck et al. Expert Rev Respir Med. 2020;14:125-136).

2.5.3. The Committee considered that the totality of currently available evidence, including the additional information provided, was not sufficient to support a positive recommendation and agreed with CaTSoP's recommendation to decline. The Committee considered there remained uncertainty regarding what benefit the specific combination regimen applied for would provide and it was still not possible to compare the value of the addition of bevacizumab from the data provided to date. The Committee considered that, while it could not support the specific regimen applied for, there did appear to be a class effect when comparing different immune checkpoint inhibitors in combination with chemotherapy regimens for the treatment of advanced NSCLC.

2.5.4. The Committee noted that application for atezolizumab monotherapy for the first-line treatment of metastatic squamous and non-squamous NSCLC with high expression of PD-L1 had been considered by CaTSoP in July 2020; and had been recommended with high priority. The Committee acknowledged CaTSoP's consideration of a class effect with the use of PD1/PD-L1 agents in the treatment of advanced NSCLC in making this recommendation.

2.5.5. The Committee noted that both PTAC and CaTSoP had previously considered pembrolizumab for the same population; and that had recommended funding with medium and high priority respectively.

2.5.6. The Committee noted CaTSoP's further discussion of the issues related to PD-L1 testing, including the dynamic nature of this biomarker and the need for standardisation to enable targeting of treatment to the population who would benefit most.

2.5.7. The Committee considered that there remained ongoing concerns regarding the implementation of appropriate and equitable testing to determine PD-L1 expression and in a way that would ensure consistency of results for patients regardless of treatment centre.

2.5.8. The Committee considered that the currently available evidence for atezolizumab monotherapy in the requested population was limited; and that particularly due to the different trial populations and PD-L1 stratification there were difficulties in comparing evidence across the class. However, the Committee considered that both itself and CaTSoP had previously noted a class effect for these agents in an advanced NSCLC population.

2.5.9. The Committee considered that it was unusual for a treatment to receive a high priority recommendation on the basis of unpublished evidence, however acknowledged that this priority took into account that there was a likely class effect in this setting and that other immune checkpoint inhibitors with published data in this setting had been previously considered and had received a high recommendation.

5.5.10 The Committee acknowledged that based on currently available evidence it appeared that the benefit from use of PD-1/PD-L1 agents as monotherapy was the same or similar across the class in the treatment of advanced NSCLC and a high PD-L1 expression population appeared to benefit most from the use of these agents.

2.6. In regards to item 7, and the review of immune checkpoint inhibitors for advanced NSCLC:

2.6.1. The Committee noted that CaTSoP considered it would be appropriate to determine whether to define a population eligible for funded access, by mandating PD-L1 testing or not in any access criteria, based on economic assessment of the most favourable cost-effectiveness taking into account the costs to the health system and implementation issues associated with PD-L1 testing as discussed in CaTSoP's July 2020 record and previous PTAC and CaTSoP records related to PD1/PD-L1 inhibitors.

2.6.2. The Committee considered that it was not clear from the drafting of the CaTSoP record that the Subcommittee's consideration of a difference in estimated median survival of three months (compared with comparator treatment) for NSCLC patients with antiPD1/PD-L1 agents irrespective of treatment line was in reference to an 'all comer' population (regardless of histology and biomarker status). The Committee considered that a high PDL1 expression subpopulation would have a larger gain than this.

2.7. The Committee noted and agreed with the Subcommittee's recorded considerations and recommendations regarding the remaining items of the July 2020 meeting.

2.8. The Committee noted that PTAC and PTAC Subcommittees may differ in the advice they provide to PHARMAC, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives, and that PHARMAC would take into consideration both committees' point of view in its assessment of this application.

3. Rituximab for membranous nephropathy

Application

3.1. The Committee reviewed the application for rituximab for the treatment of membranous nephropathy.

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

Recommendation

3.3. The Committee **recommended** that rituximab for the treatment of membranous nephropathy in the first line in patients at a high risk of progression to end stage renal disease despite conservative measures be funded with a high priority, subject to the following Special Authority Criteria:

Restricted
Indication – Membranous nephropathy
Nephrologist or practitioner on the recommendation of a nephrologist. Approvals valid for 6 weeks.
All of the following:

1. Patient has biopsy-proven primary/idiopathic membranous nephropathy*; and
2. Patient remains at high risk# of progression to end-stage kidney disease despite more than 3 months of treatment with conservative measures^; and
3. The total rituximab dose would not exceed the equivalent of 375mg/m^2 of body surface area per week for a total of 4 weeks.

high risk of progression to end-stage kidney disease (e.g. defined as >5g/day proteinuria and creatinine clearance (estimated glomerular filtration rate (eGFR)) ≥ 40 ml/min/1.73 m^2)
^conservative measures include renin-angiotensin system blockade, blood-pressure management, dietary sodium and protein restriction, treatment of dyslipidaemia, and anticoagulation agents.

Continuation – Membranous nephropathy
Nephrologist or practitioner on the recommendation of a nephrologist. Approvals valid for 6 weeks.
All of the following:

1. Patient was previously treated with rituximab for membranous nephropathy*; and
2. Treatment with rituximab was previously successful, but the condition has relapsed, and the patient now requires repeat treatment; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/m² of body surface area per week for a total of 4 weeks.

Note: Indications marked with * are unapproved indications.

3.4. The Committee **recommended** that rituximab for the treatment of membranous nephropathy in patients at a high risk of progression to end stage renal disease despite conservative measures, and/or at a high risk of adverse events from immunosuppressive agents, and/or for patients where alternative treatment regimens have resulted in inadequate response or intolerable side effects, be funded with a high priority, subject to the following Special Authority criteria:

Restricted
Indication –Refractory membranous nephropathy
Nephrologist or practitioner on the recommendation of a nephrologist. Approvals valid for 6 weeks.
All of the following:

1. Patient has biopsy-proven primary/idiopathic membranous nephropathy*; and
2. Treatment with corticosteroids for at least a period of 3 months has been ineffective or associated with evidence of corticosteroid toxicity; and
4. Treatment with ciclosporin and/or tacrolimus for at least a period of 3 months has been ineffective or discontinued due to intolerable or unacceptable side effects; and
5. Treatment with cyclophosphamide for at least a period of 3 months has been ineffective or discontinued due to intolerable or unacceptable side effects; and
3. The total rituximab dose would not exceed the equivalent of 375mg/m^2 of body surface area per week for a total of 4 weeks.

Continuation – Refractory membranous nephropathy
Nephrologist or practitioner on the recommendation of a nephrologist. Approvals valid for 6 weeks.
All of the following:

1. Patient was previously treated with rituximab for membranous nephropathy*; and
2. Treatment with rituximab was previously successful, but the condition has relapsed, and the patient now requires repeat treatment; and
3. The total rituximab dose used would not exceed the equivalent of 375 mg/m² of body surface area per week for a total of 4 weeks.

Note: Indications marked with * are unapproved indications.

3.5. In making the above recommendations, the Committee considered the high health need of this patient group, the suitability of rituximab based on its favourable safety profile compared with current immunosuppressive treatment options, and the evidence supporting a reduction in proteinuria following treatment.

3.6. The Committee considered that, although the evidence for rituximab for the treatment of membranous nephropathy comes primarily from its use as a first-line treatment, nonetheless the higher complete or partial remission rate at 2 years, the lower relapse rate compared with immunosuppressive agents and/or calcineurin inhibitors, and the higher health need of these patients (compared with first-line setting) also supports use of rituximab in a second-line setting following inadequate response or intolerable side effects from immunosuppressive agents.

Discussion

3.7. The Committee noted the clinician application for the use of rituximab in the treatment of membranous nephropathy for adult patients at high risk of developing end stage renal

disease (ESRD) despite conservative measures, including those at high risk of adverse events from immunosuppressive therapy or who are intolerant to currently available treatments.

3.8. The Committee considered that the application specified rituximab for use in patients at high risk of adverse events from immunosuppressive treatments, and/or in patients where immunosuppressive treatment regimens have resulted in inadequate response or intolerable side effects. However, the Committee considered that the available evidence supports the use of rituximab in a first-line setting following trial of conservative measures. The Committee considered that the different lines of therapy should therefore be considered separately when making any recommendations.

3.9. The Committee considered that early intervention with rituximab may better control disease progress and reduce onset of disease related complications (including ESRD), as opposed to later use of rituximab as an organ rescue treatment.

3.10. The Committee noted the estimated incidence of membranous nephropathy is between 8-10 cases per million population worldwide. The incidence in New Zealand is unknown but there may be about 16 incident cases per year. The Committee noted that spontaneous recovery occurs in approximately 30% of membranous nephropathy patients. For those who continue to experience symptoms, 40-50% are expected to develop ESRD over a period of 10 years.

3.11. The Committee noted that ESRD may lead to renal failure requiring dialysis (with an associated impact on overall survival) or kidney transplant, which both come at a significant cost to the health system. The Committee also noted that New Zealand has a comparatively low kidney donation rate compared with other countries. Treatments that effectively reduce the need for renal transplantation are therefore particularly relevant to New Zealand.

3.12. The Committee noted that anti-PLA2R circulating antibodies are present in approximately 70% of the membranous nephropathy population, although the diagnosis of membranous nephropathy is based primarily on clinical presentation. The Committee also noted, however, that anti-PLA2R antibodies can be used as a confirmatory diagnostic technique and to assess treatment effectiveness.

3.13. The Committee noted that rituximab is a monoclonal antibody that binds specifically to the CD20 surface antigen on B-cells, with this initiating immunologic reactions, induces cell death by apoptosis and depletion of CD20 positive B-cells, which result in decreased subendothelial immune deposits in the glomeruli of the kidney. The Committee noted that dysfunctional B-cells play a role in the pathogenesis of membranous nephropathy, with the resultant B-cell depletion responsible for rituximab's therapeutic effect.

3.14. The Committee noted that the current treatment paradigm for patients with membranous nephropathy begins with conservative measures including renin-angiotensin system blockade, blood-pressure management, dietary sodium and protein restriction, treatment of dyslipidaemia, and treatment with anticoagulation agents. The Committee noted that response following conservative measures alone occurs in approximately 10% of membranous nephropathy patients.

3.14.1. The Committee also noted that patients presenting with a moderate to high risk of disease progression, and deteriorating kidney function despite conservative measures, are initiated on immunosuppressant therapies and corticosteroids, with the Ponticelli regimen (cyclophosphamide, corticosteroids) considered the most widely used treatment regimen. The Committee considered that the Ponticelli regimen is the appropriate comparator for rituximab in this indication.

3.14.2. The Committee noted that the currently available immunosuppressant treatments for membranous nephropathy, though effective, are typically associated with potentially severe adverse effects and are therefore poorly tolerated and often discontinued. The Committee noted that cyclophosphamide with corticosteroids, whilst effective in 60-70% of patients, has been linked with an increased risk of cancer, hyperglycaemia, infection, myelosuppression, thromboembolism, haemorrhagic cysts, infertility, and increased hospitalisation. The Committee also noted that whilst treatment with calcineurin inhibitors (ciclosporin or tacrolimus) are effective, these are similarly associated with adverse effects such as hypertension and risk of nephrotoxic effects further reducing kidney function with persistence beyond treatment discontinuation.

