Record of the Cancer Treatment Subcommittee of PTAC Meeting held on 15 & 16 October 2020

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

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

The Cancer Treatment Subcommittee may:

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

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

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

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

The record of this Subcommittee meeting will be reviewed by PTAC at its February 2021 meeting.

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

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

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Present from the Cancer Treatment Subcommittee:
Marius Rademaker (Chair)
Allanah Kilfoyle
Anne O'Donnell
Chris Frampton
Lochie Teague
Michelle Wilson *(via zoom, part of)*
Peter Ganly
Richard Isaacs
Robert Matthew Strother
Scott Babington
Tim Hawkins

1. The role of PTAC Subcommittees and records of meetings

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

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

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

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

1.5. PHARMAC considers the recommendations provided by both the Cancer Treatment Subcommittee and PTAC and any other relevant PTAC Subcommittees when assessing applications for treatments for malignancy.

2. Summary of recommendations

2.1. The Subcommittee reiterated its previous **recommendation**, that daratumumab (in combination with bortezomib & dexamethasone) for relapsed/refractory multiple myeloma be listed within the context of treatment of malignancy, with a **low priority**.

2.2. The Subcommittee reiterated its previous **recommendation**, that the application for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) be **declined**, within the context of treatment of malignancy.

2.3. The Subcommittee **recommended** that pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma be **declined**, within the context of treatment of malignancy.

2.4. The Subcommittee **recommended** widening access of sunitinib and pazopanib to good prognosis RCC patients with a **high priority** within the context of treatment of malignancy, subject to Special Authority criteria.

2.5. The Subcommittee **recommended** that lenvatinib in combination with everolimus be funded for patients with advanced renal cell carcinoma who have progressed after one prior targeted therapy for the second-line treatment of patients with metastatic renal

cell carcinoma with a **medium priority**, within the context of treatment of malignancy, subject to Special Authority criteria.

2.6. The Subcommittee **recommended** that lenvatinib be funded for the treatment of radioactive iodine-refractory differentiated thyroid cancer with a **high priority**, within the context of treatment of malignancy, subject to Special Authority criteria.

2.7. The Subcommittee **recommended** that lenvatinib be funded for the first-line treatment of unresectable hepatocellular carcinoma with a **low priority**, within the context of treatments for malignancy, subject to Special Authority criteria.

2.8. The Subcommittee **recommended** that trastuzumab emtansine be funded for the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment with a **high priority**, within the context of treatment of malignancy, subject to Special Authority criteria.

2.9. The Subcommittee **recommended** that bendamustine be funded for the treatment of relapsed or refractory Hodgkin's lymphoma with a **medium priority**, within the context of treatment of malignancy, subject to Special Authority criteria.

2.10. The Subcommittee **recommended** that durvalumab be funded for patients with unresectable non-small cell lung cancer (NSCLC) who have PD-L1 positive (>1%) disease with a **high priority**, in the context of treatment of malignancy, subject to Special Authority criteria.

3. Record of Subcommittee meeting held Friday, July 3, 2020

3.1. The Subcommittee reviewed the minutes of the PTAC meeting held on 3 July 2020 and agreed that the minutes be accepted.

4. Correspondence and Matters Arising

Atezolizumab in combination with chemotherapy for first-line treatment of metastatic NSCLC

4.1. The Subcommittee reviewed correspondence from Roche that was received by PHARMAC in August 2020 regarding the application for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

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

Recommendation

4.3. The Subcommittee reiterated its previous **recommendation**, within the context of treatment of malignancy, that the application for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) be **declined**.

4.3.1. In reiterating its previous recommendation, the Subcommittee considered that the correspondence did not provide any new information that would change the Subcommittee's view and considered that the Subcommittee's previous records regarding this application remain the Subcommittee's assessment.

Discussion

4.4. The Subcommittee noted that, in April 2019**,** CaTSoP reviewed the application for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) and recommended that the application be declined, noting that the currently available evidence was insufficient to support a positive recommendation for the specific combination regimens at that time.

4.5. The Subcommittee noted that, in February 2020, Roche submitted new information in response to CaTSoP's April 2019 recommendation to decline, including new data from a number of Roche trials, an updated final analysis of the IMpower150 trial (which provided the key evidence for the supplier's initial application), and a recent expert review of the first-line atezolizumab combination regimen.

4.6. The Subcommittee noted that, in July 2020, CaTSoP reviewed the updated information from Roche, considered that the additional information provided by the supplier was not sufficient to alter its previous assessment such that a different recommendation could be made, and reiterated its previous recommendation that atezolizumab in combination with paclitaxel and carboplatin (with or without bevacizumab) for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC) be declined.

4.7. The Subcommittee noted that, in August 2020, in response to the July 2020 CaTSoP record, Roche submitted a letter that discussed overall survival outcomes from the IMpower150 trial in PD-L1 subgroups in the ITT-WT population, in patients with sensitising EGFR mutations, and in patients with liver metastases; also submitted were conference presentation slides regarding the final OS analysis of the IMpower150 clinical trial data (where PHARMAC staff had considered these likely corresponded to the abstract presented at the American Association for Cancer Research meeting in April 2020 by Socinski et al. (Cancer Res 2020;80(16 Supplement) CT216; DOI: 10.1158/1538-7445.AM2020-CT216).

4.8. The Subcommittee noted that atezolizumab in combination with paclitaxel and carboplatin is now Medsafe-approved for the first-line treatment of patients with metastatic NSCLC whose tumours have PD-L1 expression greater than or equal to 1%.

4.9. The Subcommittee noted that the Roche submission sought further consideration of the subgroup analyses, in particular, from the IMpower150 trial. The Subcommittee considered that the updated correspondence, while hypothesis generating, did not provide any meaningful new data to support a change in the recommendation, and noted that the IMpower150 trial data cut-off date for the newly submitted information had been the same as that of the data reviewed at the July 2020 CaTSoP meeting.

4.10. The Subcommittee considered that its previous assessment of the four-drug regimen (atezolizumab, bevacizumab, paclitaxel and carboplatin) has been clearly articulated in previous records. The Subcommittee considered again that, as detailed in the previous records, the clinical trial data does not provide sufficient information for assessment of the risks and benefits of the three-drug regimen (atezolizumab, paclitaxel and carboplatin) because not all relevant data was reported for all treatment arms, as a consequence of the trial design and prospective decision rules with the IMpower150 trial's statistical analysis and data publishing plans. Members considered that it was disappointing that a formal analysis to inform assessment of the intervention of interest (ie atezolizumab, paclitaxel and carboplatin versus a relevant comparator ie paclitaxel and carboplatin) would not be forthcoming from the IMpower150 trial.

4.11. The Subcommittee considered that the new correspondence did not provide new information that would change the Subcommittee's view, and considered that the Subcommittee's previous records regarding this application and the three- and four-drug treatment regimens remain accurate representations of the Subcommittee's assessment.

Gemtuzumab ozogamicin for de novo acute myeloid leukaemia

Discussion

4.12. The Subcommittee noted that at its July 2020 meeting it had recommended that gemtuzumab ozogamicin (one dose only, with intensive chemotherapy) be funded for the treatment of de novo acute myeloid leukaemia with a high priority within the context of treatment of malignancy, subject to Special Authority criteria.

4.13. The Subcommittee noted the applicant's correspondence and request to remove the capped dosing at 5 mg for all patients if one dose were to be funded. The Subcommittee considered that this would require a large proportion of the population to need greater than one vial of gemtuzumab-ozogamicin for patients with acute myeloid leukemia (AML).

4.14. The Subcommittee reviewed the dosing regimen for gemtuzumab-ozogamicin in the AML15 and AML16 trials (Hills et al. Lancet Oncol. 2014;15:986-96; Burnett et al. J Clin Oncol. 2011;29:369-77; Burnett et al. J Clin Oncol. 2012;30:3924–31), and unpublished emerging evidence (AML 19 and AML 18 trial data]), and considered that it was appropriate for the recommendation for dosing to reflect this evidence. Therefore, the Subcommittee considered that it was appropriate to change the recommended dosing regimen to 3 mg per m^2.

4.15. The Subcommittee noted that most patients would require more than one vial, and considered that there would not be the ability to undertake vial sharing, given the low frequency of administration of gemtuzumab-ozogamicin. The Subcommittee considered that the increased requirement for vials would incur a significant additional cost, although noted that rounding weight-based dosing volumes to the nearest 10% is very common for similar products, which may reduce some of that large cost increment to a small extent.

4.16. The Subcommittee maintained its high priority recommendation for gemtuzumab ozogamicin in this setting, even with the removal of the capped dosing regimen.

Daratumumab (in combination with bortezomib & dexamethasone) for relapsed/refractory multiple myeloma

4.17. The Subcommittee reviewed correspondence from Janssen that was received by PHARMAC in March 2020 regarding daratumumab (in combination with bortezomib & dexamethasone) for relapsed/refractory multiple myeloma.

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

Recommendation

4.19. The Subcommittee reiterated its previous **recommendation**, that daratumumab (in combination with bortezomib & dexamethasone) for relapsed/refractory multiple myeloma be listed within the context of treatment of malignancy, with a **low priority**.

Discussion

4.20. The Subcommittee noted that in October 2019 it recommended funding daratumumab (in combination with bortezomib & dexamethasone) with a low priority. The Subcommittee considered that the progression free survival benefit was substantial but the low priority was due to the high cost and the lengthy infusion time for daratumumab intravenous (IV) treatment.

4.21. The Subcommittee noted the updated information from the CASTOR trial provided by the applicant. The Subcommittee considered that the population included in this trial, having received one prior line of treatment was reflective of the New Zealand patient population for which funding was requested.

4.22. The Subcommittee noted that in October 2019 limited evidence supporting a 90-minute infusion for daratumumab IV was reviewed which had been presented at the 2019 American Society of Haematology annual meeting (ASH) and that a subcutaneous formulation of daratumumab (daratumumab SC) had been developed.

4.23. The Subcommittee noted the information provided by the applicant comparing infusion times for daratumumab and carfilzomib. The Subcommittee noted that the 90-minute infusion regimen was not present on the Medsafe datasheet. The Subcommittee noted that the infusion time over two years for carfilzomib (70 mg/m^2 once weekly [QW] from the ARROW trial (Moreau P, et al. Lancet Oncology. 2018;19:953-64) remained less than that of the daratumumab 90 minute accelerated IV infusion protocol from week 3 onwards. However, the Subcommittee noted that it had reviewed the ARROW trial data, and that while carfilzomib 70 mg/m^2 QW could be considered an option, there was insufficient evidence to mandate this dosing regimen over that used in the ENDEAVOUR trial (56 mg/m^2 twice weekly [BIW]). The Subcommittee noted the information provided by the applicant highlighting that carfilzomib would require more frequent infusions than daratumumab. The Subcommittee considered that both daratumumab and carfilzomib would have significant impact on infusion services on day wards.

4.24. The Subcommittee noted the unpublished information provided by the applicant about the CASTOR trial, indicating that with 40.0 months median follow-up, the risk of death was reduced by 45% for daratumumab IV / bortezomib plus dexamethasone (DVd) treated patients versus Vd patients. The Subcommittee noted that in the ENDEAVOUR trial, after 44 months median follow-up, the risk of death was reduced by 23% for carfilzomib plus dexamethasone (Kd) versus Vd (Orlowski R, et al. Clin Lymphoma Myeloma Leuk. 2019;19:522-530). The Subcommittee noted that DVd reportedly increased the median PFS by 19.1 months (Weisel K, et al. J Clin Oncol. 2019 37:15_suppl, 8040-8040), compared to 12.1 months for Kd (Moreau P, et al. Leukemia. 2017;31:115–22). The Subcommittee noted that cross trial comparisons are usually problematic, however the Subcommittee considered that populations present in both the CASTOR and ENDEAVOUR trials were similar (in terms of age, International Staging System staging, prior lines of therapy) and noted that the comparator was bortezomib plus dexamethasone (Vd) in both trials.

4.25. The Subcommittee noted the update provided by the supplier for the CASTOR trial with a median follow up of 50.2 months. The Subcommittee noted that for patients who had received one prior line of therapy, the median PFS was 27.0 months vs 7.9 months (HR, 0.21; 95% CI, 0.15-0.31, P <0.0001) for D-Vd vs Vd. In comparison, the median PFS was 22.2 months vs 10.1 months (HR, 0.45; 95% CI, 33-0.61, P <0.0001) for Kd vs Vd (Moreau P, et al. Leukemia. 2017;31:115–122).

4.26. The Subcommittee noted that daratumumab IV and carfilzomib IV have different mechanisms of action, and considered their toxicity profiles to be different. The

Subcommittee noted the cardiovascular toxicity associated with carfilzomib, which is not observed for daratumumab. The Subcommittee considered that this may influence the number of patients that would be considered fit for carfilzomib IV compared to daratumumab.

4.27. The Subcommittee considered that if these products were compared solely on efficacy and tolerability, that daratumumab IV may be more favourable than carfilzomib. The Subcommittee noted that it had not previously reviewed detailed data supporting a 90-minute infusion for daratumumab and that it was not present ihe nen the Medsafe datasheet. The Subcommittee considered that the new evidence for a reduced infusion time daratumumab was not sufficient to improve the low priority recommendation for daratumumab IV and that the significant cost of daratumumab IV remained a significant factor.

4.28. The Subcommittee noted the information provided by the applicant regarding a comparison of the daratumumab SC and daratumumab IV. The Subcommittee noted that Medsafe approval for daratumumab SC is anticipated by end of year. The Subcommittee considered that there would be considerable benefit in the reduction in infusion time that would occur with daratumumab SC.

