

**Cancer Treatments Subcommittee of PTAC
Meeting held 25 August 2017**

(minutes for web publishing)

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

The Cancer Treatments Subcommittee may:

- a) recommend that a pharmaceutical be listed by PHARMAC on the Pharmaceutical Schedule and the priority it gives to such a listing;
- b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or
- c) recommend that PHARMAC decline to list a pharmaceutical on the Pharmaceutical Schedule.

These Subcommittee minutes will be reviewed by PTAC at its 9 & 10 February 2018 meeting.

1. Correspondence and Matters Arising

Mercaptopurine oral solution for children with acute lymphoblastic leukaemia

Application

- 1.1. The Subcommittee reviewed a funding application for mercaptopurine oral suspension for the treatment of children with acute lymphoblastic leukaemia (ALL) from Link Pharmaceuticals.

Recommendation

- 1.2. The Subcommittee **recommended** that mercaptopurine oral suspension for the treatment of children with acute lymphoblastic leukaemia (ALL) be funded for children who require a dose of less than one full 50 mg tablet per day, with a high priority.

Discussion

- 1.3. The Subcommittee noted that mercaptopurine is part of the standard treatment for ALL, which requires a long course of chemotherapy, but is highly curative, with the current five-year overall survival rate estimated at greater than 85%. The incidence of ALL peaks between 2 and 5 years, with >80% of childhood ALL diagnosed before 9 years of age.
- 1.4. The Subcommittee noted that the tablet form of mercaptopurine can be dissolved in water and have been used for infants, however, as the standard dosing is 75 mg/m² per day and only 50 mg tablets are available, tablets may need to be divided and/or dissolved if part dosages are required in children.
- 1.5. The Subcommittee noted that mercaptopurine requires cellular uptake and slow intracellular anabolism to thioguanine nucleotides (TGNs) for cytotoxicity. Consistent long-term dosing with mercaptopurine provides reliably elevated plasma levels, which is not itself correlated with benefit, but possibly allows for optimal uptake by red blood cells at a critical point in the cell cycle.
- 1.6. The Subcommittee noted the suitability benefits of this product include accurate and acceptable dosing without the theoretical risk of exposure to cytotoxic dust arising from breaking and/or crushing tablets.
- 1.7. The Subcommittee estimated the product would likely be used in all patients aged 4 or less years, 50-60% of those aged 5-9 years and 10% of those aged 11 to 14 years if open access was permitted, although it may be more appropriate to target the use to the younger patients who need smaller doses.
- 1.8. The Subcommittee noted there were approximately 40 patients per year aged 4 or less years receiving treatment for ALL.
- 1.9. The Subcommittee noted the cost of mercaptopurine oral suspension per milligram is considerably higher than the tablets, so it may be appropriate to limit these to the children who require them the most, but as the number of patients was small, the overall budget impact would also likely to be small.

Bendamustine

- 1.10. The Subcommittee noted communications from Janssen to Medsafe regarding a safety update for bendamustine and the issuance of Dear Health Care Professional (DHCP) letter in the United Kingdom. The Subcommittee noted that DHCP letter

noted potentially increased mortality in recent clinical trials when bendamustine was used in non-approved combination treatments (obinutuzumab and rituximab) or outside the approved indications (follicular lymphoma). Fatal toxicities were mainly due to (opportunistic) infections, but some fatal cardiac, neurological and respiratory toxicities were also reported.