3.14.3. The Committee noted that patients who are not able to tolerate immunosuppressants may be treated with mycophenolate mofetil or adrenocorticotropic hormone (ACTH); however, the Committee considered there to be limited evidence supporting the use of these agents, with use throughout New Zealand unclear.

3.15. The Committee noted the evidence from an open-label, randomised controlled trial that compared the use of corticosteroids and cyclophosphamide with supportive therapy (dietary sodium restriction, diuretics and antihypertensive agents excluding renin-angiotensin system blockade) in adults with nephrotic syndrome caused by idiopathic membranous nephropathy (Jha et al. J Am Soc Nephrol. 2007;18(6):1899-904). The Committee noted that initial remission (defined as complete when proteinuria declined to <200 mg/d on at least three occasions, and partial when proteinuria was >200 mg/d but <2 g/d or <50% of baseline) was achieved within one year of randomisation in 29% of the treatment group and 9% of the supportive therapy group, and that relapses occurred in 25% of participants in each treatment group, which were subsequently managed by renin-angiotensin system blockade. The Committee noted that complete remission at ten years was achieved in 25% of the control group and 59% of the treatment group, and that 45% of the control group required dialysis treatment compared with 11% of the treatment group. However, the Committee considered that poor endpoints, and proportion of patients lost to follow-up and/or dropping out of the study, impacted the overall robustness and validity of the trial.

3.16. The Committee noted the evidence from a randomised, open-label, multicentre study (n=95) comparing methylprednisolone plus chlorambucil with methylprednisolone plus cyclophosphamide for the treatment of idiopathic membranous nephropathy (Ponticelli et al. J Am Soc Nephrol. 1998;9(3):444-50). The Committee noted that either chlorambucil or cyclophosphamide with corticosteroids protected renal function, and that there was no meaningful difference in effect between agents. The Committee considered that this regimen (Ponticelli regimen) is the current standard of care.

3.17. The Committee noted that use of ciclosporin versus cyclophosphamide had been noted by the applicant to vary dependent on patient characteristics and patient-clinician preferences. The Committee noted that cyclophosphamide is predominantly used in New Zealand, Australia, and Europe, while ciclosporin is used predominantly in North America.

3.18. The Committee noted a report by Kidney Disease: Improving Global Outcomes (KDIGO) summarising the evidence available for studies that have investigated cyclophosphamide with corticosteroids in the treatment on membranous nephropathy (Rojas-Rivera et al. Clin Kidney J. 2019;12(5):629-38). The Committee noted that induction of complete remission had occurred in approximately 20-25% of patients at 24 months, and that complete remission had occurred in approximately 30-35% of patients in the 40 to 60-month follow-ups.

3.19. The Committee noted a meta-analysis of 36 randomised controlled trials comparing the effectiveness and tolerance of immunosuppressive treatments (cyclophosphamide versus

ciclosporin A or tacrolimus) for idiopathic membranous nephropathy (Ren et al. PLoS One. 2017;2(9):e0184398). The Committee noted that overall, immunosuppressant treatment was more effective at managing membranous nephropathy than non-immunosuppressive treatment, with no meaningful differences in the probability of remission between ciclosporin A and cyclophosphamide, noting drug withdrawal was more likely with cyclophosphamide than with ciclosporin A or tacrolimus. The Committee noted that the evidence for treatment with calcineurin inhibitors beyond 12-18 months is lacking, however this treatment remains common in the USA. The Committee noted that the relapse rate with immunosuppressants is approximately 25%.

3.20. The Committee noted the results from an open label, randomised, multi-centre, non-inferiority, phase III trial (MENTOR trial, n=130), in which patients with membranous nephropathy with proteinuria of 5 g/day despite at least 3 months of renin-angiotensin system blockade, and a glomerular filtration rate (eGFR) of at least 40 mL/min/1.73 m2 were treated for 12 months with either rituximab (1000 mg IV on days 1 and 15, repeated at 6 months in the event of partial remission) or dose-adjusted ciclosporin, where the primary outcome was a composite of complete or partial remission of proteinuria at 24 months (Fervenza et al. N Eng J Med. 2019;381(1):36-46). The Committee considered proteinuria to be a well-established and useful surrogate marker for ESRD.

3.21. The Committee noted that 39/65 patients (60%) in the rituximab group and 34/65 (52%) in the ciclosporin A group achieved complete or partial remission at 12 months (P<0.004), and that 23 rituximab patients (35%) and no ciclosporin A patients achieved complete remission at 24 months. The Committee noted that 26 patients (40%) of the rituximab group and 52 patients (80%) of the ciclosporin group experienced treatment failure by 24 months (hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.21 to 0.54). The Committee noted that the rate of treatment failure for the rituximab group was approximately 5%, compared to 62% in the ciclosporin group during the 12-month observation period (HR 0.05, 95% CI 0.01 to 0.23). The Committee noted that serious adverse events were less common with rituximab, occurring in 11/65 patients (17%) versus 20/65 (31%) in the ciclosporin A group (P=0.06), and that kidney function was better preserved in the rituximab group. The Committee noted that the decline in anti-PILA2R antibodies was faster and of greater magnitude in rituximab group, which reflected improvement in clinical presentation

3.22. The Committee noted however that the trial did not include the use of cyclophosphamide or corticosteroids, which would be relevant for comparison with the New Zealand membranous nephropathy patient population, and that baseline eGFR differed between the two treatment groups. The Committee considered the definitions of partial and complete response to be unclear, and that response rates for patients treated with immunosuppressants plateau after 4 years and considered that a 2-year follow-up study may be too short to glean clinically meaningful longer-term results. The Committee also noted that there is no evidence for the use of rituximab following immunosuppressive therapy.

3.23. The Committee noted a retrospective, observational cohort study (n=103) in which the safety of rituximab was compared with corticosteroids and cyclophosphamide in the treatment of membranous nephropathy (van den Brand et al. J Am Soc Nephrol. 2017;28(9):2729-37). The Committee noted that there were fewer adverse events in the rituximab treatment group, in both serious (11 vs. 46, adjusted HR 0.32, 95% CI 0.15-0.68) and non-serious (52 vs. 127, adjusted HR 0.23, 95% CI 0.13-0.41) adverse events. The Committee noted that rates of complete remission and the composite renal end point did not differ between groups.

3.24. The Committee noted that there are currently two clinical trials underway investigating the use of rituximab compared with other treatments for membranous nephropathy:

3.24.1. The RI-CYCLO study of rituximab versus corticosteroids and cyclophosphamide in the treatment of idiopathic membranous nephropathy (ClinicalTrials.gov identifier: NCT03018535)

3.24.2. The STARMEN study, a European multicentre and open-label controlled randomised trial to evaluate the efficacy of sequential treatment with tacrolimus-rituximab versus corticosteroids plus cyclophosphamide in patients with primary membranous Nephropathy (Rojas-Rivera et al. Clin Kidney J. 2015;8(5):503-10, ClinicalTrials.gov Identifier: NCT01955187).

3.24.3. The Committee considered that the results from these trials may provide more robustness to the evidence for the use of rituximab in the treatment of membranous nephropathy.

3.25. The Committee considered that funding rituximab for the treatment of membranous nephropathy may increase DHB associated costs secondary to the requirement for multiple hospital based infusions, but considered that there would also likely be cost offsets associated with a delay in the requirement for management of complications due to nephrotic syndrome, and renal replacement therapy as a result of rituximab treatment. The Committee considered that duration of response with rituximab after 2 years is unknown and it is unclear if patients would require re-treatment after this time.

4. Adjuvanted quadrivalent influenza vaccination for people aged 65 years and over

Application

4.1. The Committee reviewed the application from Seqirus (NZ) Ltd for adjuvanted inactivated quadrivalent influenza vaccine (aQIV) for use in people aged 65 years and over.

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

Recommendation

4.3. The Committee **recommended** that adjuvanted inactivated quadrivalent influenza vaccine (aQIV) for use in people aged 65 years and over be declined, due to low quality evidence of benefit for aQIV over an unadjuvanted quadrivalent influenza vaccine (QIV).

Discussion

4.4. The Committee noted that those most at risk of developing complications from seasonal influenza are: people aged 65 years and over, people of any age with comorbidities, and pregnant women. The Committee noted that those populations and children who have had respiratory hospital admissions are eligible for the currently funded unadjuvanted quadrivalent influenza vaccination.

4.5. The Committee noted that the currently available unadjuvanted quadrivalent influenza vaccine (QIV) includes 2 A strains and 2 B strains of the influenza virus. The Committee noted that influenza immunisation uptake is monitored by the Ministry of Health, however healthcare providers may provide private market immunisation, which may not always be included in national coverage data if a provider does not record the vaccination event in the National Immunisation Register.

4.6. The Committee noted that the aQIV vaccine under consideration is the currently funded influenza vaccine in Australia for those aged 65 years and over, and for all Aboriginal and Torres Strait Islander people. The Committee also noted that people aged 65 years and

over in the United Kingdom are eligible for funded adjuvanted trivalent influenza vaccination (aTIV), but not QIV or aQIV.

4.7. The Committee noted that the use of an adjuvant may increase the immunogenicity of a vaccine and may make it more effective in older people with immunosenescence. The Committee considered that an alternative approach to dealing with immunosenescence is to use vaccines with a higher antigen dose, but it had seen no head-to-head trials comparing high dose QIV against aQIV.

4.8. The Committee noted data presented from the Southern Hemisphere Influenza and Vaccine Effectiveness Research and Surveillance (SHIVERS) study, outlining the influenza burden per million people over one influenza season in the Auckland region. The Committee noted that over a single season 26% of the population are infected with influenza, and of those 20% are symptomatic, and of those 23% visit a GP. The Committee noted that if extrapolating from the SHIVERS data, there would be approximately 6 deaths, 23 stays in ICU, and 471 hospitalisations per million people each year in New Zealand from seasonal influenza.

4.9. The Committee noted that hospitalisation rates for influenza-positive severe acute respiratory infections (SARI) for 2020 have been almost nil. The Committee considered that this may be due less imported influenza, to the social distancing and isolation effects of the nationwide lockdown response for the COVID-19 pandemic on person-to-person transmission of all airborne infectious diseases, plus unprecedented levels of influenza vaccination for older adults and the Pacific population over a much shorter period of time than previous seasons.

4.10. The Committee noted two studies by Khieu et al. investigating hospitalisation and mortality incidence rates in New Zealand attributable to influenza from 1994 to 2008 (Khieu et al. Vaccine 2015;33:4087-92, Khieu et al. J Infect 2017;75:225-33). The Committee noted that the hospitalisation rate (62.4 per 100,000) and mortality rate (13.5 per 100,000) presented in these studies were appreciably higher than those in the SHIVERS data (hospitalisation 47.1 per 100,000 and mortality 0.6 per 100,000). The Committee considered that the mortality incidence presented by Khieu et al. was reasonable, and that mortality rates estimated from routine coded data (Ministry of Health, SHIVERS) is likely an underestimate of the population burden of disease.

4.11. The Committee noted that the Khieu studies reported marked ethnic and socioeconomic inequalities, particularly with hospitalisation rates and mortality. The Committee also noted that Māori and Pacific peoples are less likely to visit a GP for influenza-like symptoms and less likely to be vaccinated against influenza than people of European/Other decent. The Committee noted that Aboriginal and Torres Strait Islander people, Canadian and US indigenous populations show similar inequalities when compared with the Caucasian populations in those countries.