4.29. The Subcommittee noted that the rate of infusion-related reactions (IRRs) were reportedly significantly reduced with daratumumab SC compared to daratumumab IV (12.7% and 34.5% respectively, p<0.0001) (Mateos M-V, et al. J Clin Oncol. 2019 37:15_suppl, 8005-8005), but the severity of adverse events was unclear for both formulations.

4.30. The Subcommittee noted that patient reported outcome measures reported higher satisfaction and more positive perception of treatment for daratumumab SC compared to daratumumab IV. The Subcommittee considered that daratumumab SC could be given as an outpatient in regional cancer centres, however, this would likely not occur for the first few administrations.

4.31. The Subcommittee considered that daratumumab SC would be advantageous. However, considered that some details are currently uncertain including the shelf-life of daratumumab SC and how this could impact use and accessibility in the community. The Subcommittee noted the parallel assessment process and that daratumumab SC is not yet Medsafe approved. The Subcommittee considered that it would be more appropriate for daratumumab SC to be reviewed at a future meeting, and encouraged a funding application for daratumumab SC when ready.

Lenalidomide maintenance following frontline autologous SCT (Eastern Cooperative Oncology Group (ECOG) performance status)

Discussion

4.32. The Subcommittee noted its April 2018 recommendation that lenalidomide as maintenance treatment for patients with multiple myeloma following first-line autologous SCT be listed with a medium priority.

4.33. The Subcommittee noted correspondence that was received during consultation related to this decision to widen access to lenalidomide as maintenance treatment for patients with multiple myeloma following first-line autologous SCT, that indicated that the Eastern Cooperative Oncology Group (ECOG) performance status score to enable eligibility for lenalidomide maintenance therapy was too restrictive and should be widened to include patients with an ECOG performance status score of 2.0.

4.34. The Subcommittee noted that the McCarthy et al. tral (N Engl J Med. 2012;366:1770-81) had included only patients with an Eastern Cooperative Oncology Group functional performance status (ECOG PS) of 0 and 1, while other trials in this setting (Palumbo et al. N Engl J Med. 2014;371:895-905**;** and Jackson et al. Lancet Oncol. 2019;20:57-73) did not include performance status as a criterion for entry.

4.35. The Subcommittee noted that fewer transplants had been performed than expected, possibly related to deferrals with the health sector response to COVID-19, which would have contributed significantly to the reduced applications for lenalidomide in this setting.

4.36. The Subcommittee considered that very few patients would not meet the criteria for access based on performance status. The Subcommittee considered that most patients post-transplant would have an ECOG status of 0 or 1 already and be commenced on lenalidomide maintenance therapy. As most clinicians expect ECOG performance status to improve, ECOG performance status would not significantly affect patients' access to maintenance lenalidomide.

4.37. The Subcommittee considered that the patient group who would not meet the criteria for treatment would primarily be for reasons other than limited performance status and therefore, the widening of access to patients with an ECOG performance status of 2 would likely not increase the number of patients eligible for treatment. Based on this, the Subcommittee considered it appropriate to remove ECOG performance status from the criteria.

Treatment holidays for pertuzumab and trastuzumab for metastatic breast cancer

Discussion

4.38. The Subcommittee noted correspondence received by PHARMAC from a clinician requesting whether a "treatment holiday" would be permissible under the current Special Authority criteria for pertuzumab and trastuzumab for patients with metastatic breast cancer, where a treatment holiday is the deliberate cessation of treatment for reasons other than disease progression. The Subcommittee noted that PHARMAC staff considered that this would not be permissible under the current criteria and were seeking advice on whether this should be permitted by Special Authority criteria.

4.39. The Subcommittee noted that the use of trastuzumab for treatment beyond disease progression was considered by CaTSoP in November 2010. At that time, CaTSoP recommended that the application for funding of further trastuzumab treatment, for HER-2 positive metastatic breast cancer following disease progression on trastuzumab, should be declined. At that time, members considered that treatment with trastuzumab should be discontinued at the time of tumour progression and further applications should be declined.

4.40. The Subcommittee noted that the use of pertuzumab re-treatment in this manner has not been specifically considered by PHARMAC's clinical advisors.

4.41. The Subcommittee noted that the use of pertuzumab in combination with trastuzumab in previously treated metastatic HER-2 positive breast cancer has been considered by PHARMAC's clinical advisors on a number of occasions. Most recently, in September 2018, CaTSoP recommended that pertuzumab in combination with trastuzumab be funded with a low priority as a second-line treatment for patients who have progressed on or after previous treatment with trastuzumab for their metastatic disease, and who have not had any other lines of treatment since stopping trastuzumab, subject to

Special Authority criteria. The Subcommittee noted that this second-line treatment setting is not the same as the re-treatment being requested.

4.42. The Subcommittee noted that CaTSoP had considered pembrolizumab retreatment within a wider discussion regarding immune checkpoint inhibitors for the treatment of advanced melanoma, including assessment of evidence in patients receiving pembrolizumab who experienced treatment holidays, at its meeting in July 2019.

4.43. The Subcommittee considered that the Special Authority criteria do not permit a treatment holiday for pertuzumab and trastuzumab, and that should a patient stop treatment without having disease progression, then they would not be considered eligible for treatment beyond disease progression.

4.44. The Subcommittee considered that there may be a fiscal rationale to allow treatment holidays, as in the short term there would be a period of time where no treatment was being funded, however there would likely be significant budgetary uncertainty if patients were able to resume treatment beyond disease progression. The Subcommittee considered that there was no clear, high quality evidence identified to support this approach for pertuzumab or trastuzumab and that if a treatment holiday were permitted under the current criteria for pertuzumab and trastuzumab that this would have significant implications for other funded treatments of malignancy. The Subcommittee considered that, in patients for whom treatment is stopped for reasons other than disease progression and who subsequently wish to restart treatment, an application could be made via PHARMAC's exceptional circumstances pathway. The Subcommittee noted that there would be no guarantee of approval via this pathway, and considered that it would be important for clinicians to gain consent from the patient regarding the risks involved with this approach.

4.45. The Subcommittee considered that it would be difficult to estimate the budgetary impact or cost-utility of allowing treatment holidays for pertuzumab and trastuzumab, in particular due to the lack of identified evidence to support this approach. The Subcommittee considered it would not, at this time, be appropriate to amend the Special Authority criteria to allow treatment holidays.

5. Pembrolizumab for first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)

Application

5.1. The Subcommittee reviewed the application for pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma.

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

Recommendation

5.3. The Subcommittee **recommended** that pembrolizumab for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma be **declined**, in the context of treatment of malignancy.

5.3.1. In making this recommendation, the Subcommittee considered: the New Zealand patient population with high incidence of HPV-positive oropharyngeal cancer; the patient population with HNSCC in the clinical trial evidence with different epidemiology, characteristics and prognosis; the lack of an appropriate comparator treatment in the key clinical trial evidence for the New Zealand

context; and the evidence for short-term outcomes of pembrolizumab only. The Subcommittee considered that longer term data would be unable to inform this assessment given the limited applicability of data in the trial population to the clinical population with HNSCC in New Zealand.

Discussion

5.4. The Subcommittee noted that head and neck cancer can affect a number of anatomical sites and that the clinical trial evidence classifies this disease into two distinct subgroups; either nasopharyngeal (associated with Epstein-Barr virus [EBV], with a poor prognosis) or mucosal-associated disease, of which the majority are squamous cell carcinomas classed as oropharyngeal. The Subcommittee noted that historically patients with squamous cell carcinoma (SCC) of the head and neck (HNSCC) had been of older age with an extensive history of smoking and alcohol use.

5.5. The Subcommittee noted that the number of patients diagnosed with HNSCC with these characteristics is changing worldwide and in New Zealand, patients diagnosed with HNSCC are younger, have less exposure to alcohol and smoking, and there is a high incidence (about 78% of cases) of human papilloma virus (HPV)-positive oropharyngeal cancer consistent with international increases in HPV-positive disease (Lucas-Roxburgh et al. PLoS One. 2017;12:e0186424). The Subcommittee considered that the future incidence of HNSCC was uncertain, given the current substantial increase in incident cases but countered by the future effects of HPV vaccination programmes.

5.6. The Subcommittee noted that patients with tumour suppressor protein p16-positive (HPV-associated) HNSCC have a relatively good prognosis, however, prognosis varies according to different AJCC 8th edition disease stages, with about two-thirds of patients with HNSCC having higher-stage disease (eg stage III and IV) at diagnosis, with likely five-year survival of about 50% for stage III and 20-40% for stage IV disease (Lydiatt et al. CA Cancer J Clin. 2017;67:122-37).

5.7. The Subcommittee noted that testing for programmed death-ligand 1 (PD-L1) is not performed as standard of care of patients with HNSCC in New Zealand, and PD-L1 combined positive score (CPS) testing is not performed at all in New Zealand. The Subcommittee considered that PD-L1 CPS testing would require substantial laboratory investment, implementation and training.

5.8. The Subcommittee considered that there is no data to indicate whether patients with HNSCC who have PD-L1 CPS of ≥1 have a different health need to those with CPS <1.

5.9. The Subcommittee noted a correlation between HPV and PD-L1 positivity, and considered that more than 85% of patients with recurrent or metastatic HNSCC may have PD-L1 CPS >1 given the increasing incidence of HPV-positive disease.

5.10. The Subcommittee noted that fit patients with HPV-positive HNSCC may be suitable for treatment with curative intent, although the effects of first-line therapy can be challenging for patients; those with recurrent or metastatic HNSCC have limited treatment options generally associated with a short duration of efficacy, leading to a progressive decline and death. The Subcommittee considered that the health of families/whānau of the population with HPV-positive HNSCC could also be affected by HNSCC, due to its the impact of the disease and its treatment on the earning potential of the patient.

5.11. The Subcommittee considered that there is no one current standard of care treatment for recurrent/metastatic HNSCC in New Zealand, and that treatment may include weekly taxane (usually paclitaxel) in the large group of younger, fit patients with HPV-positive disease, or cisplatin and 5-fluorouracil in a smaller proportion of patients (fit, older patients without significant comorbidities; about one quarter of cases), although some patients would decline or be too unwell for second line treatment and be managed supportively with palliative care.

5.12. The Subcommittee noted that in 2017 there were 553 registrations for HNSCC (ICD C00-C14), with age-standardised registration rates of 11.1 and 5.1 per 100,000 for males and females respectively, and there were 136 deaths due to HNSCC in 2013 (2.7 and 1.2 per 100,000 for males and females, respectively, age-standardised; Ministry of Health, 2016). The Subcommittee considered that increasing registration rates over time were consistent with increasing incidence worldwide, and that the stable (or possibly decreased) mortality rate was related to the curative treatment of an increasingly HPV-positive population.

5.13. The Subcommittee noted that age-standardised incidence rates of oropharyngeal HNSCC are higher for Māori (relative risk 1.4) and for people in areas of higher deprivation (relative risk 2.7) than non-Māori (Chelimo et al. Aust N Z J Public Health. 2015;39:162-7). The Subcommittee noted that Māori have worse survival from HNSCC than non-Māori, and that timely access to treatment is a factor (Cancer Control Agency. 2020. Head and Neck Cancer Quality Performance Indicators: Draft descriptions for review). The Subcommittee considered that Pacific people also have a high relative risk of acquiring HPV-associated HNSCC.

5.14. The Subcommittee noted the findings of the GLANCE study, an international review of treatment and outcomes in recurrent/metastatic HNSCC that was funded by MSD (Grunwald et al. Oral Oncol. 2020;102:104526). The Subcommittee noted that GLANCE included a small proportion (30%, N = 221) with oropharyngeal disease, of which 25% (N = 56) were tested for HPV status and 15% (N = 35) were p16 positive. The Subcommittee considered that survival of the GLANCE population after relapse (median OS 8.0 months in patients who received cetuximab + platinum +/- 5-fluorouracil) was influenced by the disease of that population, which was different to that of the current New Zealand population with HNSCC.

5.15. The Subcommittee noted that pembrolizumab was proposed as a first-line treatment option for patients with recurrent or metastatic HNSCC, either as monotherapy in the population with PD-L1 combined positive score [CPS] ≥1, or in combination with platinum and 5-fluorouracil for all patients irrespective of PD-L1 CPS.

5.16. The Subcommittee noted that pembrolizumab is approved by Medsafe for several oncology indications and is currently being evaluated by Medsafe for first-line treatment of recurrent or metastatic HNSCC. The Subcommittee noted that at the time of submission, the application for recurrent or metastatic HNSCC was considered to meet PHARMAC's criteria for consideration under the parallel assessment pathway, which provides for consideration of cancer medicines at the same time as they are assessed by Medsafe.

5.17. The Subcommittee noted the key evidence for pembrolizumab in recurrent/metastatic HNSCC comes from the three arm, open-label, randomised, phase III Keynote-048 trial of pembrolizumab alone vs pembrolizumab plus platinum and 5-fluorouracil vs cetuximab plus platinum and 5-fluorouracil in 882 patients with SCC of the oropharynx (about 38%), oral cavity, hypopharynx and larynx (Burtness et al. Lancet. 2019;394:1915-28).

5.17.1. The Subcommittee noted that median follow-up in Keynote-048 was 11.5 months, 13 months, and 10.7 months for the three treatment groups, respectively; these median values were the same at the second interim analysis and at the final analysis. The Subcommittee considered these analyses were performed early relative to expected outcomes in HNSCC but that this follow-up may have been skewed by crossover, as almost half of patients in each arm received subsequent anticancer therapy.