- 1.11. The Subcommittee noted the UK indication for bendamustine for indolent non-Hodgkin's lymphomas is as monotherapy in patients who have progressed during or within 6 months following treatment with rituximab or a rituximab containing regimen; whereas the New Zealand indication is untreated indolent Non-Hodgkin's Lymphoma and Mantle Cell Lymphoma, in combination with rituximab in CD20 positive patients.
- 1.12. The Subcommittee noted the current Special Authority criteria limits the use of bendamustine for NHL to use in combination with rituximab when CD20+ (98% of patients) and that PHARMAC staff had asked the Subcommittee to consider whether mandating this combination remained appropriate.
- 1.13. The Subcommittee noted that the best evidence for the use of bendamustine in combination with rituximab comes from the BRIGTH and StiL studies (Flinn et al. Blood. 2014;123:2944-52; Rummel et al. Lancet. 2013;381:203-10). The Subcommittee noted the 5-year follow up of BRIGTH had recently been presented at ASCO (Flinn I. ASCO 2017). This and other similar long-term follow up data have shown that, in general, bendamustine (and rituximab) are more tolerable in the short-term than R-CHOP or R-CVP, but in the longer term are associated with a small increased risk of infections and secondary malignancies (due to longer-term T-cell depression). Overall survival ultimately appears similar between these treatment options for iNHL and MCL.
- 1.14. The Subcommittee noted as-yet unpublished data provided by Roche on the GALLIUM study comparing obinutuzumab with rituximab in patients with CD20-positive previously untreated follicular lymphoma. The Subcommittee noted this study was not designed to specifically compare efficacy and safety by chemotherapy induction regimen, which was allocated by participating centre (rather than allocated as individual participants per a non-cluster randomised protocol). The Subcommittee however considered the GALLIUM study to be useful, as it differs from others given that it includes a period of maintenance with obinutuzumab or rituximab for up to two years in the absence of disease progression. The Subcommittee considered this period of ongoing immunosuppression would likely provide some useful information if there was a safety concern associated with bendamustine. The Subcommittee noted the point estimates of fatal adverse events not associated with disease progression were more common in bendamustine-treated patients in both obinutuzumab and rituximab arms, but the numbers of events were very small, and considered that the lack of chemotherapy randomisation limited the ability to make any clear conclusions from this early data.
- 1.15. The Subcommittee considered there is a possible small safety signal for bendamustine in combination with rituximab or obinutuzumab, but the evidence for this is not currently sufficient to warrant any amendment to the Special Authority criteria. The health benefits for the combination of bendamustine and rituximab combination for NHL were considered to remain positive.
- 1.16. The Subcommittee **recommended** the current Special Authority criteria for bendamustine remain unchanged, but asked for a copy of these minutes to be sent to Medsafe and requested that Medsafe be asked to review this issue.

Aprepitant

- 1.17. The Subcommittee noted there had been recent issues with supply of the aprepitant Tri-Pack presentation (cap 2 x 80 mg and 1 x 125 mg) and that CaTSoP had provided advice to PHARMAC that the 40 mg capsules were an acceptable substitute, in the interim period, to replicate in effect the current regimen.
- 1.18. The Subcommittee noted that some Members had expressed an interest in looking at the evidence for the 165 mg stat dose formulation available in Australia. The Subcommittee noted that subsequent to this, PHARMAC had received correspondence from a Medical Oncologist regarding the equivalence of an aprepitant stat dose to the Tri-Pack regimen.
- 1.19. The Subcommittee noted that PHARMAC staff had not anticipated prescribers would use the replacement 40 mg tablets to form a 160 mg stat dose. The Subcommittee noted this dosing had been used in some centres, who were now disappointed that the 40 mg was now to be delisted following restoration of supply of the Tri-Pack presentation.
- 1.20. The Subcommittee noted the MASCC/ESMO Guidelines (Roila et al. Ann Onc. 2016;5:119–33) recommend a single dose 150 mg IV fosaprepitant or 3-day oral aprepitant (in addition to the newer neurokinan-1's not yet approved by Medsafe). Members noted that the EMA, but not the FDA, has approved the 165 mg PO single dose of aprepitant.
- 1.21. The Subcommittee noted that no clinical trials have tested the 165 mg stat dose against the 3-day regimen. The Subcommittee noted strong clinical evidence to suggest that the three day aprepitant regimen is the same as 150 mg fosaprepitant (Grunberg et al. J Clin Oncol. 2011;29:1495-501; Yang et al. Eur J Cancer Care (Engl). 2017:DOI:10.1111/ecc.12668) and some pharmacokinetic evidence that 150 mg fosaprepitant is equivalent to 165 mg of oral aprepitant (Shadle et al. Clin Pharmacol Drug Dev. 2012;1:93-101; Van Laere et al. Clin Pharmacol Ther. 2012;92:243-50). The Subcommittee considered that this provided sufficient evidence to support the efficacy of the 165 mg stat dose, and indicated they would support funding as an alternative to the Tri-Pack formulation, noting there was potential for delayed emesis despite treatment with either formulation.
- 1.22. The Subcommittee advised that it did not need to see an application for a stat dose presentation unless additional expenditure was to be incurred.