4.12. The Committee noted that the appropriate comparator for aQIV in New Zealand is QIV, but because there are no head-to-head trials of aQIV comparing with a QIV, the supplier had instead provided an indirect comparison with aTIV as the common comparator.

4.13. The Committee noted a phase III multi-centre, double-blind, randomised clinical trial that compared aTIV to aQIV using haemagglutination inhibition (HI) as a surrogate endpoint (Essink et al. Vaccine. 2020;38(2):242-50). The Committee noted that aQIV produced a similar immune response to aTIV against homologous influenza strains, and that the immune response against B strains was below the those of the FDA's Centre for Biologics Evaluation and Research (CBER) criteria. The Committee noted that this was presented by the supplier in the application as an unpublished report of a phase III multicentre, randomised, double-blind, controlled, clinical trial (V118_20, ClinicalTrials.gov Identifier: NCT03314662) of safety and immunogenicity of aQIV compared with aTIV in elderly

adults (n=1778). The Committee considered that there was a low risk of bias in the trial, and that aQIV was shown to be non-inferior to aTIV for safety and immunogenicity.

4.14. The Committee noted a prospective, non-experimental cohort study (n=107,661, 170,988 person-years) in a community setting (excluding residents of aged-care facilities) comparing aTIV with unadjuvanted TIV in northern Italy (Mannino et al. Am J Epidemiol. 2012; 176(6):527-33). The Committee noted that the primary endpoint was the incidence of hospitalisation for influenza or pneumonia across three consecutive influenza seasons, which were assessed over three time periods around peak influenza incidence (narrow, intermediate, and broad). The Committee noted that the study was limited by not using PCR or culture to confirm influenza but rather measured rates of hospitalisations corresponding to the influenza seasons as a surrogate indicator for influenza. The Committee also noted that the administration of aTIV versus TIV was not randomised and that the aTIV was given to a frailer population with more comorbidities, as per local guidelines, hence introducing a potentially large selection bias.

4.14.1. The Committee noted that Mannino study used a propensity score to adjust for multiple confounders, and that several variables used in the derivation of the propensity score had also been used as explanatory variables in their multivariate model. The Committee noted that adjusting for the same confounders twice may lead to error.

4.14.2. The Committee also noted that for the narrow time window (the period of adjacent weeks having an influenza rate of >1 case per 1000 person-weeks) the adjusted odds ratio (OR) was 0.75 (95% CI, 0.57 to 0.98) for aTIV relative to TIV with a point estimate of vaccine efficacy of 25%, but that while for the other time windows aTIV was also favoured, the point estimates of relative effectiveness for these longer time windows were less and were not statistically significant (OR 0.83, 95% CI, 0.68 to 1.03 for the intermediate time window; OR 0.88, 95% CI, 0.76 to 1.02 for the broad time window). All the point estimates were associated with wide confidence intervals with the upper confidence limits being close to or crossing a boundary, consistent with no effect.

4.14.3. The Committee noted the intermediate time window odds-ratio (OR) of 0.83 (95% CI, 0.68 to 1.03) was that used by the supplier to inform reduced hospitalisations from aQIV vs QIV. The Committee noted the limitations of the estimate, where the OR was not statistically significant (as the confidence interval crossed null), and that the Mannino et al. study had a number of other methodological flaws that might lead to a bias favouring aTIV, and further that this was not the same comparator for New Zealand, in relation to TIV versus QIV. The Committee considered that the intermediate time window OR would be more appropriate to use in PHARMAC's modelling of reductions in hospitalisations and other morbidity, relative to any potential use of the narrow time window estimate of 0.75 (95% CI, 0.57 to 0.98), as the intermediate time window is more conservative and where a conservative approach would be recommended in light of the poor quality of evidence; but that sensitivity analysis could incorporate the other time windows.

4.15. The Committee noted four other studies identified by the supplier that compared the relative effectiveness of aTIV compared to TIV:

4.15.1. Gravenstein et al. Unpublished -IDWeek Abstract 996. 2018: reporting a prospective open-label cluster randomised controlled trial (n=50,012 total participants) for those aged 65 years or older living in a nursing home for at least 100 days. In all, 411 US nursing homes were reported to be randomised to provide aTIV as standard of care for their residents, with 409 nursing homes randomised to provide TIV as standard of care. There were three primary outcomes for the study, of which the first listed was time to any hospitalisation.

The Committee noted that the unadjusted hazard ratio (HR) for all-cause hospitalisations was 0.94 (95% CI 0.88 to 1), P=0.05 for aTIV relative to TIV. The incidence of all-cause hospitalisation was 18.8% in the aTIV group and 20.0% in the TIV group, consistent with a point estimate for relative vaccine effectiveness of 6% greater than TIV. The Committee considered the trial reporting to date, as a conference abstract, was inadequate to reasonably assess the study's validity, including (but not confined to) that there was no description of randomisation methods, and overall a lack of sufficient methodological description in the poster. The Committee also noted that the description of the cohort characteristics was incomplete, and considered the likely more elderly and morbid population seen in American nursing homes was unlikely to be reflective of the whole New Zealand 65+ years population, so considered the results would not be relevant to a New Zealand population at this stage, pending the full publication of the study, including patient characteristics and other features necessary for reasonable interpretation of internal validity and then generalisation to the New Zealand funding setting.

4.15.2. Iob et al. Epidemiol Infect. 2005;133(4):687-93: a prospective non-experimental study (n=3173) of residents of long-term care facilities, aged mostly 65 and over in which the primary endpoint was incidence of influenza-like-illness (ILI). The Committee noted that the OR for any vaccination was 0.56 (95% CI, 0.45 to 0.68) with a point estimate relative any vaccine effectiveness of 44%. The Committee considered that the study's analysis of results was incorrect as it had failed to adjust for individuals clustered within residential care facilities and so the study, when properly analysed from the reported summary data, had no evidence of a difference between residents who had or had not received any vaccination (recalculated OR 0.83 (95% CI 0.58 to 1.12), P=0.31). The assessment of the validity of the comparison of aTIV versus TIV not only did not take account of clustering but variably included or excluded care facilities from the analysis. As a result of these issues with the analysis in this study, the Committee considered that it could not be used for modelling purposes.

4.15.3. van Buynder et al. Vaccine. 2013;31(51):6122-8: a small prospective case control study (n=282) of patients aged 65 years and older, with a primary endpoint of incidence of laboratory confirmed influenza over a single influenza season. The Committee noted that the odds ratio for aTIV relative to TIV was 0.37 (95% CI, 0.14 to 0.96) with a point estimate for relative vaccine effectiveness of 63%. The Committee noted that influenza seasons can differ greatly from year to year, and that observing only one influenza season may not be as effective as longer-term, multi-season studies.

4.15.4. Lapi et al. Expert Rev Vaccines. 2019;18(6):663-70: a retrospective case control study (n=43,000) of patients aged 65 years or older, with a primary endpoint of hospitalisation from influenza associated complications. The Committee noted that the odds ratio for aTIV relative to TIV was 0.61 (95% CI, 0.39 to 0.96).

4.16. The Committee noted one systematic review of non-experimental studies comparing aTIV to TIV across a range of endpoints (Domnich et al. Vaccine. 2017;35(4):513-20). The Committee noted that the pooled analysis of 4 case-control studies gave point estimates for vaccine effectiveness between 30% and 61% for hospitalisation from pneumonia and influenza, with vaccine effectiveness estimates favouring aTIV over TIV.

4.17. The Committee noted that in its modelling, the supplier applied the reduced rate of hospitalisations (OR 0.83, 95% CI, 0.68 to 1.03) from Mannino et al. 2012, to the difference in mortality between individuals administered aQIV or QIV. The Committee considered that it was not appropriate to assume reduced mortality from the intervention based on Mannino et al. or any of the other evidence presented, due to poor quality of the evidence. The Committed noted the evidence only reported reduction in hospitalisation,

and not mortality, attributable to aTIV compared to TIV. In addition, the Committee noted that Mannino et al. 2012 had reported on a different vaccine with a different comparator and had considered that that study had a number of methodological flaws. Further, the Committee noted that the Gravenstein et al. 2018 study had reported reduced hospitalisations but no difference in mortality between aTIV and TIV groups.

4.18. The Committee considered that although the evidence is limited for a reduction in mortality rates from complications arising from influenza, even a small reduction in hospitalisation rates resulting from using an adjuvanted vaccine could reduce the burden on New Zealand health systems. The Committee considered, however, that there was considerable uncertainty on the magnitude of benefit of an aQIV over QIV, based on the indirect comparisons considered with very wide confidence intervals for all estimates of effectiveness.

4.19. The Committee considered that although the incidence of adverse events with aQIV is similar to that of aTIV, adjuvanted vaccines are more reactogenic (local injection site reactions), which might reduce vaccine uptake in subsequent years. The Committee also considered that having a quadrivalent vaccine with a similar name for those aged over 65 may increase the risk of pregnant women or children being inadvertently vaccinated with the incorrect vaccine.

5. Crizotinib - Non-small cell lung cancer, locally advanced or metastatic, ROS1 gene translocation

Application

5.1. The Committee reviewed the application for crizotinib for the treatment of non-small cell lung cancer (NSCLC), locally advanced or metastatic, ROS1 gene translocation.

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

Recommendation

5.3. The Committee **recommended** that crizotinib for non-small cell lung cancer, locally advanced or metastatic, ROS1 gene translocation be listed with a low priority, due to:

- The high health need of patients with ROS1 non-small cell lung cancer; and
- Lack of funded targeted treatments for this patient group; and
- Low quality evidence of moderate benefit; and
- Uncertain impact on the health system.

5.4. In making this recommendation, the Committee considered that there are a number of newer tyrosine kinase inhibitors which may be at least as, or more effective than crizotinib for patients with ROS1 NSCLC.

5.5. The Committee considered that advice from CaTSoP and specialists involved in the treatment of lung cancer in New Zealand could be sought regarding: appropriate Special Authority criteria; the proportion of people with ROS1 NSCLC expected to be unfit for funded platinum-based chemotherapy currently; the proportion of people expected to be tested for the ROS1 gene mutation if a tyrosine kinase inhibitor (TKI) for ROS1 NSCLC were funded, and the sequence of wider NSCLC mutation testing if a ROS1 targeted treatment were funded; and the incremental cost of adding ROS1 to a concurrent panel of tests when compared with a separate, subsequent ROS1 test.

Discussion

5.6. The Committee noted a letter of support for this application from the New Zealand Lung Oncology Special Interest Group (NZ LOSIG).

5.7. The Committee noted the genetic driver, ROS1, accounts for approximately 1% of non-small cell lung cancers (NSCLC). The Committee noted that ROS1 is usually mutually exclusive to epidermal growth factor receptor (EGFR) and anaplastic-lymphoma kinase (ALK) rearrangements.

5.8. The Committee considered the health need of patients with ROS1 NSCLC to be similar to that of patients with NSCLC with EGFR or ALK rearrangements. The Committee noted that NSCLC patients with driver mutations including ROS1 are often younger and non-smokers and considered the health-related impacts of families and whānau of people with ROS1 NSCLC may therefore be different. The Committee noted there may be a higher incidence of ROS1 NSCLC in Asian populations compared with other ethnicities.