5.17.2. The Subcommittee noted that Keynote-048 included known p16 status for patients with oropharyngeal disease (positive in ~20% of the trial population), stratified patients by PD-L1 expression (50% threshold) based on the IHC 22C3 assay which is not used in New Zealand, and tested PD-L1 CPS. The Subcommittee considered that the baseline characteristics of trial participants represented a historical profile of HNSCC which would make the results difficult to interpret for current and future HNSCC patients as the profile continues to evolve.

5.17.3. The Subcommittee noted pembrolizumab 200 mg was administered three-weekly until progression, intolerable toxicity or for a maximum of 35 cycles. The Subcommittee noted that the Keynote-048 trial provided no evidence for any difference in risks or benefits between pembrolizumab dosing regimens (ie 200 mg three-weekly vs 400 mg six-weekly).

5.17.4. The Subcommittee noted that Keynote-048 used cetuximab plus platinum and 5-fluorouracil (the EXTREME regimen) as comparator, and considered this was not applicable to New Zealand patients with HNSCC as cetuximab is not funded in this setting.

5.17.5. The Subcommittee noted that Keynote-048 had 14 primary hypotheses with hypothesis testing both sequentially and in parallel, however, the specific methodology and analysis rules were hard to locate. The Subcommittee noted that the statistical plan was based on the aggregated patient population without subgroup analysis (eg of HPV-positive oropharyngeal disease) and was complicated by the number of outcomes, treatment arms and analyses (two interim and one final), risking type 1 error conflation. The Subcommittee considered that the primary hypothesis was likely exploratory in nature, the validity of the approach was unclear, and the alpha may have been overspent in multiple analyses.

5.17.6. The Subcommittee noted that 12-month overall survival (OS) in Keynote-048 was 57% with pembrolizumab alone vs 44% with cetuximab and chemotherapy and was 35% vs 19%, respectively, at 24 months in the CPS ≥1 population. The Subcommittee noted that OS in the total population was 53% with pembrolizumab and chemotherapy vs 44% with cetuximab and chemotherapy at 12 months and 29% vs 19% at 24 months, respectively. The Subcommittee considered it was uncertain whether the reported OS benefit would continue or diminish due to heavy censoring of data after 15 months and extrapolation beyond two years**,** noting that <15% of the starting population were available for follow-up after 2 years.

5.17.7. The Subcommittee noted that median progression free survival (PFS) was 3.2 months with pembrolizumab alone vs 4.9 months with pembrolizumab and chemotherapy; PFS estimates in these two groups were 28% vs 45%, respectively, at 6 months and 20% vs 17% at 12 months, respectively. The Subcommittee noted the data indicated PFS2 (the difference in time after

progression before a patient received their next line of treatment) was improved with pembrolizumab alone and pembrolizumab with chemotherapy, and considered that this suggested some duration of response, although tempered by the data being heavily censored beyond 24 months.

5.17.8. The Subcommittee noted that grade ≥3 treatment-related adverse events occurred in 17%, 72%, 69% of patients who received pembrolizumab alone, pembrolizumab with chemotherapy, and cetuximab with chemotherapy, respectively. The Subcommittee noted that there were 3 (1%), 11 (4%) and 8 (3%) treatment-related deaths reported in patients who received pembrolizumab alone, pembrolizumab with chemotherapy, and cetuximab with chemotherapy, respectively. The Subcommittee considered these event rates were as would be expected for this population with decreased health status.

5.17.9. The Subcommittee considered that Keynote-048 provided moderate quality evidence suggesting an improvement at 12 months from pembrolizumab for the patients with recurrent/metastatic HNSCC, although whether the benefit was sustained beyond this time-point or diminished was uncertain due to short-term follow-up, and the proposed five-year treatment benefit was therefore uncertain. The Subcommittee considered that the survival data for the Keynote-048 population with HNSCC underrepresented HPV-positive oropharyngeal disease and therefore would not reflect outcomes for the New Zealand patients with predominantly HPV-associated oropharyngeal SCC, and considered that these two patient populations represent distinct subtypes, which each having different epidemiology, characteristics and prognosis. The Subcommittee considered that longer term data would be unable to inform this assessment given the limited applicability of data in the trial population to the clinical patient population.

5.18. The Subcommittee noted an unpublished technical report on a systematic review and meta-analysis that was funded by MSD, which indicated a benefit of pembrolizumab over other agents for first-line treatment of R/M HNSCC. The Subcommittee considered that although the methodology appeared robust, the analysis could have been vulnerable to possible bias due to the influence of the modeller's decision making regarding assumptions used.

5.19. The Subcommittee noted that NICE (England and Wales) had suspended their review of pembrolizumab for recurrent/metastatic HNSCC in July 2020**,** pending clarification regarding differences between the trial population and the clinical patient population.

5.20. The Subcommittee considered that, if pembrolizumab were funded for recurrent/metastatic HNSCC, the majority of uptake would be in younger, fit patients who would receive pembrolizumab in combination with cisplatin and 5-fluorouracil; and considered that an estimated 3.6% increase in incident cases was likely an underestimate, considering p16 positivity (and therefore HPV-associated disease) in New Zealand. The Subcommittee considered there would likely also be uptake in patients with co-morbidities that preclude chemotherapy, and in these patients pembrolizumab would be used as a single agent.

5.21. The Subcommittee considered that the changing epidemiology of HNSCC in New Zealand would likely mean the proportion of PD-L1 CPS positive patients would be greater than expected. The Subcommittee considered that the prognostic and/or predictive value of PD-L1 in recurrent/metastatic HNSCC and the characteristics of an HNSCC population defined by PD-L1 were unclear, due to limited data with inconsistent findings; however, Members noted that there is some evidence to suggest

that PD-L1 expression may be higher in HPV-positive HNSCC and that this may be associated with better OS (eg. Hong et al. Oral Oncol. 2019;92:33-9**;** Lilja-Fischer et al. Acta Oncol. 2020;59:666-72).

5.22. The Subcommittee considered that funding pembrolizumab for recurrent/metastatic HNSCC would result in substantial increased costs to the health system, due to PD-L1 CPS testing and oncology clinic visits for treatment and for management of immune-related adverse events; palliative care costs and treatment of secondary oropharyngeal cancers (occurring in those with prior HPV exposure who may have remaining tissue at risk) may be deferred but not eliminated. The Subcommittee considered it difficult to quantify the health system costs arising from patients who develop immune-related adverse events, as these patients require substantial clinical management, that varies greatly dependant on the organ at risk and its impacts (eg hepatitis, pneumonitis).

5.23. The Subcommittee considered that the epidemiology and incidence of HPV-associated malignancies was changing and could decrease in future decades as a result of immunisation programmes, and considered that New Zealanders could benefit from increased uptake of HPV vaccination in certain age groups (eg under 16 or under 20 years). The Subcommittee considered that the Immunisation Subcommittee could review the evidence for HPV vaccination in groups relevant to the New Zealand patient population including people aged 27 to 45 years (as considered by the US Centers for Disease Control [CDC]; Meites et al. MMWR Morb Mortal Wkly Rep 2019;68:698–702) and the evidence for potential diminishing efficacy in older patients, with respect to the updated New Zealand Immunisation Handbook (Ministry of Health, 2020).

5.24. Overall, the Subcommittee considered that the clinical trial evidence for pembrolizumab for recurrent/metastatic HNSCC suggested an uncertain survival benefit beyond 12 months and the study population did not align particularly well with the current New Zealand patient population with increasingly HPV-associated disease. The Subcommittee considered that it would welcome a submission with evidence for use in a relevant population with HPV-associated, oropharyngeal, recurrent/metastatic SCC.

6. Tyrosine kinase inhibitors (sunitinib, pazopanib) for the treatment of renal cell carcinoma (advanced or metastatic) - good prognosis patients (widening access)

Application

6.1. The Subcommittee reviewed a clinician application for the access widening of sunitinib and pazopanib for first line treatment of renal cell carcinoma (RCC) for patients with a good prognosis.

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

Recommendation

6.3. The Subcommittee **recommended** widening access of sunitinib and pazopanib to good prognosis RCC patients with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria (additions in bold and deletions in strikethrough):

Sunitinib

Initial application — (RCC) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1 The patient has metastatic renal cell carcinoma; and
2 Any of the following:
2.1 The patient is treatment naïve; or
2.2 The patient has only received prior cytokine treatment; or
2.3 The patient has only received prior treatment with an investigational agent within the confines of a *bona fide* clinical trial which has Ethics Committee approval; or
2.4 Both:
2.4.1 The patient has discontinued pazopanib within 3 months of starting treatment due to intolerance; and
2.4.2 The cancer did not progress whilst on pazopanib; and
3 The patient has good performance status (~~WHO~~/ECOG grade 0-2); and
4 The disease is of predominant clear cell histology; and
~~The patient has intermediate or poor prognosis defined as:~~
~~5 Any of the following:~~
~~5.1 Lactate dehydrogenase level > 1.5 times upper limit of normal; or~~
~~5.2 Haemoglobin level < lower limit of normal; or~~
~~5.3 Corrected serum calcium level > 10 mg/dL (2.5 mmol/L); or~~
~~5.4 Interval of < 1 year from original diagnosis to the start of systemic therapy; or~~
~~5.5 Karnofsky performance score of less than or equal to 70; or~~
~~5.6 2 or more sites of organ metastasis; and~~
~~6~~5 Sunitinib to be used for a maximum of 2 cycles.

Renewal — (RCC) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
Both:
1 No evidence of disease progression; and
2 The treatment remains appropriate and the patient is benefiting from treatment.

Notes: Sunitinib treatment should be stopped if disease progresses.
~~Poor prognosis patients are defined as having at least 3 of criteria 5.1-5.6. Intermediate prognosis patients are defined as having 1 or 2 of criteria 5.1-5.6.~~

Pazopanib

All of the following:
1 The patient has metastatic renal cell carcinoma; and
2 Any of the following:
2.1 The patient is treatment naïve; or
2.2 The patient has only received prior cytokine treatment; or
2.3 **The patient has only received prior treatment with an investigational agent within the confines of a *bona fide* clinical trial which has Ethics Committee approval; or**
2.4 Both:
2.4.1 The patient has discontinued sunitinib within 3 months of starting treatment due to intolerance; and
2.4.2 The cancer did not progress whilst on sunitinib; and
3 The patient has good performance status (~~WHO~~/ECOG grade 0-2); and
4 The disease is of predominant clear cell histology; and
~~The patient has intermediate or poor prognosis defined as:~~
~~5 Any of the following:~~
~~5.1 Lactate dehydrogenase level > 1.5 times upper limit of normal; or~~
~~5.2 Haemoglobin level < lower limit of normal; or~~
~~5.3 Corrected serum calcium level > 10 mg/dL (2.5 mmol/L); or~~
~~5.4 Interval of < 1 year from original diagnosis to the start of systemic therapy; or~~
~~5.5 Karnofsky performance score of less than or equal to 70; or~~
~~5.6 2 or more sites of organ metastasis; and~~
~~6~~5 Pazopanib to be used for a maximum of 2 cycles.

Renewal — (RCC) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
Both:
1 No evidence of disease progression; and
2 The treatment remains appropriate and the patient is benefiting from treatment.

Notes: Pazopanib treatment should be stopped if disease progresses.
~~Poor prognosis patients are defined as having at least 3 of criteria 5.1-5.6. Intermediate prognosis patients are defined as having 1 or 2 of criteria 5.1-5.6.~~

6.3.1. The Subcommittee made this recommendation based on the high unmet health need for these patients, the strong evidence demonstrating benefit for good prognosis patients, particularly if the overall cost-effectiveness of sunitinib and/or pazopanib was improved through PHARMAC's competitive tender process. The Subcommittee also considered that it should review checkpoint inhibitors in combination treatment in the first line setting for RCC with a high priority.

Discussion

6.4. The Subcommittee noted that sunitinib and pazopanib are orally administered tyrosine kinase inhibitors, both of which are Medsafe approved for the treatment of clear cell renal cell carcinoma (clear cell RCC). The Subcommittee noted that in 2017, the rates of kidney cancer registration for Māori compared to non-Māori were 11.3 to 7.6, respectively, per 100,000 (Ministry of Health, 2020). The Subcommittee also noted the Effect of Comorbidity on Care and Cancer Survival Inequalities Study – known as the C3 (Quantitative) study – conducted by Otago university in 2014 reported that Māori kidney cancer patients were 52% more likely to die of their cancer than non-Māori (HR: 1.52; 95% CI, 1.01 to 2.29) (Sarfati et al. 2014. Wellington: University of Otago).

6.5. The Subcommittee noted that currently sunitinib and pazopanib are funded for treatment of clear cell RCC for intermediate to poor prognosis patients, defined by any of the following: lactate dehydrogenase level > 1.5 times upper limit of normal; haemoglobin level < lower limit of normal; corrected serum calcium level > 10 mg/dL (2.5 mmol/L); interval of < 1 year from original diagnosis to the start of systemic therapy; Karnofsky performance score of less than or equal to 70; 2 or more sites of organ metastasis. The Subcommittee noted that these criteria are based on, but not identical to, the Memorial Sloan-Kettering Cancer Center (MSKCC/Motzer) score for clear cell RCC. The Subcommittee considered that approximately 35% of newly diagnosed RCC patients are expected to have a good prognosis. The Subcommittee noted that current Special Authority criteria for sunitinib and pazopanib requires patients to have at least two sites of distance metastases and considered that this should be removed from the criteria regardless of access widening as this limits access to some intermediate and poor prognosis patients and is not a part of the MSKCC scoring system, nor the more widely used IMDC (International Metastatic RCC Database Consortium) score used to assess prognostic group.