2. Atezolizumab for locally advanced or metastatic non-small cell lung cancer after prior chemotherapy

Application

- 2.1. The Subcommittee considered an application from Roche (NZ) Limited for the funding of atezolizumab for the second or third-line treatment of adult patients with locally advanced metastatic non-small cell lung cancer (NSCLC) after prior chemotherapy.

Recommendation

- 2.2. The Subcommittee **recommended** that atezolizumab for the second or third-line treatment of adult patients with locally advanced metastatic NSCLC after prior

chemotherapy be funded with low priority, subject to the following Special Authority criteria:

ATEZOLIZUMAB - Special Authority for Subsidy – PCT only
Initial application- (NSCLC) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1. Patient has locally advanced or metastatic non-small cell lung cancer; and
2. Patient has an ECOG 0-1; and
3. Patient has documented disease progression following treatment with platinum-based chemotherapy; and
4. Either:
 - 4.1. There is documentation confirming that the disease does not express activating mutations of EGFR tyrosine kinase; or
 - 4.2. Both:
 - 4.2.1. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
 - 4.2.2. The patient has documented disease progression following treatment with erlotinib or gefitinib; and
5. Atezolizumab is to be used as monotherapy at a dose of 1200 mg every 3 weeks for a maximum of 12 weeks; and
6. Baseline measurement of overall tumour burden is documented as per RECIST criteria.

Renewal – (NSCLC) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:

1. Any of the following:
 - 1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
 - 1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
 - 1.3. Patient has stable disease according to RECIST criteria; and
2. Response to treatment in target lesions has been determined by radiologic assessment following the most recent treatment period; and
3. No evidence of disease progression according to RECIST criteria; and
4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
5. Atezolizumab is to be used as monotherapy at a dose of 1200 mg every 3 weeks for a maximum of 12 weeks.

Discussion

- 2.3. The Subcommittee noted that atezolizumab is a humanised immunoglobulin monoclonal antibody programmed cell death protein ligand 1 (PD-L1) inhibitor that can bind directly to PD-L1 on both tumour infiltrating immune cells or tumour cells, thereby preventing the binding of the receptor programmed cell death protein 1 (PD-1) and CD80 on activated T-lymphocytes and other immune cells. Members noted that theoretically this may preserve the number of PD-L1 expressing T-cells, which can be lost to antibody dependent cytotoxicity, as well as avoiding effects on immune system homeostasis, but that the evidence for this was confined to being pre-clinical at present.
- 2.4. The Subcommittee noted that PTAC had previously considered applications for two anti- PD-1 immune checkpoint inhibitors, nivolumab and pembrolizumab, in the same patient groups, namely as 2nd or 3rd line treatments for NSCLC. The Subcommittee noted that PTAC had recommended both be funded with low priority primarily due to immaturity of current data, particularly on overall survival, and uncertainty regarding long-term clinically meaningful gains.
- 2.5. The Subcommittee noted that atezolizumab and nivolumab were indicated for use in NSCLC irrespective of histology or biomarker, whereas pembrolizumab was indicated for PD-L1 positive NSCLC patients.