5.9. The Committee noted that patients with ROS1 NSCLC currently receive platinum-based doublet chemotherapy, and that there is currently no publicly funded targeted treatment available. The Committee noted that platinum-based doublet chemotherapy can be associated with significant toxicity and may not be suitable for patients with poor performance status (i.e. poorer general well-being and activities of daily life). The Committee considered that people with ROS1 NSCLC may be more pemetrexed sensitive than those with ALK or EGFR gene rearrangements.

5.10. The Committee noted that crizotinib is a tyrosine kinase inhibitor (TKI), which specifically inhibits ALK, Hepatocyte Growth Factor Receptor (HGFR, c-Met), ROS1 and Recepteur d'Origine Nantais (RON) receptor tyrosine kinases. The Committee noted that crizotinib binds more tightly and appears to be five times more potent against ROS1 than ALK fusion cell lines, however that this does not result in five times greater efficacy in ROS1 over ALK NSCLC (Huber. Nature. 2014;508:222–7).

5.11. The Committee considered that there is low quality evidence of moderate benefit for crizotinib in ROS1 NSCLC patients. The Committee noted that the evidence for crizotinib in advanced ROS1 NSCLC comes from small, open-label, single-arm studies, which predominantly include people with previously treated disease. The Committee considered that due to lack of evidence, it was difficult to extrapolate the benefit of crizotinib from these studies to the first-line setting as per the indication sought in the funding application.

5.12. The Committee noted that the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines support the use of crizotinib in the first-line treatment of ROS1 NSCLC, despite the evidence being predominantly for its use in the second line.

5.13. The Committee noted that while the quality of evidence is low for crizotinib for ROS1 NSCLC, it acknowledged that it is unlikely that higher quality evidence will be published, in part due to the rarity of the ROS1 gene rearrangement and thus barriers to adequately powered studies.

5.14. The Committee noted the results of the following single-arm, phase I and II studies:

5.14.1. The PROFILE 1001 study, which reported crizotinib outcomes in ROS1 (n=50) NSCLC patients, with a median duration of treatment of 64.5 weeks (Shaw et al. N Engl J Med 2014;371:1963-71). The Committee noted the median progression free survival (PFS) was 19.2 months and the overall survival rate at 12 months was 85% (95%CI 72-93%). The Committee noted that that the majority of ROS1 patients included in the study had been previously treated and that patients with brain metastases were excluded. The updated results (n=53), with a median

duration of treatment of 22.4 months, reported a median progression free survival (PFS) of 19.3 months, and a median overall survival (OS) of 51.4 months (Shaw et al. Ann Oncol. 2019;30:1121-6).

5.14.2. A study of 127 East Asian adults with advanced ROS1 positive NSCLC, treated with crizotinib for a median duration of treatment of 18.4 months (Wu et al. J Clin Oncol. 2018;36:1405-11). The Committee noted that 18.9% of patients had not received prior treatment regimens for advanced disease, however that results were not stratified by line of treatment. The Committee noted that an objective response rate (ORR) of 71.7% was reported, with a median PFS of 15.9 months and a median OS of 32.5 months.

5.14.3. EUCROSS studied 34 adults with advanced/metastatic ROS1 rearranged lung cancer (Michels et al. J Thorac Oncol. 2019;14:1266-76). The Committee noted that the overall response rate was 70%, the median PFS was 20.0 months, and that the median OS was not met at the data cut off. The Committee noted that this study included people with brain metastases.

5.14.4. AcSé studied 37 adults with ROS1 NSCLC, treated with crizotinib for a median duration of 14.7 months (Moro-Sibilot. Ann Oncol. 2019;30:1285-91). The Committee noted that the ORR following two 28-day cycles of crizotinib was 47.2%. The Committee noted that the median PFS was 5.5 months, and a median OS of 17.2 months was reported.

5.15. The Committee also noted the results of two retrospective publications of crizotinib in ROS1 NSCLC:

5.15.1. The EUROS1 study of 31 patients with stage IV, ROS1, lung adenocarcinoma treated with crizotinib. The Committee noted this was a retrospective case series, reporting an ORR of 80% and a median PFS of 9.1 months (Mazieres et al. J Clin Oncol. 2015;33:992-1001).

5.15.2. The results of a retrospective review of studies of ROS1 NSCLC patients treated with one of several different TKIs or pemetrexed (Park et al. J Thorac Oncol. 2018;13:1373-82). The Committee noted that patients treated with pemetrexed-based chemotherapy had an ORR of 53.3% and a PFS of 8.0 months, compared with an ORR and PFS of 70.7% and 12.7 months in patients treated with a TKI. The Committee noted that brain metastasis was more often observed during TKI treatment (15.5%) than during pemetrexed-based chemotherapy (6.7%).

5.16. The Committee noted that resistance is a predominant issue with TKIs and that it is reported that the vast majority of patients with ROS1 NSCLC treated with crizotinib eventually experience disease progression on therapy and as such creates a hurdle for durable response.

5.17. The Committee noted there was a lack of certainty about the natural history of this disease in the context of single-arm studies, and that the impact of crizotinib treatment for ROS1 NSCLC on health-related quality of life was uncertain.

5.18. The Committee noted that crizotinib currently has the longest follow up data of the relevant TKIs for ROS1 NSCLC, and noted there are a number of ongoing clinical trials for newer generation TKIs in ROS1 NSCLC. The Committee noted the results of the following early published results for newer TKIs in ROS1 NSCLC including those for ceritinib, lorlatinib and entrectinib:

- Lim et al. J Clin Oncol. 2017;35:2613-8
- Drilon et al. Cancer Discov. 2017;7:400-9
- Shaw et al. Lancet Oncol. 2017;18:1590-9

- Shaw et al. Lancet Oncol. 2019;20:1691-701

5.19. The Committee considered that, in the context of ROS1 NSCLC, there appears to be a class effect for TKIs that act on ROS1, with the exception of alectinib, which appears to be of limited benefit in ROS1 NSCLC.

5.20. The Committee considered that as further results are published, a number of these TKIs may demonstrate greater efficacy than crizotinib in ROS1 NSCLC, particularly in patients with brain metastases, based on central nervous system bioavailability of these agents.

5.21. The Committee considered that approximately 10 patients would receive crizotinib each year if it were funded for the first-line treatment of ROS1 NSCLC. The Committee considered that platinum-doublet chemotherapy is the appropriate comparator, and that there are no published randomised trials comparing crizotinib with platinum-doublet chemotherapy.

5.22. The Committee noted that crizotinib is an oral treatment, which would be more suitable than current infusion-based treatment options.

5.23. The Committee considered that if crizotinib were to be funded there would likely be a commensurate increase in demand for radiology services to monitor for progression, as well as other cancer services including hospital services, pathology, surgery and oncologist resource. The Committee also considered that the impact that treatment-related adverse events from crizotinib would have on the health system were unclear, and that the financial and resource impacts on the health sector would be difficult to quantify. The Committee noted that these impacts should be considered in the economic and budget impact analyses undertaken by PHARMAC.

5.24. The Committee noted that if crizotinib, or another tyrosine kinase inhibitor (TKI) were to be funded for ROS1 NSCLC, testing for ROS1 gene rearrangements would be required. The Committee noted testing for ROS1 gene rearrangements can be performed using fluorescent in situ hybridisation (FISH), polymerase chain reaction (PCR), immunohistochemistry (IHC) and next-generation sequencing.

5.25. The Committee noted that not all regional cancer centres currently test for the ROS1 mutation, and considered that if mutation testing was mandated through Special Authority criteria then the availability of testing should be considered in regard to equity of access.

6. Durvalumab as first-line maintenance for locally advanced, unresectable NSCLC

Application

6.1. The Committee reviewed a supplier application for durvalumab (Imfinzi) as first-line maintenance for locally advanced, unresectable, non-small cell lung cancer (NSCLC) whose disease has not progressed following platinum-based chemoradiation therapy.

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

Recommendation

6.3. The Committee **recommended** that durvalumab be funded as first-line maintenance ("consolidation") therapy for locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy with a medium priority, subject to Special Authority criteria.

6.4. In making this recommendation, the Committee considered there was or were:

- a high health need in patients with locally advanced, unresectable NSCLC, especially Māori and Pacific populations who have a high incidence of NSCLC;
- good quality evidence of a substantial survival benefit from durvalumab in this setting from one randomised controlled trial (but noting wide confidence interval approaching 1);
- evidence of no difference in health utility or quality of life between durvalumab and placebo groups, but evidence of a difference in the same between progression-free survival and median time to death or distant metastases;
- concerns regarding the incidence, impact and management of long-term immune-related adverse events associated with durvalumab;
- challenges associated with PD-L1 positivity thresholds and testing; and
- the likely significant resource impact of the proposed durvalumab dosing schedule and use of this agent in this maintenance setting.

6.5. The Committee requested advice from CaTSoP regarding: the sequencing of agents in NSCLC (in particular, use as maintenance treatment or in a metastatic setting); the size of the patient population if durvalumab were funded in this setting; appropriate Special Authority criteria for durvalumab in this setting; and the likely proportion of patients who would receive a biologic therapy for the treatment of adverse events after receiving durvalumab, if it were funded.

Discussion

6.6. The Committee noted that lung cancer is the largest cause of cancer death in New Zealand, resulting in over 1600 deaths per year (Ministry of Health [MoH], 2016). The Committee noted that in 2017 there were 2,226 lung cancer registrations (age standardised rate of 27.7 per 100,000), that the number of new registrations increases with age, and that there were slightly more registrations for women than men (MoH, Mortality 2017 data tables [provisional]).

6.7. The Committee noted that Māori are more likely to be diagnosed with lung cancer at a younger age, that the rate of lung cancer incidence for Māori was three times that of non-Māori (82.9 vs 22.6 per 100,000 in the population, respectively) in 2017, and that there is evidence that Pacific populations also have a higher incidence of lung cancer (Meredith et al. Cancer Causes Control. 2012;23:1173-84). The Committee considered that these groups have a particularly high health need and that Māori and Pacific patients have higher mortality rates due to lung cancer (New Zealand Cancer Registry, MoH).

6.8. The Committee noted that the current International Association for the Study of Lung Cancer (IASLC) staging system (2016) classifies a range of cases of non-metastatic disease with primary tumour size ranging from <3 cm to >7 cm and variable extent of nodal involvement as stage III disease. The Committee noted that stage IIIC ("wet" stage III disease) may include a subgroup of patients with cancer-related pleural effusions.

6.9. The Committee considered that the health need of patients with locally advanced, unresectable NSCLC is apparent in the clinical trial evidence, which reports poor outcomes after the current standard of care treatment using chemoradiation, noting that progression-free survival (PFS), time to death or distant metastasis, and overall survival (OS) are reported to be 5.6 months, 16.2 months and 29 months, respectively, in the control arm (standard of care) patient group of the key clinical trial evidence for this application (Antonia et al. N Engl J Med. 2018;379:2342-50).

6.10. The Committee noted that durvalumab is a monoclonal antibody that blocks programmed-death ligand 1 (PD-L1; the same target as atezolizumab) from binding to programmed

death 1 (PD-1) and CD80 receptors on the cell membrane, enhancing T-cell anti-tumour immune responses. The Committee noted that durvalumab has a different target to pembrolizumab and nivolumab, which are also immune checkpoint inhibitors but instead block PD-1.