6.6. The Subcommittee noted that sunitinib had been previously considered by CaTSoP for the treatment of good prognosis RCC patients in November 2010 at which time the Subcommittee considered that sunitinib should be funded for all patients with metastatic RCC, but due to its high cost the Subcommittee recommended sunitinib be declined for funding for good prognosis patients. Sunitinib was funded for intermediate and poor prognosis patients in 2010. The Subcommittee noted that funding for pazopanib was considered at the CaTSoP April 2011 meeting where the Subcommittee considered that that because sunitinib was already funded, there was no evidence of an unmet health need that pazopanib would address, and it was recommended for funding with a low priority for patients with intolerable side effects on sunitinib, and cost-neutral as an alternative to sunitinib. Pazopanib was funded for intermediate and poor prognosis patients in 2012. The Subcommittee noted that sunitinib and pazopanib are currently only funded for first-line treatment of intermediate to poor prognosis RCC, and patients are only permitted to switch between the two

medicines if they experience intolerable side effects on one or the other within three months of commencement of either therapy.

6.7. The Subcommittee noted that ESMO and NCCN guidelines recommend sunitinib and pazopanib for use in good, intermediate, and poor prognosis patients only as alternatives following failure of preferred first line treatments. The Subcommittee considered that patients in New Zealand do not have funded access to first-line treatments which are currently available and considered to be preferable internationally, based on the most recent treatment guidelines.

6.8. The Subcommittee considered that the evidence for use of sunitinib in the first line treatment of good prognosis RCC patients was of high strength and quality from large and well powered randomised phase III trials with appropriate control arms and mature follow-up data. The Subcommittee noted that more data was unlikely to be published, as treatment paradigms internationally have shifted from use of these agents in the first line. The Subcommittee noted that evidence for benefit for pazopanib in the treatment of RCC patients with a good prognosis is not as strong as that for sunitinib but considered that it was an appropriate alternative to sunitinib. The Subcommittee considered that although sunitinib and pazopanib are both TKIs, they have different side-effect profiles, and considered that it was important that both remain funded, rather than being considered as two equivalent drugs from the same class.

6.9. The Subcommittee noted an international multicentre randomised open label phase III trial (Motzer et al. J Clin Oncol. 2009;27(22):3584-90**)** reporting the overall survival results from a prior publication (Motzer et al. N Engl J Med. 2007;356(2):115-24) comparing sunitinib to interferon alpha in 750 patients with metastatic RCC, including poor, intermediate, and good prognosis patients. The Subcommittee noted that interferon alpha is no longer used to treat RCC in New Zealand and is therefore not an appropriate comparator for the New Zealand patient population. However, there are no studies comparing with “watch and wait”, which is the true comparator to current practice in New Zealand.

6.9.1. The Subcommittee noted that progression-free survival was significantly improved with sunitinib compared to interferon alpha (HR = 0.42, 95% CI 0.32 to 0.54, p<0.001) and that the difference remained statistically significant across all prognostic groups. The Subcommittee noted that the median overall survival probability was not statistically significant between the two treatment groups (HR = 0.821, 95% CI 0.673 to 1.001, p = 0.051); however, subgroup analysis showed that patients who did not go on to receive treatment following the trial had a median overall survival with sunitinib twice that of the interferon alpha treatment group (28.1 vs 14.1 months respectively, HR = 0.647, 95% CI 0.483 to 0.870, P=0.003). The Subcommittee considered that this group is representative of the New Zealand patient population for whom there are no funded second line treatment options.

6.9.2. The Subcommittee also noted that for patients with a good prognosis, the median progression-free survival had not been reached at the time of the analysis, as compared with a median survival of 8 months for 121 patients in the interferon alfa group (HR for disease progression: 0.37; 95% CI 0.21 to 0.64).

6.10. The Subcommittee noted that RCC patients with a good prognosis are often asymptomatic and generally have a low tumour burden, in non-critical locations, with indolent disease and are likely to be observed without treatment initiation for some time. The Subcommittee noted that good prognosis patients with disease progression

or metastatic disease in a critical site but who still fall into the good prognosis risk category are the target cohort in this application. The Subcommittee noted that in time, these patients would eventually fulfil the current Special Authority criteria, meaning that they would likely experience symptoms as they progress. The Subcommittee considered that treatment prior to disease progression (ie. treatment of good prognosis patients) would be beneficial for some patients as it would lessen the risk of potentially dangerous outcomes, as disease progression could occur in critical areas such as in bone or spinal cord.

6.11. The Subcommittee noted that if sunitinib and pazopanib were to be funded for all RCC patients regardless of prognosis, there would be a slight increase on health system burden through an increase in appointments, requirements for blood testing, and to a lesser degree increased need for imaging facilities and treatments to manage treatment related toxicities such as thyroid issues and diarrhoea.

6.12. The Subcommittee noted that the median number of treatment cycles of sunitinib that patients received in the Motzer at al trial was 7.9; however, the Subcommittee noted that this number would differ depending on prognosis. The Subcommittee noted a 2018 study in which clinical outcomes of sunitinib treatment in metastatic RCC patients were assessed based on risk group Rini et al. Clin Genitourin Cancer. 2018;16:298-304). The Subcommittee noted that the median number of sunitinib cycles for good, intermediate, and poor prognosis patients was 12, 8 and 2 cycles respectively. The Subcommittee noted that the number of treatment cycles would be similar for patients treated with pazopanib.

6.13. The Subcommittee considered that there would be a prevalent pool of patients who would be eligible for treatment with sunitinib or pazopanib if access were widened to include first line treatment of good prognosis RCC but considered that this pool of patients would be quite small due to there already being a number of good prognosis patients already accessing treatment under the current criteria. The Subcommittee considered that PHARMAC's estimate of 40 patients per year in total for all prognosis groups may be an overestimate.

6.14. The Subcommittee noted that sunitinib and pazopanib had been included in PHARMAC's draft invitation to tender, and that if included in the final list there was the possibility of a brand change for either or both of these medicines. The Subcommittee considered that PHARMAC should carefully consider the number of available dosage forms proposed in any tender bids, as it would be important to maintain dosing flexibility. The Subcommittee noted that sunitinib and pazopanib are small molecule medicines and considered these would be fully replicable in the context of alternative brands. The Subcommittee noted that PHARMAC would only propose to fund a brand that had been approved by Medsafe and assessed against a suitable reference product and considered that in this context any brand change would not be associated with a change in efficacy. Members considered that these medicines may be appropriate for a "principal supply status" arrangement for patients who did not tolerate a brand change due to side effects as Members considered that some patients stable on their current treatment may have difficulty switching to a new brand of tyrosine kinase inhibitor. The Subcommittee considered PHARMAC's standard implementation activities would otherwise be appropriate for a brand change for either or both of these medicines.

7. Lenvatinib in combination with everolimus for patients with advanced renal cell carcinoma who have progressed after one prior targeted therapy; and the use of tyrosine kinase inhibitors (including sunitinib, and

pazopanib) for the second-line treatment of patients with metastatic renal cell carcinoma

Application

7.1. The Subcommittee reviewed the application for from a supplier (Eisai) for the use of lenvatinib in combination with everolimus for the second-line treatment of patients with advanced renal cell carcinoma (RCC) who have progressed after one prior vascular endothelial growth factor (VEGF) targeted therapy.

7.2. The Subcommittee also reviewed, as part of a separate clinician application, the use of tyrosine kinase inhibitors sunitinib and pazopanib in the second-line setting for metastatic RCC.

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

Recommendation

7.4. The Subcommittee **recommended** that lenvatinib in combination with everolimus be funded for patients with advanced renal cell carcinoma who have progressed after one prior targeted therapy for the second-line treatment of patients with metastatic renal cell carcinoma with a **medium priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

> LENVATINIB
> **Initial application** from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1 The patient has metastatic clear cell renal cell carcinoma; and
> 2 The patient has received one prior line of targeted treatment; and
> 3 The patient has good performance status (WHO/ECOG grade 0-1); and
> 4 Lenvatinib with be prescribed in combination with everolimus
>
> **Renewal –** (renal cell carcinoma) only from a relevant oncologist or gastroenterologist or hepatologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1 No evidence of disease progression; and
> 2 The treatment remains appropriate and the patient is benefitting from treatment
>
> Notes: Lenvatinib with everolimus treatment should be stopped if disease progresses.
>
> EVEROLIMUS
> **Initial application** — (RCC in combination with lenvatinib) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 3 months for applications meeting the following criteria:
> 1 The patient has histologically verified metastatic clear cell renal cell carcinoma; and
> 2 The patient has received one prior line of targeted treatment; and
> 3 Must be used in combination with lenvatinib
>
> **Renewal –** (RCC in combination with lenvatinib) only from a relevant oncologist or gastroenterologist or hepatologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1 No evidence of disease progression; and
> 2 The treatment remains appropriate and the patient is benefitting from treatment
>
> Notes: Lenvatinib with everolimus treatment should be stopped if disease progresses.

7.4.1. The Subcommittee made this recommendation based on the high and urgent unmet health need for patients with clear cell, metastatic renal cell carcinoma,

with a lack of second-line treatment options for these patients, evidence of efficacy for lenvatinib with everolimus for improved progression-free survival, noting the difficulty of interpreting the data presented in the New Zealand context where checkpoint inhibitors are not funded for RCC.

7.4.2. The Subcommittee **recommended** that the use of tyrosine kinase inhibitors (including sunitinib, and pazopanib) for the second-line treatment of patients with metastatic renal cell carcinoma be deferred pending a review of the entire renal cell carcinoma treatment setting.

Discussion

7.5. The Subcommittee noted that there are currently no funded second-line targeted treatments for renal cell carcinoma (RCC) in New Zealand, and that treatment options are limited, and are not consistent with best practice recognised internationally. The Subcommittee noted that the health need for patients with RCC who have progressed after first-line targeted therapy (currently funded sunitinib or pazopanib) is high, and that most patients with intermediate or high risk disease will progress and would benefit from access to a second-line targeted therapy.

7.6. The Subcommittee noted that since the introduction of targeted therapies in 2005, patients with advanced or metastatic RCC as a group have a median overall survival of 9.0 months, a 1-year survival of 38%, and a 3-year survival of 17% (Li et al. Cancer Med. 2016;5:169-81). The Subcommittee considered that the health needs of patients, families, and whānau of RCC patients is similar to that of many untreated progressive cancers, in that the average age of diagnosis is 65, there is a progressive loss of quality of life for patients and whānau, eventually culminating in the death of the patient.

7.7. The Subcommittee noted the incidence of kidney cancer in New Zealand has been stable since 2008, and that risk factors include smoking, obesity, hypertension, acute diabetes, male sex, and possibly occupational exposure to solvents, petroleum products, asbestos and heavy metals. The Subcommittee noted that Māori have consistently higher rates of kidney cancer than non-Māori, and that an Otago University study in 2014 reported that Māori kidney cancer patients were 52% more likely to die of their cancer than non-Māori (Sarfati et al. 2014. Wellington: University of Otago).

7.8. The Subcommittee noted that lenvatinib is a multiple tyrosine kinase inhibitor (TKI) that inhibits the kinase activities of vascular endothelial growth factor receptors and other proangiogenic and oncogenic pathway related receptor tyrosine kinases, which must be used in combination with everolimus, an orally administered mammalian target of rapamycin (mTOR) inhibitor. The Subcommittee also noted two other TKIs under consideration:

10.9.1 sunitinib, an orally administered therapy which works by blocking tyrosine kinases (receptors for platelet-derived growth factor and vascular endothelial growth factor), thus inhibiting cellular signalling, angiogenesis, and growth-stimulating proteins in the cancer cell itself; and

7.8.2. pazopanib, an orally administered, potent multi-target TKI of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor (PDGFR)-α and –β, and stem cell factor receptor (c-KIT).

7.9. The Subcommittee noted that lenvatinib with everolimus, sunitinib, and pazopanib were all under consideration as second-line targeted treatments for clear cell metastatic RCC at this discussion.

7.10. The Subcommittee noted a randomised, phase II, open label, multicentre trial (n=153) comparing the efficacy and safety of lenvatinib, everolimus, and lenvatinib plus everolimus treatment in patients with clear cell RCC and progressive or advanced disease who have had VEGF-targeted treatment (HOPE 205 trial, Motzer et al. Lancet Oncol. 2015;1473-82). The Subcommittee noted that lenvatinib plus everolimus significantly prolonged progression-free survival compared with everolimus alone (median 14.6 months [95% CI 5.9 to 20.1] vs 5.5 months [95% CI 3.5 to 7.1]; HR 0.40, 95% CI 0.24 to 0.68; p=0.0005).

7.11. The Subcommittee noted that in the post-hoc updated analysis (data cut-off 10 December 2014), the difference in overall survival between patients assigned lenvatinib with everolimus compared with those allocated single-agent everolimus was significantly increased (median overall survival 25·5 months vs 15·4 months; HR 0·51, 95% CI 0·30 to 0·88; p=0·024). The Subcommittee noted the study was not powered to assess overall survival and considered that prolonged follow-up with its small number of patients would mean significant uncertainty with the results.