- 2.6. The Subcommittee noted that the health need of New Zealand patients with advanced lung cancer had been previously considered by both PTAC and CaTSoP, and that this was well described in recent previous minutes for lung cancer treatments such as nivolumab and pembrolizumab.
- 2.7. The Subcommittee noted that the primary evidence for the use of atezolizumab for the treatment of advanced NSCLC is from two randomised clinical trials, the POPLAR and OAK studies.
- 2.8. The Subcommittee noted the POPLAR study was an open-label, phase II randomised controlled trial comparing atezolizumab (fixed dose 1200 mg every 3 weeks, n=142) with docetaxel (75 mg/m² every 3 weeks, n=135) in patients with NSCLC who progressed post-platinum chemotherapy (Fehrenbacher et al. Lancet 2016;387:1837-46). Members noted that eligibility criteria included ECOG 0-1 and no prior treatment with docetaxel or any other immunotherapy.
- 2.9. The Subcommittee noted overall survival (OS) in the intention-to-treat (ITT) population, the primary endpoint, was 12.6 months (95% CI 9.7–16.4) for atezolizumab versus 9.7 months (8.6–12.0) for docetaxel (hazard ratio [HR] 0.73 [95% CI 0.53–0.99]; p=0.04).
- 2.10. The Subcommittee noted the OAK study was a randomised, open-label, phase III trial comparing atezolizumab (fixed dose 1200 mg every 3 weeks, n=425) with docetaxel (75 mg/m² every 3 weeks, n=425) in patients with locally advanced or metastatic NSCLC that had progressed during or after treatment with a platinum-containing regimen (Rittmeyer et al. Lancet 2017;389:255-65).
- 2.11. The Subcommittee noted eligibility criteria included squamous or non-squamous NSCLC, age 18 years or older, measurable disease as per RECIST v1.1, ECOG 0-1, prior treatment with 1-2 previous cytotoxic chemotherapy regimens (1 or more platinum-based) for stage IIIb or IV disease. The Subcommittee noted that patients with EGFR mutations or ALK fusion oncogene were additionally required to have received treatment with a tyrosine kinase inhibitor (TKI). Members noted that there are currently no mutation targeted treatments for ALK+ lung cancer funded in New Zealand.
- 2.12. The Subcommittee noted that exclusion criteria included a history of autoimmune disease, or prior treatment with docetaxel, anti-CTLA4 or immune therapies targeting PD-L1 or PD-1 pathways.
- 2.13. The Subcommittee noted that patients were stratified by number of previous chemotherapy regimens, histology, and five PD-L1 expression groups based on percentage expression on tumour cells or tumour-infiltrating immune cells from archival or fresh tissues. The Subcommittee considered that the definition of PD-L1 expression cohorts was clear and transparent, but differed from those used in the trials of nivolumab and pembrolizumab. The Subcommittee also noted the outstanding issues regarding PD-L1 expression testing outlined during its consideration of the funding applications for pembrolizumab as a NSCLC treatment remained pertinent.
- 2.14. The Subcommittee noted that treatment was administered until unacceptable toxicity or disease progression as assessed by the investigator, but that treatment could continue beyond disease progression if the investigator deemed the patient to be receiving clinical benefit.