6.11. The Committee noted that durvalumab is Medsafe-approved for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy.

6.12. The Committee noted that durvalumab is proposed as maintenance ("consolidation") therapy for the treatment of locally advanced stage III unresectable NSCLC for patients who have already undergone at least 2 cycles of their first-line platinum-based chemoradiotherapy and have no disease progression, commencing within six weeks of end of chemoradiotherapy. Treatment with durvalumab is proposed for a maximum of 12 months or until a patient experiences confirmed disease progression or unacceptable toxicity; this was noted to be shorter than the total maximum duration of pembrolizumab trial protocols in a maintenance setting (up to two years).

6.13. The Committee noted that the key evidence for durvalumab comes from the phase 3, randomised (2:1), double-blind, placebo-controlled PACIFIC trial of intravenous durvalumab (10 mg per kg) or placebo every two weeks for up to 12 months in 709 patients with locally-advanced, unresectable stage III NSCLC with no disease progression after concurrent chemoradiotherapy (Antonia et al. N Engl J Med. 2017;377:1919-29).

6.13.1. The Committee noted in PACIFIC that treatment was discontinued if a patient experienced disease progression or unacceptable toxicity, started alternative anticancer therapy or withdrew consent.

6.13.2. The Committee noted that 98% of PACIFIC participants had stage IIIa or IIIb disease; only 2% had stage IIIc disease. The Committee noted that just over half of PACIFIC participants had non-squamous histology (the remainder having squamous histology); most (91%) were current or previous smokers; and 79% had PD-L1 status of >1% according to immune cell (IC) or tumour cell (TC) testing.

6.13.3. The Committee considered the placebo comparator appropriate for the New Zealand context, given that standard of care does not currently include maintenance treatment of any kind.

6.13.4. The Committee considered that PACIFIC participants were slightly younger (mean age 64 years) than the average New Zealand patient with NSCLC and noted that the trial did not include Māori or Pacific patients who are overrepresented in the New Zealand NSCLC patient population, therefore this may slightly diminish the applicability of the trial evidence to a substantial portion of New Zealand patients.

6.13.5. The Committee noted that median progression-free survival (PFS) in PACIFIC was 16.8 months with durvalumab vs 5.6 months with placebo (hazard ratio (HR) 0.52; 95% CI 0.42 to 0.65; P<0.001) and considered that this was evidence of a significant benefit from durvalumab.

6.13.6. The Committee noted from analysis of updated median overall survival (OS) from the intention-to-treat PACIFIC trial population over 25.2 months' median follow-up, that OS was not estimable for durvalumab vs 28.7 months with placebo, with the durvalumab arm experiencing cumulative deaths insufficient to assign a median survival time, but that the authors reported durvalumab extending OS as compared with placebo (stratified HR 0.68; 99.73% CI 0.47 to 0.997) (Antonia et al. N Engl J Med. 2018;379:2342-50). The Committee considered the lessened

precision with this wide confidence interval to be a limitation of otherwise good evidence from this single randomised controlled trial.

6.13.7. The Committee noted that durvalumab was administered for a median of 40.1 weeks. Of the PACIFIC participants who received subsequent anticancer therapy, 8.0% of those who had been randomised to receive durvalumab and 22.4% of those who had received placebo, subsequently received additional biological immune therapy.

6.13.8. The Committee noted that the median time to death or distant metastasis in the PACIFIC trial was 28.3 months with durvalumab vs 16.2 months with placebo (HR 0.53; 95% CI 0.41 to 0.68) and that there was a significant difference in overall survival at two years (66.3% with durvalumab vs 55.6% with placebo [95% CI, 48.9 – 61.8%, P=0.005]). Members noted that the PACIFIC data was limited by small participant numbers at three years, but considered that the observed benefit of durvalumab could continue for a number of years.

6.14. The Committee noted that grade 3 or 4 adverse events of any cause were reported in 29.9% of participants with durvalumab vs 26.1% with placebo, P=0.33. The Committee considered that PACIFIC patients could have had reduced health status at trial baseline from prior chemoradiation, and considered that the safety profile was generally similar between groups during the safety data collection period, with no significant differences between groups irrespective of event severity.

6.14.1. The Committee considered that the safety data collection period may have been too short to identify long-term immune-related adverse events in the PACIFIC trial, which generally occur more than 90 days after treatment completion. However, the Committee considered that long-term immune-related adverse events (e.g. pneumonitis or autoimmune hepatitis) are known to occur in approximately 20-30% of lung cancer patients treated with these agents, and many affected patients require substantial clinical management in terms of health service resource and impact on patient quality of life. Members noted that some patients may require lifelong management including high-dose corticosteroids, methotrexate, cyclophosphamide, mycophenolate mofetil, tacrolimus and thymoglobulin.

6.15. The Committee noted that the PACIFIC trial patient reported outcomes were collected until 48 weeks, and that there were generally no clinically relevant between-group differences in patient reported outcomes (Hui et al. Lancet Oncol. 2019;20:1670-80). The Committee considered that at this time, some patients would have experienced disease progression accompanied by a decrease in quality of life, while others would be progression-free, and noted that EQ-5D-5L data from the PACIFIC trial was modelled (by an independent Evidence Review Group, based on the National Institute for Health and Care Excellence NICE] single technology appraisal [STA] for durvalumab in this setting) to estimate health utility values of 0.810 and 0.776 for progression-free status and disease progression, respectively (Witlox et al. PharmacoEconomics 2020;38:317-24). The Committee considered that, as with all settings where patients go on to receive additional treatment, patient-reported outcome data was confounded by use of subsequent treatments post disease progression.

6.16. Overall, the Committee considered that PACIFIC provided high quality, high strength evidence of a substantial survival benefit from durvalumab consolidation therapy compared with placebo for patients with stage IIIa or IIIb (not stage IIIc) NSCLC regardless of PD-L1 status without significant treatment-related adverse events or compromised quality of life for the majority. The Committee noted this assessment was based on one randomised controlled trial that was limited by the upper bounds of some survival-related effect size confidence intervals approaching 1. Furthermore the participants in PACIFIC might not resemble a New Zealand patient population, with the higher incidence of NSCLC

in Māori and Pacific people. The Committee considered that Special Authority criteria should exclude stage IIIc disease, on the basis of an absence of evidence in this group.

6.17. The Committee noted a published review including survival outcomes from the PACIFIC trial and survival outcomes from the LUN 14-179 single arm phase II trial of pembrolizumab consolidation following chemoradiation, which reported a similar survival benefit from pembrolizumab in patients with stage III NSCLC; 12 month OS was 83.1% with durvalumab (PACIFIC trial) vs 80.5% with pembrolizumab (LUN 14-179 trial); and 24 month OS of 66.3% and 68.7%, respectively (Botticella et al. Ther Adv Respir Dis. 2019;13:1753466619885530).

6.18. The Committee noted that a significant proportion of PACIFIC participants (21%) had PD-L1 expression of <1%, and that a post-hoc analysis of outcomes according to PD-L1 status suggests that patients with PD-L1 expression levels of <1% did not experience improved overall survival with durvalumab consolidation therapy (J Thorac Oncol. 2020;15:288–93), although the Committee considered this analysis was subject to bias. The Committee considered that accurate and consistent pre-treatment PD-L1 testing may help to target treatment with durvalumab to those who would likely benefit most, noting that the UK (NICE) and Scotland (SMC) recommended a requirement for expression of PD-L1 on ≥ 1% of tumour cells in order to be eligible for funded durvalumab in this setting. However, the Committee considered that there were a number of issues associated with the consistent and equitable implementation of PD-L1 testing, which are detailed in previous clinical advice records for PD-1/PD-L1 inhibitors.

6.19. The Committee noted that it is well documented that clinical trials for PD-L1 and PD-1 inhibitors use different assays (with varying sensitivity) to test and categorise PD-L1 status in NSCLC, leading to challenges with the use of set thresholds and definitions for patient populations across these agents. The Committee considered that the cost-effectiveness of durvalumab in this setting may prove to be reasonable even if pre-treatment PD-L1 testing was not included in the eligibility criteria for funded treatment. The Committee considered therefore, that Special Authority criteria for durvalumab in this setting may not need to require PD-L1 status confirmation and that further advice could be sought from CaTSoP on this topic.

6.20. The Committee considered that the two-weekly dosing of durvalumab (up to a maximum of 1 year) would significantly impact the DHB health resource as this population would otherwise receive monitoring only. The Committee considered that as seen for PD-1/PD-L1 in other indications it was likely that evidence would emerge regarding different dosing schedules. Members considered that at present, it is not feasible for this type of cancer treatment to be delivered in primary care (in part, due to administration as an infusion and patient management, given the adverse event profile), therefore any additional treatment infusions would impact on secondary and tertiary care.

6.21. The Committee considered that the survival benefit that patients with NSCLC could gain could likely be optimised by the appropriate sequencing of anticancer therapies, given the possible additional benefits that may result from prior treatments e.g. an abscopal effect: shrinkage of untreated tumours elsewhere occurring concurrently with shrinkage of tumours form local treatment; resulting from prior chemoradiotherapy, that may expose an epitope to subsequent PD-L1 or PD-1 targeting treatment.

6.22. The Committee considered that it is important to determine whether the greatest benefits result from using checkpoint inhibitors in the early, consolidation or metastatic phases of the disease, especially given that earlier use may preclude later use. Members noted that first-line durvalumab (in a non-maintenance setting) did not significantly improve OS in the MYSTIC trial (Rizvi et al. JAMA Oncol. 2020;6:661-74).

6.23. The Committee considered that there was likely to be a class effect from use of PD-1/PD-L1 agents as maintenance treatment, as current data for pembrolizumab indicated it may

provide similar health benefits in this setting, although the data is currently limited. The Committee considered that the evidence for PD-1/PD-L1 agents in the treatment of NSCLC, and other indications, was continuing to evolve rapidly. The Committee considered that this application should be considered in the context of the wider treatment paradigm for NSCLC.

6.24. The Committee considered that early use should preclude subsequent funded use, as there is currently limited evidence of the use of multiple lines of PD-1/PD-L1 agent; the Committee noting CaTSoP's previous advice that, based on the current evidence for PD-1/PD-L1 agents in NSCLC, it is appropriate for only one line of funded treatment with an immune checkpoint inhibitor (such as durvalumab) to be accessed once per patient lifetime. The Committee considered that treatment should be discontinued in patients who experience a lack of treatment response, and that the Special Authority criteria should reflect this.

6.25. Overall, the Committee considered that there is evidence of a significant benefit in PFS and OS from durvalumab in patients with NSCLC, with a generally manageable safety profile.

7. Osimertinib for first-line treatment of EGFRm NSCLC

Application

7.1. The Committee reviewed the application for osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC).

7.2. The Committee also reviewed additional information submitted for the previous 2017 application for osimertinib in the second-line treatment of locally advanced or metastatic EGFRm T790M positive NSCLC.

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

Recommendation

7.4. The Committee **recommended** that osimertinib for the first-line treatment of EGFRm NSCLC be funded **if cost-neutral** to current first-line pharmaceuticals in this indication, due to:

- The high health need of people with lung cancer and the current availability of two effective agents in the same class funded for this indication; and
- High quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and
- Uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and
- The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

7.5. The Committee considered that PHARMAC could seek subsequent advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the sequence of treatments in this indication, and appropriate Special Authority criteria for osimertinib in the first-line setting.