7.12. The Subcommittee considered that although the trial indicated that lenvatinib with everolimus prolonged progression-free survival over either agent alone, the study was small, and the role of lenvatinib with everolimus following immune checkpoint inhibitors is uncertain. The Subcommittee also noted that the study was not blinded, and a longer follow-up was needed before a significant difference in outcomes was detected.

7.13. The Subcommittee noted a phase III, multi-centre, randomised, double-blind, placebo-controlled trial (RECORD-1 trial), in which RCC patients were randomly assigned in a 2:1 ratio to receive everolimus (n=272) 10mg or placebo (n=138) with best supportive care (Motzer et al. Lancet. 2008;372:449-56). The Subcommittee noted that the results indicated a median progression free survival of 4 months with everolimus, compared to 1.9 in the placebo group (HR 0.30, 95% CI 0.22 to 0.40, p<0.0001). The Subcommittee considered that this trial provided indirect supportive evidence for the use of lenvatinib with everolimus to treat RCC, and that there are no other studies comparing lenvatinib with everolimus to best supportive care. The Subcommittee also noted that everolimus is not funded or currently Medsafe approved for use in combination with lenvatinib for RCC.

7.14. The Subcommittee considered that the strength of evidence supporting the use of lenvatinib with everolimus in the second-line treatment of metastatic RCC was limited but of good quality. The Subcommittee did not identify any evidence for the use of sunitinib or pazopanib in the second-line setting following prior targeted therapy with the same agents. The Subcommittee also noted that some of the patients in the relevant trial had prior exposure to checkpoint inhibitors. As checkpoint inhibitors are not funded for the treatment of RCC in New Zealand, the Subcommittee considered that the results from the trial may not be relevant in a New Zealand patient context.

7.15. The Subcommittee noted that the clinical risks of funding these treatments are related to expected side effects of each individual TKI agent. The Subcommittee noted that increased fatigue, hypertension, diarrhoea, and proteinuria are known class side-effects of VEGF-targeting agents, and that major side effects of mTOR inhibitors include stomatitis, rash, fatigue, and pneumonitis. The Subcommittee considered that, if these agents were to be funded for second-line use, additional benefits would accrue from increased progression-free survival for a group of cancer patients who have no

funded treatments currently other than best supportive care. The Subcommittee noted that lenvatinib with everolimus, sunitinib, and pazopanib are not preferred second-line therapies in international practice for the treatment of RCC.

7.16. The Subcommittee considered that if one or more TKIs were to be funded for the second line treatment of RCC, that there would be limited consequences for the health system, apart from an increased need for monitoring of patients for expected toxicities, as dose adjustments are frequently required with these agents to manage adverse events. The Subcommittee considered that approximately 60 new patients per year would require second-line therapies for metastatic RCC.

7.17. The Subcommittee considered that, because New Zealand does not currently fund preferred treatments for RCC that are recommended in international treatment guidelines, there should be a broader review of the whole RCC treatment setting, where current treatments and internationally recommended treatments can be assessed together in the context of the New Zealand patient population. The Subcommittee would also welcome applications for combination use checkpoint inhibitors, such as nivolumab, for both first and second line RCC treatments. The Subcommittee also considered that PHARMAC staff should engage with clinical specialists directly such as the Genitourinary Special Interest Group of the NZ Society for Oncology (GU SIG NZSO) regarding the overall treatment landscape for RCC in New Zealand.

8. Lenvatinib for progressive, locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer

Application

8.1. The Subcommittee reviewed the application for lenvatinib for the treatment of progressive, locally advanced or metastatic, radioactive iodine-refractory differentiated thyroid cancer.

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

Recommendation

8.3. The Subcommittee **recommended** that lenvatinib be listed for the treatment of radioactive iodine-refractory differentiated thyroid cancer with a **high priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

Lenvatinib
INITIAL APPLICATION – (thyroid cancer) Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1 The patient has locally advanced or metastatic differentiated thyroid cancer; and
2 The patient has radiologically determined progressive disease; and
3 The patient must be radioactive iodine (RAI) refractory, defined as:
3.1 A lesion without iodine uptake in a RAI scan; or
3.2 Receiving cumulative RAI >600 mCi; or
3.3 Experiencing progression after a RAI treatment within 12 months; or
3.4 Experiencing progression after two RAI treatments administered within 12 months of each other; and
4 The patient must have thyroid stimulating hormone (TSH) adequately repressed; and
5 The patient must not be a candidate for radiotherapy with curative intent; and
6 Surgery is inappropriate; and
7 The patient must have a ECOG performance status of 0-1.

RENEWAL – (thyroid cancer) Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1 No evidence of disease progression; and

2 The treatment remains appropriate and the patient is benefiting from treatment.

8.4. In making this recommendation, the Subcommittee considered the high clinical need of patients with radioactive iodine-refractory differentiated thyroid cancer, the disproportionate rate of thyroid cancer in Māori and Pacific peoples, and the moderate strength, good quality evidence of the benefit of lenvatinib in this patient population.

Discussion

8.5. The Subcommittee noted that 95% of thyroid cancer is differentiated, of which approximately 5 to 10% of patients will develop metastatic disease, and 60 to 70% of these patients 5-10% patients will become radioiodine refractory (Fugazzola et al. Eur Thyroid J. 2019;8:227–45).

8.6. The Subcommittee noted that patients with thyroid cancer in New Zealand are relatively young, with approximately 75% of patients aged 25-64 years (New Zealand Cancer Registry. 2017). The Subcommittee noted that females have a higher rate of thyroid cancer of 8.3 per 100,000, compared with 4.0 per 100,000 for males (New Zealand Cancer Registry. 2017).

8.7. The Subcommittee noted that Māori are disproportionately affected by thyroid cancer, with an age-standardised rate of thyroid cancer registration in 2015 of 8.6 per 100,000 for Māori compared with 5.4 per 100,000 for non-Māori, while mortality from thyroid cancer was 1.7 for Māori compared with 0.3 per 100,000 for non-Māori (Ministry of Health. 2020, *provided to supplier*). The Subcommittee also noted that Pacific people have previously been reported to have a higher age-standardised rate of thyroid cancer compared with European/other New Zealanders; standardised rate ratio 1.27 for Pacific males compared with European/other males (95% confidence interval (CI): 0.74-2.18) and 3.58 (2.87-4.47) for Pacific females compared with European/other females (Meredith et al. Canc Caus Contr. 2012;23:1173-84).

8.8. The Subcommittee noted the results of the randomised (2:1), double-blind, placebo-controlled phase III SELECT trial after the primary data cut-off in November 2013 (Schlumberger et al. N Engl J Med. 2015;372:621-30). The Subcommittee noted that 10-15% of trial participants had poorly differentiated thyroid cancer and that this patient group was not included as part of this application. The Subcommittee noted that the median progression-free survival was 18.3 months in the lenvatinib group compared with 3.6 months in placebo; hazard ratio (HR) for progression or death 0.21 (95% CI: 0.14-0.31; P<0.001). The Subcommittee noted that the response rate was 64.8% in the lenvatinib group compared with 1.5% in the placebo group, odds ratio 28.9 (95% CI: 12.5-66.9; P<0.001).

8.8.1. The Subcommittee noted that 95.6% of patients originally assigned to placebo crossed over to lenvatinib in the subsequent optional open-label extension phase of the trial. The Subcommittee noted that the crude overall survival was not statistically significant, and considered that this was likely due to the large amount of cross over; however, when adjusted to correct for potential cross-over effects (resampling with a bootstrapping method), the reported crossover-corrected hazard ratio was 0.62 (95% CI: 0.40- to 1.00, P=0.051; Figure S4 in the Supplementary Appendix to Schlumberger et al. 2015).

8.9. The Subcommittee noted that NICE guidance published in August 2018 regarding lenvatinib (and sorafenib) for treating differentiated thyroid cancer after radioactive iodine had reported that "in SELECT, median overall survival for lenvatinib was 41.6 months compared with 34.5 months for placebo. After correcting for crossover, there was a statistically significant overall survival benefit for lenvatinib compared with placebo (RPSFT-adjusted HR 0.54, 95% bootstrapping CI 0.36 to 0.80)", where RPSFT referred to the rank preserving structural failure time method. The Subcommittee noted that the supplier application had stated this was based on analysis of an August 2015 data cut-off with median OS of 41.6 months for lenvatinib versus 19.1 months for placebo. The Subcommittee considered the statistical methodology to be appropriate and that the statistically adjusted crossover-corrected results appeared credible.

8.10. The Subcommittee noted that the RECIST v1.1 response rate according to RECIST v1.1 in the lenvatinib group, from an updated analysis with data cut-off in September 2016, was 64.8% compared with 1.5% in the placebo group (odds ratio 28.87, 95% CI: 12.46-66.86, P<0.001). The Subcommittee also noted that the median duration of response for all lenvatinib responders was 30 months, indicating lenvatinib responders having prolonged, durable and clinically meaningful responses (Gianoukakis et al. Endocr Relat Cancer. 2018;25:699-704).

8.11. The Subcommittee considered that this single randomised controlled trial represented good quality evidence of moderate strength.

8.12. The Subcommittee considered the Special Authority proposed by the supplier was overall appropriate. The Subcommittee considered that the WHO performance status should be amended to the Eastern Cooperative Oncology Group (ECOG) performance status, noting that while the two measurements are very similar in practice, New Zealand clinicians are more familiar ECOG, and that this would also maintain consistency with other oncology Special Authority criteria.

8.13. The Subcommittee considered that under the proposed Special Authority criteria, approximately 5-6% of all thyroid cancer patients (equal to approximately 20 patients per year) would be eligible for lenvatinib treatment if it were funded, and noted that many of these patients would have likely received one or more courses of radioactive iodine.

8.14. The Subcommittee noted that patients with radioactive iodine refractory differentiated thyroid cancer currently receive best supportive care and considered that this is appropriate comparator for lenvatinib in this indication.

8.15. The Subcommittee noted that hypertension was a common adverse event associated with lenvatinib in the SELECT trial, and therefore considered that anti-hypertensives would likely be used concurrently in many patients.

8.16. The Subcommittee considered that if lenvatinib were funded, there may be an increased need for imaging resources which would align with imaging requirements in the SELECT trial, however as an oral medication it was unlikely to have any other substantial impacts to health system resources.

8.17. The Subcommittee considered likely uptake in the first year could be 60%, rising in later years to 90-95%, reflective of the crossover uptake seen in the SELECT trial. The Subcommittee considered that the duration of response of 30 months demonstrated in the SELECT trial would indicate that patients may remain on treatment into a third year.

9. Lenvatinib for the first-line treatment of unresectable hepatocellular carcinoma

Application

9.1. The Subcommittee reviewed the application for lenvatinib in the first-line treatment of unresectable hepatocellular carcinoma The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

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

Recommendation

9.2. The Subcommittee **recommended** that lenvatinib be funded for the first-line treatment of unresectable hepatocellular carcinoma with a **low priority** within the context of treatments for malignancies, subject to the following Special Authority criteria:

> Initial application – (hepatocellular carcinoma) only from an oncologist or gastroenterologist or hepatologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 The patient has systemic-treatment-naïve, advanced or intermediate (unresectable), Barcelona Clinic Liver Cancer Stage B or C Hepatocellular carcinoma; and
> 2 The patient has preserved liver function (Childs Pugh A); and
> 3 The patient has good performance status (ECOG ≤ 2); and
> 4 Patient must not be suitable for Trans arterial Chemoembolisation (TACE)
>
> Renewal – (hepatocellular carcinoma) only from a relevant oncologist or gastroenterologist or hepatologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1 No evidence of disease progression; and
> 2 The treatment remains appropriate and the patient is benefitting from treatment

9.3. In making its recommendation, the Subcommittee considered the unmet need for effective treatment options for patients with unresectable hepatocellular carcinoma and, the relatively high incidence of this disease in Māori and Pacific people, together with the low quality, low strength evidence of benefit from lenvatinib.

Discussion

9.4. The Subcommittee noted hepatocellular carcinoma makes up approximately 90% of all liver cancers and is predominantly associated with chronic liver disease, most commonly cirrhosis. The Subcommittee noted that common causes of cirrhosis include hepatitis B, hepatitis C, heavy alcohol consumption, diabetes mellitus, obesity, and haemochromatosis. The Subcommittee noted that hepatocellular carcinoma is often diagnosed at an advanced stage and that patients with advanced hepatocellular carcinoma have a poor quality of life, with a five-year survival of 7% and median survival of 7 months.

9.5. The Subcommittee noted that Māori are disproportionately affected by liver cancer, making up 23% of registrations and have a reported 3-5 times higher age-standardised rate of liver cancer compared to non-Māori (Ministry of Health. 2019; Chamberlain et al. Aust NZ J Pub Heal. 2013;37:520-6). The Subcommittee noted that Pacific people also have a higher age-standardised rate of liver cancer compared to European/other New Zealanders (Meredith et al. Canc Caus Contr. 2012;23:1173-84).

9.6. The Subcommittee noted that viral hepatitis increases the risk of developing hepatocellular carcinoma, and considered that rates of this risk factor are likely to

decline over time. The Subcommittee considered that rates of metabolic syndrome and non-alcoholic steatohepatitis (NASH) are likely to increase over time and associated with the risk of hepatocellular carcinoma. The Subcommittee considered that these risk factors may disproportionately effect groups of people currently experiencing disparities in access to healthcare.

9.7. The Subcommittee noted that there are currently no funded, targeted pharmacological treatments for the first line treatment of unresectable hepatocellular carcinoma. The Subcommittee noted that current treatments include radical therapy (such as surgery, liver transplant or radiofrequency ablation), for patients with early stage disease (Barcelona Clinic Liver Cancer (BCLC) 0 or A), trans arterial chemoembolisation (TACE) for patients with intermediate stage disease (BCLC B), and best supportive care for patients with BCLC B stage disease that is unsuitable for TACE, and end stage disease (BCLC C and D). The Subcommittee considered that there is disparity in access to TACE around the country.

9.8. The Subcommittee noted the results of the randomised, open-label, phase III, multicentre, non-inferiority REFLECT trial, which investigated the use of oral lenvatinib compared with sorafenib in patients with unresectable hepatocellular carcinoma (Kudo et al. Lancet. 2018;391:1163-73). The Subcommittee noted that no statistically significant difference in overall survival was observed between the lenvatinib group and sorafenib group, hazard ratio (HR) 0·92, 95% confidence interval (CI): 0·79–1·06. The Subcommittee noted that significant differences, favouring lenvatinib, were observed between groups in the secondary outcomes of median progression free survival (HR 0·66, 95% CI: 0·57−0·77, p<0·0001), median time to progression (HR 0·63, 95% CI: 0·53–0·73, p<0·0001) and objective response rate (odds ratio 3·13, 95% CI: 2·15–4·56, p<0·0001). The Subcommittee considered that the strength and quality of the evidence of lenvatinib for hepatocellular carcinoma was low.

9.9. The Subcommittee noted that the frequency of adverse events reported in the REFLECT trial was similar between lenvatinib and sorafenib treated groups.

9.10. The Subcommittee noted that an application for sorafenib for advanced hepatocellular carcinoma had previously been assessed by PTAC and its Subcommittees, most recently receiving a decline recommendation from CaTSoP due to limited clinically meaningful benefit and the associated high expense given this limited benefit (more information regarding sorafenib can be found here).

9.11. The Subcommittee noted that as there are currently no funded targeted pharmacological treatments for unresectable hepatocellular carcinoma, the appropriate comparator for lenvatinib in this indication is best supportive care, including TACE. The Subcommittee noted that there is currently no published randomised evidence comparing lenvatinib with placebo and considered that it is unlikely such evidence would be published.

9.12. The Subcommittee noted a covariate adjustment provided by the supplier which indirectly compared lenvatinib and placebo, using the sorafenib vs placebo SHARP and ASIA-PAC trials (Llovet et al. N Eng J Med. 2008;359:378-90, Cheng et al. Lancet Oncol. 2009;10:25-34), and the lenvatinib vs sorafenib REFLECT trial. The Subcommittee noted the results of this indirect analysis indicated that compared with placebo, lenvatinib showed a general trend toward greater efficacy: HR for overall survival of 0.63 (95% CI: 0.50-0.80), progression free survival 0.38 (95% CI: 0.30-0.49), and objective response rate of 56.49 (95% CI: 4.53-704.99). The Subcommittee noted that the full methodology of this comparison was not received and as such was not reviewed by the Subcommittee.

9.13. The Subcommittee considered that the prevalent pool of hepatocellular carcinoma patients is small due to the short median survival of patients. The Subcommittee therefore considered that the prevalent pool of patients that would require treatment would be minimal in addition to the incident patients if lenvatinib were funded in this indication.

9.14. The Subcommittee noted that the supplier assumed in its analysis that the incidence of liver cancer would decline over time due to the increased availability of hepatitis C treatments; however, the Subcommittee considered that it would likely remain constant, noting the increasing prevalence of metabolic syndrome and NASH with hepatic sequelae including hepatocellular carcinoma.

9.15. The Subcommittee considered under the proposed Special Authority criteria, approximately 60-70 patients would be treated with lenvatinib each year. The Subcommittee considered that if lenvatinib were funded in this indication, it would be appropriate to assume an uptake rate of 90%.

9.16. The Subcommittee considered that, should lenvatinib be funded in this indication then it may be used as a bridge to liver transplantation, and considered that PHARMAC could seek further advice on this from transplantation clinicians. The Subcommittee considered that, should lenvatinib be funded for this indication then there may be a modest increase in health resource required to manage adverse events, largely use of loperamide to manage diarrhoea.

9.17. The Subcommittee considered that there is emerging evidence for atezolizumab and bevacizumab in this indication and that it would be interested to review data for additional classes of medicines, given the unmet need in this patient group.

10. Trastuzumab emtansine for HER2 positive early breast cancer

Application

10.1. The Subcommittee reviewed the application for trastuzumab emtansine (T-DM1) in the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment.

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

Recommendation

10.3. The Subcommittee **recommended** that trastuzumab emtansine be funded for the treatment of HER2 positive early breast cancer in patients who have residual disease after neoadjuvant systemic treatment with a **high priority**, within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application- (early breast cancer) only from a relevant. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Patient has early breast cancer expressing HER2 IHC3+ or ISH+; and
2. Documentation of pathological invasive residual disease in the breast and/or auxiliary lymph nodes following completion of surgery; and
3. Patient has completed systemic neoadjuvant therapy with trastuzumab and chemotherapy prior to surgery; and
4. Disease has not progressed during neoadjuvant therapy; and
5. Patients has left ventricular ejection fraction of 45% or greater; and
6. Adjuvant treatment with trastuzumab emtansine to be commenced within 12 weeks of surgery; and
7. Trastuzumab emtansine to be discontinued at disease progression; and

8. Total adjuvant treatment duration must not exceed 42 weeks (14 cycles).

10.4. The Subcommittee made this recommendation based on the high quality of evidence of benefit, prevention of relapse, and the curative intent of treatment with T-DM1 in this setting but considered that the unmet health need for these patients is not high as they already have relatively good prognosis from currently available funded treatments.

Discussion

10.5. The Subcommittee noted 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.

10.6. The Subcommittee 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 Subcommittee 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 Subcommittee noted that T-DM1 is approved by Medsafe for the requested indication.

10.7. The Subcommittee 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 Subcommittee 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 Subcommittee noted that the supplier had considered that patient response to neoadjuvant treatment with trastuzumab would be assessed either pre-surgery by clinical or radiological measures, or post-surgery in resected tissue.

10.8. The Subcommittee noted that PTAC reviewed this application at its August 2020 meeting**.** The Subcommittee noted that PTAC 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 but sought advice from CaTSoP regarding a number of specific topics.

10.9. The Subcommittee considered that the current treatment paradigm for HER2 positive early breast cancer is surgery without prior treatment for tumours less than 2 centimetres diameter, or neoadjuvant therapy with trastuzumab and chemotherapy for tumours with diameter greater than 2 cm. The Subcommittee considered that following surgery, patients will generally continue to receive trastuzumab without chemotherapy for an additional six months, or up to a year if there is residual disease in the breast or axillary node positivity. The Subcommittee noted that under current Special Authority criteria for trastuzumab, patients with early breast cancer can only take trastuzumab for a total of 52 weeks in the neoadjuvant and/or adjuvant setting.

10.10. The Subcommittee noted that approximately 70% of HER2 positive, early breast cancer patients receive neoadjuvant therapy with trastuzumab. The Subcommittee considered that capecitabine is not routinely used in the treatment of HER2 positive breast cancer but is used in triple negative breast cancers with residual disease following neoadjuvant therapy. The Subcommittee noted that that the relapse rate following adjuvant therapy is approximately 20%.

10.11. The Subcommittee noted that most studies with anthracyclines and taxanes demonstrate a 50-60% pathological complete response (pCR, ie. no tumour in breast or axilla) rate, indicating that 40-50% of patients have residual disease following neoadjuvant treatment. The Subcommittee noted a meta-analysis of nearly 12,000 patients from 12 studies, which reported pCR to be a predictor for an increase in event free survival and overall survival (Cortazar et al. Lancet. 2014;384:164-72).

10.12. The Subcommittee noted that surrogate endpoints (objective response, disease-free survival, and event-free survival) for overall survival in the context of cancer treatments were discussed at its July 2019 meeting, where the Subcommittee considered that the relationship between surrogate endpoints and their ability to predict desired clinical effects (such as overall survival or quality of life improvements), can be highly variable in different cancers and in different disease stages and with different pharmaceutical agents. While the Subcommittee considered at the time that surrogate endpoint data should be interpreted with caution, endpoints such as progression-free survival were less likely than overall survival to be confounded by treatment crossover and post-progression treatment. The Subcommittee noted that, in general, disease-free survival has some inherent variability as it depends upon the timing of follow-up (which can differ between trials) compared with overall survival (which is specifically event driven).

10.13. The Subcommittee noted a recently published meta-analysis of 8 studies (n=21480 patients) of disease-free survival as a surrogate for overall survival in patients with HER2 positive early breast cancer treated with anti-HER2 antibody treatments (trastuzumab, pertuzumab, or trastuzumab emtansine) for up to 12 months (Saad et al. Lancet Oncol. 2019;20:361-70). The Subcommittee noted that both individual patient data and overall trial associations were analysed, and that patient level correlations between disease-free survival and overall survival were strong (r^2 = 0.90, 95% CI 0.89 to 0.90), while trial-level associations were less strong but still significant (r^2 0.75, 95% CI 0.50 to 1.00). The Subcommittee considered that the study supported the use of disease-free survival as a surrogate for overall survival in the HER2 positive early breast cancer patient population.

10.14. The Subcommittee noted a phase III, two-arm, randomised, open-label, multicentre trial (KATHERINE, Clinicaltrials.gov identifier: NCT01772472) in which patients (n=1486) with HER2 positive early breast cancer who had residual disease at surgery after receiving neoadjuvant therapy plus HER2 targeted therapy (at least 9 cycles of prior trastuzumab therapy) were treated with either adjuvant T-DM1 or trastuzumab every 3 weeks for 14 cycles (Von Minckwitz et al. 2019. N Engl J Med 380(7):617-28). The Subcommittee noted that 73% of the study participants were primarily white and had HER2 positive disease, and that the primary endpoint of the study was invasive disease-free survival.

10.15. The Subcommittee noted that the 3-year invasive disease-free survival in KATHERINE was 77.0% for the trastuzumab treatment arm, and 88.3% for the T-DM1 treatment arm (unstratified HR 0.50, 95% CI 0.39 to 0.64, p<0.0001), and that benefit was also demonstrated across the majority of subgroups analysed, including clinical stage at presentation, hormone receptor status, pathological nodal status, and age. The Subcommittee noted that those treated with T-DM1 had 6-7% lower incidence of recurrence of disease when compared with trastuzumab (unstratified HR = 0.60, 95% CI 0.45 to .079), and there was no difference in unexpected deaths between the two treatment groups. The Subcommittee noted that preliminary overall survival was not significantly different at 60 months and considered that additional follow-up would be necessary to evaluate the true effect of T-DM1 on overall survival.

10.16. The Subcommittee noted that more adverse events occurred in the T-DM1 treatment group, including adverse events leading to treatment discontinuation such a platelet count and blood bilirubin decreases, but noted that cardiovascular toxicity was similar between those treated with T-DM1 and trastuzumab. The Subcommittee noted that the safety data were consistent with known manageable toxicities of T-DM1, and that the increased with T-DM1 were to be expected.

10.17. The Subcommittee considered the KATHERINE trial to be highly relevant to the New Zealand population, as neoadjuvant therapy is becoming standard of care for this patient group. The Subcommittee considered that although the trial participants were primarily European, it is unlikely that Māori and Pacific patients in New Zealand would have differences in treatment effect, and that although Māori and Pacific people have a higher incidence of HER2 positive disease, poorer outcomes in these groups stem from later diagnoses and differences in access to healthcare as opposed to tumour biology.

10.18. The Subcommittee considered that if T-DM1 were to be funded in this setting, there would be no change in the proportion of patients receiving neoadjuvant trastuzumab as part of their therapy. The Subcommittee considered that of the 3500 new breast cancer registrations every year, approximately 220-280 would be candidates for neoadjuvant chemotherapy plus trastuzumab. The Subcommittee considered that of these 220-280, approximately 50% would achieve pathological complete response, meaning at least 110 women per year would be candidates for adjuvant T-DM1 treatment.

10.19. The Subcommittee considered that should T-DM1 be funded in this setting, there would be no material impact on clinical resource use, as patients would otherwise continue to receive trastuzumab alone. The Subcommittee considered that there would be approximately 10% fewer women needing treatment for metastatic disease were T-DM1 to be funded in this setting, and that the number of women relapsing following adjuvant therapy would decrease by approximately 50 should T-DM1 be used after neoadjuvant therapy. The Subcommittee considered that unless evidence of activity on re-treatment was shown, practitioners would not advocate for re-treatment with T-DM1 in the metastatic setting following prior use as adjuvant therapy, but that clinicians would still want the option to use trastuzumab in the metastatic setting.

11. Bendamustine for relapsed/refractory Hodgkin lymphoma (HL)

Application

11.1. The Subcommittee reviewed the application for bendamustine for the treatment of relapsed or refractory Hodgkin's lymphoma as part of the BeGeV regimen.

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

Recommendation

11.3. The Subcommittee **recommended** that bendamustine be funded for the treatment of relapsed or refractory Hodgkin's lymphoma with a **medium priority** within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application – (Hodgkin's lymphoma) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1 Patient has Hodgkin's lymphoma requiring treatment; and
2 Patient has a ECOG performance status of 0-2; and

3 Patient has received one prior line of chemotherapy; and
4 Patient's disease relapsed or was refractory following prior chemotherapy; and
5 Bendamustine is to be administered in combination with gemcitabine and vinorelbine (BeGeV) at a maximum dose of no greater than 90 mg/m^2 twice per cycle, for a maximum of four cycles.