7.6. The Committee **recommended** that osimertinib for the second-line treatment of EGFRm NSCLC be **deferred**, pending publication and peer-review of the AURA-3 overall survival results.

Discussion

Osimertinib in the first-line

7.7. The Committee noted that lung cancer is the leading cause of cancer death in New Zealand. The Committee noted that in New Zealand approximately 89% of lung cancer is non-small cell lung cancer (NSCLC), and 22% of NSCLC patients tested for the Epidermal Growth Factor Receptor mutation (EGFRm) have EGFRm positive tumours. The Committee noted that, in general, Māori are disproportionally impacted by lung cancer compared with non-Māori, with younger age of onset, late diagnosis and worse outcomes. The Committee noted that there is a higher tested and reported incidence of EGFRm in South-East Asian patients (40%) and Pacific patients (24%) than in New Zealand European (18%) or Māori patients (10%) (McKeage et al. Technical report for the Heath Innovation Partnership of the Health Research Council of New Zealand and National Health Committee. 2015).

7.8. The Committee noted that people with lung cancer have a high health need; however, considered that there are inequities in regard to outcomes and available treatment options between lung cancer subgroups. The Committee considered that people with EGFRm NSCLC generally have a longer baseline survival than other subsets of lung cancer. The Committee noted that there are two currently funded first-line tyrosine kinase inhibitors (TKIs) that target EGFR mutations. Members therefore considered that the unmet need for osimertinib in this first-line setting may be lower than in other lung cancer subgroups for which a targeted treatment is not funded.

7.9. The Committee noted that resistance often develops following tyrosine kinase inhibitor (TKI) treatment and that this is most commonly caused by the T790 mutation. The Committee noted that osimertinib is an orally administered third generation TKI that is a selective and irreversible inhibitor of EGFRs harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations. The Committee noted that osimertinib has similar side effects to other funded TKIs.

7.10. The Committee noted the results of the FLAURA phase III, double-blind, randomised control trial, which investigated the use of osimertinib compared with gefitinib or erlotinib in patients with locally advanced or metastatic EGFRm NSCLC.

7.10.1. The Committee noted the median progression free survival (PFS) was 18.9 months in the osimertinib group compared with 10.2 months in the comparator group, hazard ratio (HR) for disease progression or death 0.46 (95% confidence interval (CI) 0.37-0.57) (Soria et al. N Engl J Med. 2018;372:113-25).

7.10.2. The Committee noted the secondary outcome of median overall survival (OS) was 38.6 months in the osimertinib group compared with 31.8 months in the comparator arm, HR for death 0.80 (95.05% CI: 0.64-1.00; p=0.046) (Ramalingam et al. N Engl J Med. 2020;382:41-50).

7.10.3. The Committee considered that the trial was of high quality, however that the results for OS were still immature with borderline significance, with the upper confidence interval limit for the HR including 1.00, and noted that the published results attained statistical significance for OS p-values only by extending the HR's CI beyond 95%, which the Committee considered differed from usual formal statistical reporting convention.

7.11. The Committee noted the results of the Japanese subset population of the FLAURA trial (Ohe et al. Jpn J Clin Oncol. 2019;49:29-36). The Committee noted that median PFS was 19.1 months in the osimertinib group compared with 13.8 months in the gefitinib group, HR 0.61 (95% CI 0.38-0.99). The Committee noted that the median OS was not reached.

7.12. The Committee also noted the FLAURA trial publications regarding central nervous system (CNS) progression (Reungwetwattana et al. J Clin Oncol. 2018;36:3290-7), a subset of Asian patients enrolled at Asian sites (Cho et al. J Thorac Oncol. 2019;14:99-106), subsequent treatment (Planchard et al. Clin Cancer Res.2019;25:2058-64), and quality of life (Leighl et al. Eur J Cancer. 2020;125:49-57).

7.13. The Committee considered that while the evidence of osimertinib in this indication was of high quality and reported improved PFS compared with gefitinib/erlotinib, the uncertainty of overall survival benefit of osimertinib over gefitinib/erlotinib and the lower unmet health need of this patient group compared with other lung cancer subtypes influenced the cost-neutral recommendation.

7.14. The Committee noted that NICE (England/Wales) did not recommend osimertinib for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults; this lack of a positive recommendation also influenced PTAC's cost-neutral recommendation over a higher positive recommendation. The Committee also noted the PBAC (Australia), CADTH's pERC (Canada) and SMC (Scotland) did not recommend osimertinib for this indication.

7.15. The Committee noted that currently funded first-line treatments for patients with EGFRm NSCLC include the oral TKIs erlotinib and gefitinib. The Committee considered that these agents were appropriate comparators to osimertinib in this treatment line. The Committee considered that while osimertinib had demonstrated efficacy in this patient population, there was no clear unmet health need for a third TKI in the first-line setting for EGFRm NSCLC. The Committee noted that following disease progression on current first-line treatment, second-line treatment is platinum-based doublet chemotherapy.

7.16. The Committee noted that EGFR mutation testing is already occurring for first-line treatment and that this proposal would therefore not result in further mutation testing.

7.17. The Committee noted when making its recommendation that the net price of the two currently funded pharmaceuticals in this line of treatment (erlotinib and gefitinib) may be different and that its cost-neutral recommendation related to cost-neutrality to the more expensive of the two agents. The Committee noted that, were osimertinib to be funded on this basis, that this would likely result in a net increase in expenditure for this line of treatment.

7.18. The Committee considered it was unclear whether targeted treatments would be a suitable option in patients who progressed on osimertinib if used in this first-line setting. The Committee considered that PHARMAC could seek advice from CaTSoP regarding the sequence of treatments in this indication.

7.19. The Committee noted that there are a number of ongoing clinical trials investigating the use of multiple TKIs in combination for the treatment of EGFRm NSCLC. The Committee considered that, pending the results of these trials, there may be requests to PHARMAC for funding of combination TKI treatment over monotherapy in the future.

Osimertinib in the second-line

7.20. The Committee noted that an application for osimertinib in the second-line treatment of EGFRm NSCLC was deferred by the CaTSoP in 2018, pending publication of longer follow-up including mature survival data from the AURA-3 trial (CaTSoP. 2018).

7.21. The Committee reviewed an abstract and conference presentation of the AURA-3 trial overall survival data provided by the supplier. The Committee noted that the results had not been published in a peer reviewed setting at the time of the meeting, and as such deferred making a recommendation on this application pending the availability of peer reviewed published results.

7.21.1. The Committee considered that further information regarding the statistical analysis methodology would be helpful in informing its assessment of the strength and quality of the evidence, including (but not limited to) the cross-over adjustments made and the abstract's intention-to-treat (ITT) analysis reporting apparently no difference in mortality. The Committee considered an assessment of the peer-reviewed data could be completed by PTAC or by CaTSoP.

7.21.2. The Committee considered osimertinib in the second-line setting would require lung re-biopsy, which would be associated with morbidity and mortality risks beyond the disease and potential side effects of the pharmaceutical itself.

8. Trastuzumab emtansine as adjuvant treatment for HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment that included HER2-targeted therapy

Application

8.1. The Committee reviewed a supplier application for trastuzumab emtansine in the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant (i.e. pre-operative) systemic treatment that included HER2-targeted therapy.

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

Recommendation

8.3. The Committee **recommended** that trastuzumab emtansine be listed for the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment that included HER2-targeted therapy with a low priority.

8.4. The Committee **recommended** that advice be sought from CaTSoP regarding:

- the current treatment paradigm for early breast cancer in New Zealand;
- the proportion of patients with residual disease following HER2 targeted therapy and whether this is used for treatment decision making currently;
- whether residual disease is a predictor of disease recurrence and death in breast cancer;
- the proportion of patients who receive neoadjuvant treatment, and whether this would differ were trastuzumab emtansine to be funded in this setting;
- the number of cycles of trastuzumab that patients currently receive in the neoadjuvant setting, and if would this change if trastuzumab-DM1 (T-DM1) were to be funded;
- the current use of adjuvant capecitabine in the treatment of early breast cancer;
- the 5-year relapse rate for patients with early breast cancer who have been treated with trastuzumab in the neoadjuvant and/or adjuvant setting;

- the relevance of the KATHERINE trial to the New Zealand patient population;
- the evidence for and suitability of complete response (CR) as a surrogate marker for overall survival (OS) improvement;
- the evidence for and suitability of invasive disease-free survival (IDFS) as a surrogate marker for OS;
- consequences to the health system if trastuzumab emtansine were to be listed in this setting;
- whether the listing of trastuzumab emtansine would affect management of metastatic disease, and what the role of this treatment would be in a metastatic setting following its earlier use;
- appropriate Special Authority criteria, including any amendment to criteria for the currently funded metastatic setting.

Discussion

8.5. The Committee noted that breast cancer is the most common cancer diagnosis in women worldwide, and that in 2017 there were 3316 new cases of breast cancer reported across both women and men in New Zealand (New Zealand Cancer Registry, 2019). The Committee also noted that approximately 80% of breast cancer patients present with early breast cancer (eBC) and that there are approximately 650 deaths from breast cancer per year in New Zealand.

8.6. The Committee noted that overexpression of human epidermal growth factor receptor 2 (HER2) occurs in around 15-20% of breast cancers in New Zealand (Lawrenson et al. NZMJ. 2018;131:51-60).

8.7. The Committee noted that Māori and Pacific people have a higher incidence of breast cancer than those of European/Other descent, are more likely to have HER2 positivity, and have a higher mortality rate. The Committee noted that Māori are usually diagnosed later than non-Māori, and that Pacific peoples are less likely to be diagnosed through screening, which is associated with their incidence of advanced breast cancer being higher (although not necessarily causing this). The Committee noted that people in the Asian population often present with larger cancers at diagnosis, are more likely to be HER2 positive than European/Other but have a lower rate of BC mortality.

8.8. The Committee noted that currently eligible patients with HER2 positive disease may be administered chemotherapy in combination with the HER2-targeted agent, trastuzumab, as neoadjuvant therapy (before surgery) aiming to shrink the tumour prior to resection, and/or as adjuvant therapy (following surgery), for a combined total of 52 weeks neo/adjuvant treatment. The Committee noted that not all patients receive neo-adjuvant treatment prior to surgery.

8.9. The Committee noted that CaTSoP, at its September 2018 meeting, considered an application for pertuzumab for the neoadjuvant treatment of HER2-positive locally advanced, inflammatory or high risk early stage breast cancer. The Committee noted that the Subcommittee had considered that at that time between 50 and 70 patients with HER2 positive breast cancer would be offered neoadjuvant therapy in New Zealand; however, this would likely increase with time, given trends for increasing neoadjuvant treatment. The Committee noted that CaTSoP 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. The Committee noted that there is a difference in the rates of neoadjuvant treatment between centres, in part due to the increased complexity around treatment planning and surgical staff availability.

8.10. The Committee also noted that in September 2018 CaTSoP had considered that the benefits associated with the use of neoadjuvant therapy include avoiding delays in treatment due to surgical complications, but had considered that the evidence available at that time for neoadjuvant treatment did not demonstrate that neoadjuvant therapy provides an overall survival advantage, although it does allow more patients to undergo breast conserving surgery rather than mastectomy, and would delay rather than prevent future treatment lines.