11.3.1. In making this recommendation, the Subcommittee considered that the evidence for bendamustine in this setting was of low quality and medium strength, noting that no further evidence would be expected in this setting; and that there are clinically important benefits of achieving a cure through use of fewer therapies in Hodgkin's lymphoma.

11.4. The Subcommittee noted that Hodgkin's lymphoma is a malignancy of the immune system diagnosed in about 100 patients per year in New Zealand, with a bimodal incidence peaking in young adults and again in older adults. The Subcommittee noted that it had previously estimated about 80% of patients with Hodgkin's lymphoma being cured by first-line chemotherapy, with or without radiotherapy (CaTSoP 2018).

11.5. The Subcommittee noted that patients with transplant-eligible Hodgkin's lymphoma, refractory to first-line treatment or relapsing after first line therapy undergo salvage chemotherapy, which aims to achieve a complete response with as few different chemotherapy regimens as possible before proceeding to autologous stem cell transplant.

11.6. The Subcommittee considered that achieving a complete response with the minimal number of chemotherapy regimen changes, and successful stem cell collection (requiring patients to undergo collection only once), both convey clinically important benefits to the patient and may avoid additional costs (eg. additional stem cell collections and additional imaging).

11.7. The Subcommittee noted that the preferred first-line salvage chemotherapy regimen for relapsed/refractory Hodgkin's lymphoma varies around the country and noted that there is not a clear single standard salvage regime that is recommended internationally. The Subcommittee noted that Hodgkin's lymphoma may respond to many regimens. The Subcommittee considered that ICE (ifosfamide, carboplatin and etoposide) would be a reasonable first-line salvage chemotherapy comparator for the majority of patients in New Zealand with relapsed or refractory Hodgkin's lymphoma for cost-effectiveness assessment, as it is used for about two-thirds of patients in this setting in New Zealand, with the remaining proportion having a comparator equally split between DHAP (dexamethasone, cytarabine and cisplatin) or IGEV (ifosfamide, gemcitabine, and vinorelbine).

11.8. The Subcommittee noted that all patients who receive standard-of-care salvage chemotherapy for Hodgkin's lymphoma receive granulocyte colony-stimulating factor (GCSF) and that mesna is used for patients who receive intravenous ifosfamide.

11.9. The Subcommittee noted that publicly funded positron emission tomography (PET) scans are performed at disease relapse, and to assess response to first line salvage chemotherapy, and may be additionally performed to assess response in a patient for whom first line salvage treatment does not provide an optimal response and needs to proceed to second line salvage. The Subcommittee noted there is evidence indicating that metabolic complete response assessed by PET scan in patients who received a salvage regimen on relapse or for refractory disease, ie. PET negative pretransplant, conveys a reduced risk of relapse (~20%) compared with a PET positive scan result which is associated with ~50% risk of relapse (Adams et al. Ann Hematol. 2016;95:695–706; Akhtar et al. Bone Marrow Transplant. 2013;48:1530-6; Broccoli et al. Br J Haematol. 2019;184:93-104; Moskowitz et al. Blood. 2012;119:1665–70).

11.10. The Subcommittee noted that patients who achieve a complete response from salvage chemotherapy proceed to autologous stem cell transplant (sometimes with additional radiotherapy); patients with a partial response receive a different salvage regimen (eg gemcitabine dexamethasone cisplatin; GDP chemotherapy), aiming to achieve a complete response before proceeding to autologous stem cell transplant; and patients who do not experience any response have limited treatment options and a poor prognosis. Members noted that these patients may attempt to access novel therapy with brentuximab vedotin or pembrolizumab via a Named Patient Pharmaceutical Assessment (NPPA) application or through private funding.

11.11. The Subcommittee noted that patients who do not receive or are not cured by autologous stem cell transplant have a poor prognosis and may use expensive unfunded salvage treatments to enable allogenic stem cell transplant, which is associated with a high risk of mortality (25%), ongoing morbidity and a very high cost to the health system (ie approximately $250,000 for allogenic stem cell transplant alone), with risks of ongoing complications of graft-versus-host disease needing years of immunosuppressive treatment with very close clinical supervision.

11.12. The Subcommittee noted that bendamustine is not Medsafe-approved for the treatment of relapsed or refractory Hodgkin's lymphoma, although it is approved by Medsafe for treatment of other types of lymphoma and leukaemia.

11.13. The Subcommittee noted that bendamustine is funded in New Zealand for the treatment of low-grade lymphoma and chronic lymphocytic leukaemia, and considered that clinicians in New Zealand who treat patients with haematological malignancies are comfortable with its use. Therefore, the Subcommittee considered that lack of Medsafe approval for the treatment of relapsed or refractory Hodgkin's lymphoma was not of concern.

11.14. The Subcommittee noted that the key evidence for bendamustine as part of the BeGeV regimen comes from a prospective, multi-centre, open-label, single-arm phase II study conducted at 10 centres in Italy, which recruited 59 transplant-eligible patients with Hodgkin's lymphoma that was refractory to or had relapsed after one previous chemotherapy line(Santoro et al. J Clin Oncol. 2016;34:3293-9; Santoro et al. Blood Adv. 2020;4:136-140).

11.15. The Subcommittee noted that first-line therapy was ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) in 56 patients (95%) and BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone) in 3 patients (5%). The Subcommittee noted that the study publication described BeGeV as a second-line salvage chemotherapy, however, this was interpreted to refer to the first salvage chemotherapy (ie second-line chemotherapy). The Subcommittee considered that in New Zealand BEACOPP is generally used in high-risk patients.

11.16. The Subcommittee noted that patients were generally young (median 33 years of age), were candidates for transplant up to the age of 70 years, almost half had primary refractory disease, and many had a complete response lasting less than one year; overall, the Subcommittee considered this was a high-risk patient group who were representative of the New Zealand patient population.

11.17. The Subcommittee noted that patients received BeGeV (gemcitabine 800 mg/m2 on days 1 and 4, vinorelbine 20 mg/m2 on day 1, and bendamustine 90 mg/m2 on days 2 and 3) for four cycles every 21 days as induction therapy before autologous stem-cell

transplantation (ASCT); then patients with complete or partial response received myeloablative therapy and then reinfusion of mobilised CD34+ stem cells.

11.18. The Subcommittee noted that after 4 cycles of BeGEV, 73% of patients (N=43) in the intention-to-treat population achieved a metabolic complete response on PET scan and 10% (N=6) achieved a partial response, with more patients with relapsed disease achieving complete response than patients with refractory disease, and most patients proceeded to autologous stem cell transplant.

11.19. The Subcommittee noted that the two-year progression-free survival (PFS) rate was 62.2% and two-year overall survival (OS) rate was 77.6%, with comparable results for patients with relapsed and refractory disease. The Subcommittee noted that PFS was higher at about 80% in patients who actually received an autologous stem cell transplant.

11.20. The Subcommittee considered that the adverse events profile of BeGeV was manageable and identified no major concerns, however, the risk of febrile neutropenia (grade 3-4 N=7, 12%) or infection (grade 3-4 N=4, 7%) was not well described and it was unclear whether patients were hospitalised eg for intravenous antibiotics. The Subcommittee noted that red blood cell and platelet transfusions were required for 8 (14%) and 3 patients (5%), respectively.

11.21. The Subcommittee noted that stem cells were successfully mobilised in 57 of 59 patients, with successful collection reported in 55 patients (96.5%), of which 42 patients (76%) only needed one collection. The Subcommittee considered this was a very high success rate with high yield and rapid engraftment reported post-transplant.

11.22. The Subcommittee noted that the updated study results published in 2020 reported data for a reasonable proportion of patients out to five years of follow-up with 5-year PFS and OS of 59% and 78%, respectively, in the intention-to-treat population and PFS and OS in patients who received an autologous stem cell transplant of 77% and 91%, respectively (Santoro et al. Blood Adv. 2020;4:136-140). The Subcommittee considered that these long-term outcomes suggested persistent PFS and OS results in the overall intention-to-treat population without relapse over time, and indicated very good PFS and OS results for those patients who received an autologous stem cell transplant.

11.23. The Subcommittee considered that the BeGeV regimen is an evolution of the IGEV regimen published by the same primary author (Santoro et al. Haematologica. 2007;92:35-41) and considered that the study designs were the same, providing support for the strength and comparability of the BeGeV evidence. The Subcommittee noted a published comparison of response rates and adverse events of older regimens (eg DHAP, ICE) and newer regimens (eg IGEV, BeGeV) and that this indicated a trend of improved remission rate with newer regimens IGEV and BeGeV, however, this was limited by the single-arm trial data (Broccoli et al. 2019). The Subcommittee noted that, compared with other salvage regimens such as ICE chemotherapy, fewer red blood cell or platelet transfusions may be required with BeGeV or IGEV but it was very difficult to quantify any differences because of the quality of data and slightly different reporting methodology (Santoro et al. 2007). The Subcommittee noted that there were no deaths due to toxicity.

11.24. The Subcommittee noted that the evidence for bendamustine for the treatment of relapsed or refractory Hodgkin's lymphoma as part of the BeGeV regimen was based on one small, multi-centre, phase II prospective study, and considered that this was of low quality and medium strength, however, it was directly applicable to the New

Zealand patient population. The Subcommittee noted that there was no evidence of a quality of life benefit from treatment with bendamustine as part of the BeGeV regimen and considered that evidence for quality of life was not expected to become available in this setting.

11.25. The Subcommittee considered that further evidence from multi-centre trials (eg a randomised controlled trial comparing BeGeV to ICE or another regimen) would not be expected in this setting, due to changes in international standard of care treatment for relapsed or refractory Hodgkin's lymphoma.

11.26. The Subcommittee noted that the intravenous administration (ie chair time) of BeGeV would be approximately two hours, which is less than that required of a comparator regimen such as ICE which is approximately 3.5 to 4 hours. The Subcommittee considered that a one-hour decrease in infusion time could make a meaningful difference for treatment centres (eg allowing for an additional patient to receive a 30-minute intravenous infusion) and noted that in some centres, patients may be admitted for up to three days for ICE to be administered. However, the Subcommittee considered that the day ward requirements of both regimens would be similar, given that ICE requires 3 days of lengthy infusions, while BEGEV requires four days of shorter infusion times.

11.27. The Subcommittee noted that the cost of bendamustine was less than the cost of a many other agents considered for the treatment of malignancy. The Subcommittee considered that, if bendamustine were funded for relapsed or refractory Hodgkin's lymphoma, it would be used to prepare patients for autologous stem cell transplant and may be used for approximately 11 patients per year.

11.28. The Subcommittee considered that uptake of BeGeV could vary across centres in New Zealand due to the treatment schedule requiring treatment to be given over four days for four cycles, if bendamustine were funded for relapsed or refractory Hodgkin's lymphoma, and noted that this was an increase from ICE which requires three days of treatment for three cycles. Members considered that an extra day of treatment would increase costs, particularly for rural patients being treated at regional cancer centres who may need accommodation for an extra night.

11.29. The Subcommittee considered that treatment with BeGeV may require fewer PET scans than other regimens if PET negativity is detected on the first PET scan after a patient's first salvage regimen treatment, prior to autologous stem cell transplant. The Subcommittee considered that the evidence did not compare BeGeV to standard of care regimens directly, however, an appropriate comparison of response rates and adverse events of older regimens and newer regimens was presented by Broccoli et al. 2019. However, due to being limited to single arm trial data, it remained unclear whether subsequent salvage therapies could be avoided by achieving higher initial metabolic complete response rates with BeGeV compared with other chemotherapy regimens.

[Considerations specific to bendamustine, brentuximab vedotin and pembrolizumab proposals]

11.30. The Subcommittee noted that currently unfunded later-line salvage therapies include brentuximab vedotin for CD30+ Hodgkin's lymphoma relapsed after two or more lines of chemotherapy (recommended for decline by PTAC in August 2016 recommended for funding by CaTSoP with a high priority in September 2018), and pembrolizumab as a bridge to transplant in patients with Hodgkin's lymphoma refractory to a second or subsequent line of chemotherapy, or relapsed after at least three lines of therapy

(most recently recommended for funding by CaTSoP with a medium priority in October 2019).

11.31. The Subcommittee considered that, if bendamustine was funded for relapsed or refractory Hodgkin's lymphoma, it was unclear what impact this may have on the number of patients who may subsequently be suitable for either brentuximab vedotin or pembrolizumab, if either were funded in a later line of treatment.

[Considerations specific to bendamustine and brentuximab vedotin proposals]

11.32. Members considered that the AETHERA trial of brentuximab vedotin consolidation therapy (16 doses) after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (Moskowitz et al. Lancet. 2015;385:1853-62) was of relevance and provides evidence suggesting a curative effect after autologous stem cell transplant for this patient population, however, this evidence for efficacy was not reviewed in detail by the Subcommittee at this time.

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

Application

12.1. The Subcommittee reviewed the application for durvalumab maintenance treatment of locally advanced, unresectable non-small-cell lung cancer (NSCLC) following chemoradiotherapy.

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

Recommendation

12.3. The Subcommittee **recommended** that durvalumab be funded for patients with unresectable non-small cell lung cancer (NSCLC) who have PD-L1 positive (>1%) disease with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

DURVALUMAB
Initial application – only from a medical oncologist or on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1 Patient has histologically or cytologically documented stage III, locally advanced, unresectable Non-Small Cell Lung Cancer (NSCLC); and
2 There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 1% as determined by a validated diagnostic test; and
3 Patient has received two or more cycles of platinum-based chemotherapy concurrently with definitive radiation therapy; and
4 Patient has no disease progression following the second or subsequent cycle of platinum-based chemotherapy with definitive radiation therapy treatment; and
5 Patient has a ECOG performance status of 0 or 1; and
6 Patient has completed last radiation dose within 6 weeks of starting treatment with durvalumab; and
7 Patient must not have received prior PD-1 or PD-L1 inhibitor therapy for this condition; and
8 Durvalumab is to be used at a maximum dose of no greater than 10 mg/kg every 2 weeks; and
9 Treatment with durvalumab to cease upon signs of disease progression.

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

12.3.1. In making this recommendation, the Subcommittee noted the benefit of a potentially curative treatment for this patient population, the benefit of durvalumab in the PD-L1 positive population and evidence that durvalumab treatment does not reduce quality of life while on treatment.

12.4. The Subcommittee **recommended** that durvalumab be funded for patients with unresectable non-small cell lung cancer (NSCLC) irrespective of PD-L1 status with a high priority, in the context of treatment of malignancy, subject to the following Special Authority criteria:

DURVALUMAB

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

All of the following:

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

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

All of the following:

1. The treatment remains clinically appropriate and the patient is benefitting from treatment; and
2. Durvalumab is to be used at a maximum dose of no greater than 10 mg/kg every 2 weeks; and
3. Treatment with durvalumab to cease upon signs of disease progression; and
4. Total continuous treatment duration must not exceed 12 months.

12.4.1. In making this recommendation, the Subcommittee considered the health need of this patient population; the benefit of a potentially curative treatment for this patient population; and the potential benefit of treatment with durvalumab in this group, noting that the post-hoc evidence for benefit from durvalumab in patients with PD-L1 negative (<1%) disease is insufficient to confirm whether there is a benefit in this group (but that a benefit could not be excluded), and that treatment with durvalumab in this context could expose patients who otherwise would not receive active treatment to potential toxicity.

12.4.2. The Subcommittee considered it could review further data for durvalumab in patients with PD-L1 <1%, if available.

Discussion

12.5. The Subcommittee noted that, in August 2020, PTAC reviewed an application for durvalumab for the maintenance treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) following chemoradiotherapy, recommended durvalumab be funded with a medium priority (subject to Special Authority criteria) and sought CaTSoP's advice regarding a number of specific points.

12.6. The Subcommittee noted that the high, unmet health need of patients with unresectable NSCLC has been well documented in previous CaTSoP and PTAC records, and considered that NSCLC remains a significant cause of mortality and morbidity, especially in Māori, who experience higher incidence rates (and are more

likely to be diagnosed at a younger age) than non-Māori (Lawrenson et al. N Z J Med. 2018;131(1479):13-23).

12.7. The Subcommittee noted that about one-third of patients with NSCLC have stage III disease at diagnosis and these patients generally receive initial curative treatment with chemoradiation and then are observed for relapse or progression (at which time chemotherapy, targeted therapy or palliative care may be given). The Subcommittee noted that patients with stage III NSCLC currently have a median progression-free survival of about 8 months, overall survival of 28 months or less and about 70-85% die by 5 years. Members considered that survival with current standard of care survival has improved over time, due to earlier diagnosis and improved staging (eg PET-CT scans).

12.8. The Subcommittee noted that durvalumab is a monoclonal antibody that blocks programmed-death ligand 1 (PD-L1) from binding to programmed death 1 (PD-1) and CD80 receptors on the cell membrane. The Subcommittee noted that durvalumab 10 mg per kg is administered over one hour every two weeks for 12 months unless disease progression or unacceptable toxicity occur.

12.9. The Subcommittee noted that durvalumab is approved by Medsafe for the treatment of patients with locally advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy. The Subcommittee considered that the rationale for durvalumab maintenance post-chemoradiation was due to a proposed synergistic effect of PD-L1 blockade following stimulation of the immune response by the definitive treatment.

12.10. The Subcommittee noted that durvalumab maintenance after chemoradiation for locally advanced, unresectable stage III NSCLC is a potentially curative therapy that is positioned earlier in this treatment paradigm than applications for other PD-1/PD-L1 inhibitors for advanced NSCLC (atezolizumab, pembrolizumab), as the latter are essentially palliative treatments. The Subcommittee noted that the patient population for this application differs from that previously considered and members considered this patient population could substantially benefit from a potentially curative treatment that may reduce the number of patients who develop metastatic disease and therefore require palliative treatment.

12.11. The Subcommittee noted that phase II/III randomised clinical trial evidence of systemic maintenance treatment with chemotherapy following chemoradiation indicated no benefit on progression-free survival (PFS) or overall survival (OS) (Cheema et al. Curr Oncol. 2019;26:37-42). The Subcommittee considered that the benefits of systemic maintenance after chemoradiation are unclear, and that there remains an unmet need in this setting.

12.12. The Subcommittee noted that the phase III, randomised (2:1) PACIFIC trial was the key evidence supporting the use of durvalumab maintenance after chemoradiation in patients with unresectable NSCLC, in which the comparator was placebo. The Subcommittee noted the results of the phase III PACIFIC trial as described by PTAC in August 2020 (Antonia et al. N Engl J Med. 2017;377:1919-29; Antonia et al. N Engl J Med. 2018;379:2342-50**;** Hui et al. Lancet Oncol. 2019;20:1670-80). The Subcommittee noted that an updated analysis of the PACIFIC trial after median follow-up of 34.2 months was presented in October 2020 (Faivre-Finn et al. Ann Oncol. 2020;31 (suppl_4):S1142-S1215).

12.12.1. The Subcommittee noted that PACIFIC recruited participants from 26 countries including Australia but not New Zealand, and considered that patients had good

performance status, were generally similar across the trial groups, and noted that participants were predominantly European with some Asian participants and a mix of histological subtypes. The Subcommittee noted that stratification was according to age, gender and smoking history, and that the study was powered for PFS and OS as primary endpoints.

12.12.2. The Subcommittee noted that PACIFIC participants had completed two platinum-based chemotherapy treatments and radiotherapy and achieved stable disease or a response, and that archival tumour samples were tested for PD-L1 status (not used for stratification). The Subcommittee noted that more than 700 participants were followed up for more than two years and that patients with disease control at 12 months who progressed in follow up could receive durvalumab again.

12.12.3. The Subcommittee noted that the first reported median 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 that there was an improvement in response rates between groups at 18 months (Antonia et al. 2017). The Subcommittee noted that the updated data presented in October 2020 reported median PFS of 17.2 months with durvalumab vs 5.6 months with placebo in the intention-to-treat population (stratified HR for progression or death 0.55, 95% CI: 0.44 to 0.67) and OS reported to be consistent with previous reports (stratified HR 0.71, 95% CI: 0.57 to 0.88; Faivre-Finn et al. 2020). The Subcommittee considered that this was evidence of a significant benefit from durvalumab maintenance in this population.

12.12.4. The Subcommittee noted that there was an absolute difference in OS in PACIFIC of about 10% at two years (66.3% with durvalumab vs. 55.6% with placebo [95% CI, 48.9 – 61.8%, P=0.005]; Antonia et al. 2018). The Subcommittee noted that the updated survival data presented in October 2020 reported median OS of 47.5 months with durvalumab vs 29.1 months with placebo (stratified HR for death 0.71, 95% CI: 0.57 to 0.88; Faivre-Finn et al. 2020). The Subcommittee considered that although there was a small number of patients available for follow-up after three years, there appeared to be an ongoing survival benefit at three and four years.

12.13. The Subcommittee noted that there was no subsequent data from PACIFIC for participants who received immunotherapy after durvalumab (8%) or placebo (22.4%), and that the type of immunotherapy received (eg durvalumab or other treatment) was not known. The Subcommittee noted that there was no other evidence of retreatment with durvalumab or other PD-1/PD-L1 inhibitors after disease progression during PD-1/PD-L1 inhibitor treatment.

12.14. The Subcommittee noted that in PACIFIC, PD-L1 status according to the Ventana SP263 assay was not required to be known at baseline and that the initial analysis did not identify a clear difference between treatment arms with respect to PD-L1 status, with a threshold of 25% PD-L1 expression and unknown PD-L1 status in about one third of patients. The Subcommittee noted that the European Medicines Authority (EMA) had requested a specific, post-hoc PD-L1 analysis using a 1% PD-L1 threshold that identified less PFS and OS benefit in patients with PD-L1 status of <1% (Faivre-Finn et al. 2020), however, the Subcommittee considered the interpretation of this analysis was limited by its post-hoc nature.

12.15. The Subcommittee reiterated its previous considerations regarding the current landscape of PD-L1 testing in New Zealand (CaTSoP, April 2019; CaTSoP, July 2020)

and considered that hierarchical sample testing and limited tumour sample availability present additional challenges.

12.16. The Subcommittee noted that in PACIFIC adverse events were more common with durvalumab than placebo in this group of patients who would otherwise not be receiving active treatment. The Subcommittee noted that treatment discontinuation rates were higher with durvalumab (~15%) than placebo (~10%), most commonly due to pneumonitis or radiation pneumonitis, and considered that these patients would likely experience disease-related symptoms and toxicities from other treatments as reflected in the discontinuation rate in the placebo group.

12.17. The Subcommittee noted that there were no new immune-related safety signals in PACIFIC and considered the immune-related adverse events reported were as expected (ie. similar to those occurring with other PD-1/PD-L1 inhibitors).

12.18. The Subcommittee noted that the PACIFIC patient-reported outcome data was collected up to 48 weeks in a high proportion of patients (Hui et al. Lancet Oncol. 2019;20:1670-80), however, it did not capture the post-treatment benefit of being without disease relapse (compared with having disease relapse), nor did it capture a difference in hospital admissions or relapse-related symptoms that may also impact family/whānau. The Subcommittee considered this data indicated that durvalumab maintenance did not decrease quality of life compared with placebo (a clinically meaningful consideration for maintenance treatment).

12.19. Overall, the Subcommittee considered that the PACIFIC trial was well-designed and provided moderate quality evidence of a clear PFS and OS benefit from 12 months of durvalumab maintenance for unresectable stage III NSCLC. The Subcommittee noted that, but that the cross-over to subsequent treatments may have actually diminished the reported OS difference between groups in the PACIFIC trial, and thus the proportion of patients who would be cured with durvalumab maintenance in the absence of cross-over was uncertain. The Subcommittee considered that the benefit of durvalumab maintenance in patients with PD-L1 <1% was unclear, that the post-hoc evidence was insufficient to confirm whether there is a benefit in this group but that a benefit could not be excluded. The Subcommittee also stressed that treatment with durvalumab could expose patients who otherwise would not receive active treatment to potential toxicity.

12.20. The Subcommittee considered that durvalumab maintenance would not replace any currently funded treatments and would be an additional cost, with vial sharing not feasible in all cases due to its short shelf life once opened, patient scheduling and patient numbers at each treatment centre. The Subcommittee considered that additional health resource would be required for durvalumab including fortnightly treatment administration, monthly clinical assessments, increased monitoring (eg three-monthly CT scans), and management of expected immune-related adverse events. The Subcommittee considered that fortnightly treatment may be challenging for rural patients and those in high deprivation areas.

Specific advice sought from CaTSoP by PTAC regarding durvalumab

12.21. The Subcommittee noted that there is currently no evidence for maintenance treatment using other PD-1/PD-L1 inhibitors (eg atezolizumab, pembrolizumab) to inform assessment of a possible class effect of these agents in the first-line maintenance setting. The Subcommittee noted that no other studies currently investigate this approach in the same patient population, and that the Keynote-799 trial of pembrolizumab in combination with chemotherapy and radiotherapy in stage III

NSCLC includes a different group of patients with advanced disease. The Subcommittee considered that over time it was likely that a class effect would be observed for the PD-1/PD-L1 inhibitors in this setting, as has been observed in other treatment settings.

12.22. The Subcommittee considered that approximately 100 patients per year (without a year 1 bolus due to commencing within 6 weeks after chemoradiation) could be eligible for durvalumab, if funded for first-line maintenance treatment of unresectable NSCLC, and considered that a funded treatment duration of 12 months was appropriate given the evidence for this treatment period.

12.23. The Subcommittee considered that the Special Authority criteria for durvalumab first-line maintenance for NSCLC should require three-monthly renewal, due to the high cost of the medicine to ensure appropriate monitoring and use, and considered that treatment with durvalumab should stop at signs of progression.

12.24. The Subcommittee considered that Special Authority criteria requiring PD-L1 testing and positivity would be reasonable to target funded treatment to those who would receive the greatest benefit, if required to appropriately control pharmaceutical expenditure, noting the health system costs and challenges associated with PD-L1 testing and the uncertain benefit in patients with PD-L1 <1%.

12.25. The Subcommittee considered that, if maintenance treatment with durvalumab were funded for unresectable NSCLC, the funding criteria for PD-1/PD-L1 inhibitors for metastatic NSCLC should be amended to exclude their use in patients who experienced disease progression on PD-L1 treatment, as there is insufficient evidence of benefits of re-treatment with a PD-1/PD-L1 inhibitor beyond progression.

12.26. The Subcommittee considered that a very small number of patients may experience immune-related adverse events with durvalumab (eg. diarrhoea or colitis) that require subsequent treatment with a biologic treatment (eg. infliximab) and additional hospital visits for management of toxicity.