8.11. The Committee noted that, internationally, the incidence of residual disease after neo-adjuvant systemic treatment with trastuzumab is considered approximately 70.5% (Gianni et al. Lancet Oncol. 2016;17(6):791-800), however the applicant had indicated from anecdotal data that the rate in New Zealand may be approximately 50-60%.

8.12. The Committee considered that there appeared to be limited data available for the use of residual disease occurrence following neoadjuvant HER2 targeted therapy as a predictor for disease recurrence or death in patients with HER2 positive early breast cancer.

8.13. The Committee noted a summary of a poster presentation by Swain et al. 2020 provided by the applicant on the risk of recurrence of HER2 positive breast cancer following HER2 targeted therapy in neoadjuvant and adjuvant settings. The Committee noted that recurrence rates reported ranged from 17-40% depending on the HER2 targeted agents used, if there was a combination of agents, and if patients achieved complete pathological response following treatment. The Committee noted that there appeared to be limited data available on 5-year recurrence rates of HER2 positive breast cancer following treatment with trastuzumab.

8.14. The Committee considered that in the absence of a complete pathological response following neoadjuvant treatment and surgery, patients can be treated with adjuvant capecitabine either as monotherapy or in combination with docetaxel. The Committee noted that the evidence for use of capecitabine in a general population was based on extrapolation of a small Japanese study in which a subset of patients with a non-pathologic response had improved outcomes from the addition of capecitabine (Masuda et al. N Engl J Med. 2017;76(22):2147-59). The Committee considered that although capecitabine is not an appropriate comparator for trastuzumab emtansine given the quality of evidence, it should be taken into account as part of the treatment paradigm if it is being used currently in New Zealand.

8.15. The Committee noted that trastuzumab emtansine (T-DM1) is a HER2-targeted antibody-drug conjugate that contains the humanised anti-HER2 IgG1, trastuzumab, covalently linked to the microtubule inhibitory drug DM1 (a maytansine derivative) with the stable thioether linker MCC. Emtansine refers to the MCC-DM1 complex. The Committee noted that the mechanism of action of T-DM1 allows the DM1 to be preferentially delivered to tumour cells, limiting the damage to surrounding tissues. The Committee noted that T-DM1 is Medsafe-approved for the requested indication.

8.16. The Committee noted that the supplier had proposed T-DM1 as the standard therapy for HER2 positive early breast cancer in patients who have residual disease after neoadjuvant treatment that included HER2-targeted therapy. The Committee noted that the supplier had considered that T-DM1 would not replace neoadjuvant trastuzumab treatment and would not be used in post-surgery treatments where patients had had a complete response. The Committee noted that the supplier had considered that patient response to neoadjuvant treatment with trastuzumab would be assessed either pre- or post-surgery in resected tissue.

8.17. The Committee noted a phase III, two-arm, randomised, open-label, multicentre trial (the KATHERINE trial, n=1486), which investigated the efficacy of T-DM1 compared with trastuzumab (both 3-weekly over 42 weeks) in patients with HER2 positive early breast cancer who were found to have residual disease at surgery after receiving neoadjuvant therapy plus HER2 targeted therapy (Von Minckwitz et al. N Engl J Med 2019;380:617-28). The Committee noted that there was no recruitment from New Zealand in the trial, however the Committee considered that the New Zealand patient population would meet similar criteria as those recruited for the trial. The Committee also noted that the adjuvant portion of the treatment course with trastuzumab is the appropriate comparator to T-DM1 in the New Zealand context.

8.17.1. The Committee noted that invasive disease was reported to be less common in the T-DM1 group compared with the trastuzumab treatment group (12.2% and 22.2%, respectively), the hazard ratio (HR) for invasive disease-free survival (iDFS) at 3 years was 0.50 (95% CI 0.39 to 0.64) favouring T-DM1, and that freedom from distant recurrence at 3 years also favoured T-DM1 (HR 0.60; 95% CI 0.45 to 0.79). The Committee also noted that although the OS data was immature, the point estimate of the hazard ratio favoured T-DM1 (HR 0.70; 95% CI 0.47 to 1.05; p=0.08). The Committee noted that there was no evidence of a different treatment effect in sub-groups of the trial participants.

8.17.2. The Committee noted that T-DM1 had an inferior safety profile compared with trastuzumab, with serious adverse events occurring in 12.7% of the T-DM1 group compared to 8.1% of the trastuzumab group, and that adverse events leading to discontinuation of treatment occurred in 18.0% of the T-DM1 group compared to 2.1% of the trastuzumab group. The Committee considered that this difference in safety was likely due to the components of the antibody-drug conjugate being more cytotoxic than trastuzumab.

8.18. The Committee noted that the primary endpoint of the KATHERINE trial was invasive disease-free survival (iDFS) as a surrogate for OS. The Committee noted that the applicant referenced a 2019 study (Saad et al. Lancet Oncol. 2019;20:361-70), in which the validity of disease-free survival (DFS) as a surrogate for OS in patients with HER2-positive early breast cancer in trials of adjuvant trastuzumab for up to 1 year was assessed via systematic review and meta-analysis, with the objective to estimate patient-level and trial-level correlations between OS and DFS. The Committee noted that patient-level associations between DFS and OS were reported to be strong (Spearman's correlation coefficient=0·90; 95% CI 0·89 to 0·90) However, the Committee considered that, in a disease such as this with multiple lines of treatment and a relatively long survival, that it was difficult to interpret the relationship of a surrogate marker such as DFS with OS.

8.19. The Committee noted patient reported outcomes from the KATHERINE trial, for which 70% of patients in the trial submitted data (Conte et al. Cancer. 2020;26:3132-9). The Committee noted that mean changes in global, cognitive, physical and fatigue scores were similar between the two treatment groups and that most changes in score were not clinically meaningful and returned to baseline.

8.20. Overall, the Committee considered there was limited evidence of moderate strength and high quality to support the use of T-DM1 as adjuvant treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant treatment that included HER2-targeted therapy.

8.21. The Committee considered that use of this agent would be associated with an increase in adverse-event related costs to the health system if T-DM1 were to be funded in this setting, and may be further compounded by an increase in demand for neoadjuvant therapy with more options available. The Committee considered that funding in this setting would likely result in an increase in clinical staff workload and demand for infusion capacity.

8.22. The Committee noted that at its August 2019 meeting it had previously considered an application for trastuzumab biosimilar and that it would be clinically acceptable for the treatment of HER2-positive early breast cancer and HER2-positive metastatic breast cancer. The Committee noted that there were several trastuzumab biosimilars available internationally. The Committee considered that, given this competition, it was likely a significant price change for trastuzumab may occur in the near future, which should be considered in any economic assessment as this would influence the cost-effectiveness of T-DM1 if it were to be funded in the proposed setting.

8.23. The Committee considered that, while a positive recommendation was supported at this time, which was based on the currently available evidence and current pricing for differential between trastuzumab and T-DM1, it was however unclear what the OS gain with use of T-DM1 in this setting would be and whether this would be of sufficient magnitude to offset the associated increase in adverse events.

8.24. The Committee considered that it was unclear what the role of T-DM1 would be in the treatment paradigm and management of patients with eBC who may go on to develop metastatic disease. The Committee noted that trastuzumab emtansine is currently funded for the second-line treatment of metastatic HER2 positive breast cancer and that it was uncertain what the response would be for patients with metastases who had received adjuvant treatment with T-DM1 for their early breast cancer and what, if any, evidence there was to support its use in this way.

8.25. The Committee noted that, contrary to instructions in the Guidelines for Funding Applications to PHARMAC, the supplier's application contained a substantial amount of information that was of limited relevance, and at times irrelevant, for the evaluation of evidence for the use of T-DM1 in the adjuvant treatment of HER2 positive early breast cancer, and considered that this increased the difficulty for the Committee to evaluate the evidence provided in a timely manner. The Committee expressed its disappointment and requested that the applicant follow the guidelines, carefully consider the material included in its submissions and limit material to only relevant documents and information.

9. Olaparib for first-line treatment of platinum sensitive high grade BRCAm ovarian cancer

Application

9.1. The Committee reviewed the application from AstraZeneca for widened access of olaparib (Lynparza) as maintenance treatment of newly diagnosed, advanced (stage III or IV) high-grade serous or endometroid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof), with a BRCA1 or BRCA2 mutation (or both), who have had a complete or partial response after one line of platinum-based chemotherapy (first-line maintenance).

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

Recommendation

9.3. The Committee recommended that access to olaparib be widened for the first-line maintenance treatment of high-grade ovarian cancer with a mutation in breast cancer susceptibility gene 1 or 2 (BRCAm) with a medium priority, subject to Special Authority criteria that would allow for once-per-patient-lifetime access to olaparib.

9.3.1. In making this recommendation, the Committee considered the high health need of this patient population and the evidence for a difference in efficacy (specifically, progression-free survival [PFS]) with the use of olaparib in the first line setting in the SOLO-1 trial compared with its documented PFS in the second line setting,

noting the occurrence of adverse events associated with olaparib and noting that the overall survival (OS) data from the SOLO-1 trial was immature. The Committee considered that a greater proportion of patients with ovarian cancer would be suitable for first-line maintenance than for second-line maintenance, therefore the overall treatment cost would increase if olaparib was funded in this initial setting.

9.4. The Committee considered that advice from CaTSoP should be sought regarding: whether there is a class affect among polyadenosine 5'-diphosphoribose polymerase (PARP) inhibitors for BRCAm ovarian cancer and whether a similar benefit would also be expected in patients with homologous recombination deficiency (HRD); the potential benefit of olaparib treatment in patients with somatic BRCAm ovarian cancer, in light of evidence suggesting a similar benefit to those with germline BRCAm; appropriate duration of funded treatment for patients who have a partial response to olaparib after two years; the proportion of patients with other gynaecological cancers (serous fallopian tube or peritoneal carcinomas) who may be within the target population for olaparib; and appropriate Special Authority criteria for widened access that would allow for one funded course -per-patient-lifetime access to olaparib.

Discussion

9.5. The Committee noted that in 2017, there were 240 new ovarian cancer patient registrations and a further 117 registrations for other gynaecological cancers (including fallopian tube and peritoneal carcinomas) in New Zealand, and that ovarian cancer alone was among the tenth most commonly registered cancers in females that year.

9.6. The Committee noted that the lifetime risk of developing ovarian cancer for a person with a BRCA1 or BRCA2 mutation is between 35-46% and 13-23%, respectively; that BRCA mutation carriers are at increased risk of developing a high-grade cancer; and that 15-17% of patents with high-grade serous ovarian cancers have a BRCA germline mutation.

9.7. The Committee noted that patients with newly diagnosed advanced ovarian cancer (including high-risk disease that is BRCA mutation positive) generally receive first-line treatment consisting of debulking surgery with or without radiotherapy, followed by platinum-based chemotherapy (carboplatin or cisplatin, with paclitaxel) for a maximum of six cycles. Following first-line treatment, patients with ovarian cancer are observed to watch and wait for disease progression; after progression, second line treatment may consist of re-challenge with platinum agents or other agents (e.g. paclitaxel, docetaxel or gemcitabine), either alone or in combination with platinum.

9.8. The Committee noted that the health need of patients with ovarian malignancies has been documented in previous committee records, and considered that this high health need predominantly results from their highly symptomatic, relapsing and remitting progressive disease. In particular, the Committee noted that patients with ovarian cancers experience progressively shorter intervals between treatments and relapses; may experience substantial disease-related events in the advanced setting (e.g. pleural effusion, ascites and bowel obstruction); often experience considerable treatment-related effects associated with chemotherapy, some of which remain long-term e.g. peripheral neuropathy; and experience problems in multiple domains of their quality of life.

9.9. The Committee noted that olaparib is an orally administered polyadenosine 5'-diphosphoribose polymerase (PARP) inhibitor, which exploits deficiencies in DNA repair pathways, preventing repair of double-strand breaks and preferentially killing cancer cells. The Committee considered that there were no particular suitability concerns regarding the oral, twice-daily formulation of olaparib.

9.10. The Committee noted that olaparib has been funded since February 2020 for the maintenance treatment of relapsed disease in patients with platinum-sensitive, BRCA-

mutated (BRCAm) ovarian cancer who have received at least two lines of platinum-based chemotherapy (second-line maintenance), subject to meeting certain clinical criteria including a requirement for pathogenic germline BRCA mutation. The Committee noted that the SOLO-2 trial (described later in this meeting record) had provided evidence for olaparib maintenance for this indication.

9.11. The Committee noted that the current funding application was for olaparib to be used at an earlier time in the disease course; as maintenance treatment of newly diagnosed, advanced (stage III or IV) high-grade serous or endometroid ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (or a combination thereof), with a mutation in BRCA1 or BRCA2 (or both), in patients who have had a complete or partial response after one line of platinum-based chemotherapy i.e. first-line maintenance.

9.12. The Committee noted that Medsafe has approved olaparib both for second-line maintenance (its currently funded indication) and for the first-line maintenance indication proposed by this application.

9.13. The Committee considered other clinical trials are investigating whether PARP inhibitors are useful in patients with ovarian cancers who have a homologous recombination deficiency (HRD). The Committee noted that HRD is one of many possible gene mutations with a BRCA-like phenotype, and the Committee considered this phenotype could be detected in approximately 50-80% of all ovarian cancers. However, the Committee noted that the current application and associated evidence was for BRCAm patients only.

9.14. The Committee noted the published results of SOLO-1, a randomised (2:1) phase III, double-blind trial of olaparib 300 mg twice daily vs placebo in 391 women with newly diagnosed advanced (FIGO stage III or IV) high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer with mutation in BRCA1, BRCA2 or both, who had and obtained either a complete response (CR) or partial response (PR) after platinum-based chemotherapy (Moore et al. N Engl J Med. 2018;379:2495-505).

9.14.1. The Committee noted that the median participant age in SOLO-1 was 53 years; three-quarters of participants had an ECOG performance status of 0; 85% of patients had ovarian cancer, of which most had stage III disease; 99% had germline BRCA mutations; most patients had BRCA1 mutation; and 82% had a complete response to prior platinum-based chemotherapy. SOLO-1 treatment was stopped at disease progression defined by RECIST 1.1; stopped after a maximum of two years for patients who experienced a complete response; but could continue (at investigator discretion) beyond two years for patients who experienced a partial response.

9.14.2. The Committee noted that, after median follow-up of 41 months and with 51% data maturity (198 of 391 events), investigator-assessed progression-free survival (PFS) in SOLO-1 was 60% with olaparib vs 27% with placebo at 3 years, and 53% with olaparib vs 11% with placebo at 4 years (hazard ratio [HR] for disease progression or death, 0.30, 95% CI: 0.23 to 0.41, P=<0.001). The Committee noted that PFS assessed by blinded independent central review (with data maturity 38%) at 3 years was 69% with olaparib vs 35% with placebo (HR 0.28; 95% CI: 0.20 to 0.39, P<0.001).

9.14.3. The Committee considered that there were a reasonable number of SOLO-1 trial participants available for analysis at 3 years, and that the reported difference in PFS indicated efficacy of olaparib with a PFS benefit from first-line maintenance.

9.14.4. The Committee noted that the median time to the first subsequent therapy or death in SOLO-1 was 51.8 with months olaparib vs 15.1 months with placebo (HR 0.30, 95% CI: 0.22 to 0.40). The Committee noted that, of the patients who received subsequent anti-cancer therapy, 33/94 (35%) in the placebo arm

received a PARP inhibitor. The Committee noted that freedom from second progression or death in SOLO-1 at 3 years (data maturity 31%) was 75% with olaparib vs 60% with placebo (HR 0.50; 95% CI: 0.35 to 0.72, P<0.001).

9.14.5. The Committee noted that the median interim overall survival (OS) was yet to be reached in either group in SOLO-1, and at 3 years (data maturity 21%) OS was 84% with olaparib vs 80% with placebo (HR 0.95, 95% CI: 0.60 to 1.53). The Committee considered that the immaturity of the OS data was a limitation of SOLO-1 trial evidence.

9.14.6. The Committee noted that grade 3 or 4 adverse events were reported in 39% of patients with olaparib vs 18% of patients with placebo in SOLO-1, and that the authors reported that most adverse events were managed by dose interruption or reduction. The Committee considered that the olaparib treatment in SOLO-1 was generally well tolerated.

9.15. The Committee noted an abstract presentation of SOLO-1 long-term follow-up data (Mathews et al. J Clin Oncol. 2019;37(Suppl 15):5541). The Committee noted the reported median PFS for patients with BRCA1 mutation was 41.4 months with olaparib vs 13.8 months with placebo (HR 0.41; 95% CI: 0.30 to 0.56); median PFS for BRCA2 mutation was not reached for olaparib vs 13.8 with placebo; and there were greater proportions of patients with BRCA2 mutations progression-free at 1, 2 and 3 years compared with BRCA1 mutations. The Committee considered that patients with BRCA2 mutation received a greater benefit.

9.16. The Committee noted the results of a post-hoc analysis of the SOLO-1 trial were presented at the European Society for Medical Oncology (ESMO) 2019 Congress (Friedlander et al. Ann Oncol. 2019;30(Suppl 9):IX77). The authors reported quality-adjusted PFS (QA-PFS) using the EQ-5D-5L instrument to measure time spent free of progression, and the time without symptoms of disease or toxicity metric (TWiST), measured in this analysis as mean PFS minus time with toxicity (specifically grade 2 or higher nausea, vomiting or fatigue). The Committee noted that the median QA-PFS was 29.75 months with olaparib vs 17.58 months with placebo (between-group difference 12.17 months [95% CI: 9.07-15.11], P<0.001) and the median TWiST was 33.15 months with olaparib vs 20.24 months with placebo (between-group difference 12.92 months [95% CI: 9.30-16.54], P<0.001). The Committee considered these results suggested a better response with olaparib despite the occurrence of adverse events.

9.17. The Committee noted that Study 19, a phase II, randomised (1:1), placebo-controlled study of olaparib in 265 patients with platinum-sensitive recurrent ovarian cancer, provided data for long-term treatment (median follow-up 6.5 years) with olaparib (Friedlander et al. Br J Cancer. 2018;119:1075-85). The Committee considered that the Study 19 patient population, who had received at least two prior lines of chemotherapy, was similar to that of SOLO-2, however, known BRCAm status was not required at study entry (retrospective germline/somatic testing determined that 74 patients who received olaparib and 62 patients who received placebo had BRCAm disease). The Committee considered that this limited interpretation of the statistically non-significant overall survival results, however, the Committee noted that 15 patients received olaparib maintenance for more than 6 years.

9.18. The Committee noted the long-term follow-up results of the SOLO-2 trial in platinum-sensitive, relapsed, BRCAm ovarian cancer which were presented at the American Society of Clinical Oncology (ASCO) 2020 conference (Poveda et al. J Clin Oncol. 2020;38 (Suppl 15):6002). The Committee noted that median OS was 51.7 months with olaparib vs 38.8 months with placebo after median 65 months follow-up (HR 0.74, 95%: 0.54 to 1.00, P=0.537), and 38.4% of patients on placebo crossed over to receive a PARP inhibitor. Members considered that this mild to moderate evidence of OS improvement from SOLO-2 suggests the lower-strength SOLO-1 evidence for 3-year survival rates may

underrepresent the potential OS benefit of olaparib first-line maintenance, noting that data maturity limited the strength of the SOLO-1 trial evidence.

9.19. The Committee noted the outcomes of a cost-effectiveness analysis of olaparib that compared data from SOLO-1 and SOLO-2 (Wolford et al. J Clin Oncol. 2019;37 Suppl 15:5545). The Committee noted that the cost of treating a patient until disease progression was higher in SOLO-1, but based on the differences in median PFS between groups in each trial, olaparib was more cost-effective when used in the first-line setting.

9.20. The Committee considered that, based on BRCA mutations occurring in about 16% of high-grade ovarian cancers, that approximately 21 to 31 patients per year may be eligible for olaparib in the first-line setting, and considered there would be high treatment uptake (likely 90-100%). Members estimated that a small number of registrations for other gynaecological cancers would be for patients with high-grade serous fallopian tube or peritoneal carcinomas and therefore would be within the target patient population, but considered that CaTSoP could comment on the likely proportion of such patients.

9.21. The Committee considered that funding olaparib in the first-line setting would incur a relatively small extra cost to the pharmaceutical budget due to a small increase in patient numbers, which would be expected as a result of treating this patient group at an earlier phase in their disease course i.e.when a larger proportion of patients may be suitable for treatment. If funded for first-line maintenance, the Committee considered that the number of patients who receive olaparib in the second-line setting would decrease over time. Members considered that, if funded for first-line maintenance, the total number of patients on olaparib treatment after 5 years of funding would be similar.

9.22. The Committee noted that approximately 10% of patients in SOLO-1 received a partial response from treatment with olaparib and continued treatment beyond two years, at investigator discretion, until disease progression. The Committee considered that CaTSoP could provide advice regarding an appropriate funded treatment duration for such patients.

9.23. The Committee considered that funding criteria should allow patients with ovarian cancer to access olaparib once per lifetime, based on the current evidence for olaparib being either in the first- or second-line setting, but not both. The Committee considered that CaTSoP could provide advice on other appropriate funding criteria for olaparib.

9.24. Members noted that use of olaparib as first- or second-line maintenance treatment for somatic BRCAm disease has been recommended by funding agencies in some jurisdictions (Australia's PBAC in March 2020, and Scotland's SMC in November 2016 and December 2019). Members considered there is evidence to suggest that patients with somatic BRCAm ovarian cancer receive a similar benefit from olaparib treatment as those with germline BRCAm. The Committee considered that CaTSoP could review and consider this evidence Mohyuddin et al. BMC Cancer. 2020;20:507; George et al. Oncotarget. 2017;8:43598-9). However, the Committee acknowledged that somatic mutation analysis may require an additional biopsy of a patient's tumour and that this could have cost, resource and patient safety implications.

9.25. The Committee noted there are clinical trials investigating other PARP inhibitors (e.g. niraparib, rucaparib, veliparib) for the treatment of high-grade serous ovarian cancer, including patients with BRCAm or homologous recombination deficiency (HRD). Members considered that these trials of PARP inhibitors in patients with HRD might identify a much larger potential patient population who could benefit from PARP inhibitors, but would be challenging to compare due to differences in HRD assays used and patient groups included (e.g. differences in disease staging and debulking surgery). The Committee considered that CaTSoP could consider whether there is a class affect among these agents for BRCAm ovarian cancer, and whether a similar benefit would also be expected in the patient population with HRD.