- 2.15. The Subcommittee noted that no crossover to atezolizumab was permitted, however, 4% patients in the atezolizumab group and 17% patients in the docetaxel group went on to receive subsequent immunotherapy treatment, primarily with nivolumab, and 40% and 31% respectively went on to receive systemic chemotherapy.
- 2.16. The Subcommittee noted that median treatment duration was 3.4 months (range 0–26) with atezolizumab and 2.1 months (range 0–23) with docetaxel. The Subcommittee noted that 40% of patients receiving atezolizumab were treated beyond progression, with a median treatment duration beyond progression of three cycles (range 1–34).
- 2.17. The Subcommittee noted that at the primary analysis (data cutoff July 7, 2016), based as intention-to-treat on the 850 patients starting, the median follow-up was 21 months and that 569 patients had died (27 fewer in the atezolizumab group than the docetaxel group).
- 2.18. In the ITT population, median OS, the primary endpoint, was 13.8 months [95% CI 11.8–15.7] with atezolizumab vs 9.6 months [8.6–11.2] with docetaxel; HR 0.73 [95% CI 0.62–0.87], $p=0.0003$, a 4.2 month difference.
- 2.19. The Subcommittee noted that grade 3 or 4 adverse events were reported in 227 (37%) of 609 patients treated with atezolizumab and 310 (54%) of 578 patients treated with docetaxel. The Subcommittee considered there did not appear to be any new safety signals in the atezolizumab arm and it appeared to be well tolerated in this NSCLC population.
- 2.20. The Subcommittee considered that the OAK study was well designed in that the primary endpoint was OS, with crossover not permitted. However, the Subcommittee considered that, given the definition of clinical benefit in the trial protocol, reliability of progression-free survival as an endpoint was less robust.
- 2.21. The Subcommittee considered the evidence for the use of atezolizumab in previously treated NSCLC patients to be generalisable to the NZ context. Members considered that outcomes for patients in the docetaxel control arm were generally better than would be expected based on previous published evidence.
- 2.22. The Subcommittee considered that due to the immaturity of currently available data and very small patient numbers remaining on treatment, there was a high level of uncertainty regarding the durability of response and long-term survival benefit from treatment with atezolizumab for previously treated NSCLC patients.
- 2.23. The Subcommittee considered that while there appeared to be a correlation between increased PD-L1 expression and increased response rates to atezolizumab, clinical benefit was also seen in patients with no PD-L1 expression (45% of the study population). Members noted that the OAK study had not been powered to differentiate and stratify for this endpoint according to levels of PD-L1 expression.
- 2.24. The Subcommittee considered that overall there was strong evidence to support the benefit of atezolizumab for previously-treated advanced NSCLC patients, although it was mainly from a single open-label phase III trial. The Subcommittee noted that its priority recommendation was influenced by the quality of the evidence and the high price being sought by the supplier.

- 2.25. The Subcommittee considered that there was a lack of comparative clinical studies to indicate that any one immune check point inhibitor provides additional health benefit or harm compared to the others in the treatment of NSCLC.
- 2.26. The Subcommittee noted a systematic review of the efficacy of immune checkpoint inhibitors compared with other chemotherapies in patients with advanced NSCLC, conducted to inform the development of clinical practice guidelines in Ontario (Ellis et al. Clin Lung Cancer 2017;18:444-59e1). The Subcommittee noted that the authors concluded there is evidence for an improvement in OS that outweighs harm, to support the use of all three agents in the treatment of NSCLC after the failure of platinum-based chemotherapy, and that there is currently insufficient evidence to select patient cohorts to best target resources on the basis of PD-L1 expression.
- 2.27. The Subcommittee considered there to be a class effect for immune checkpoint inhibitors in the treatment of previously-treated advanced NSCLC and that, based on currently available evidence, atezolizumab, nivolumab and pembrolizumab had the same or similar clinical effect in this patient population.
- 2.28. The Subcommittee considered that if an immune checkpoint inhibitor were to be funded for advanced NSCLC patients this would likely have a significant impact on DHB infusion services. Members considered that, when compared to docetaxel, there was a reduced requirement for premedication with atezolizumab. Members considered that once patients progressed with immune checkpoint inhibitor treatment they would likely receive a further line of treatment with docetaxel or vinorelbine.
- 2.29. The Subcommittee considered that uptake of atezolizumab would likely be higher than estimated given the clinical interpretation of ECOG status, which would mean that some patients with ECOG status greater than 1 would likely receive treatment with this agent.
- 2.30. The Subcommittee considered that, if more than one immune checkpoint inhibitor were to be funded for the treatment of previously-treated advanced NSCLC patients, it would be appropriate for patients to switch agents due to infusion reactions, and that a definition of this should be included in the access criteria as follows:
- Both:
 The patient has discontinued [immune checkpoint inhibitor] due to infusion reaction,
 and
 The cancer did not progress whilst on [immune checkpoint inhibitor]
- 2.31. The Subcommittee considered it would not be appropriate to allow patients to switch between immune checkpoint inhibitor agents due to immune adverse events.
- 2.32. The Subcommittee noted that this application had been considered by PTAC at its meeting on 11 and 12 August 2017. The Subcommittee was informed that while the minute of that PTAC meeting had yet to be finalised, that PTAC had made a positive recommendation.

3. Immune Response Criteria Discussion

Recommendation

- 3.1. The Subcommittee reviewed a supplementary paper from PHARMAC staff on immune response criteria and their relevance in terms of access criteria for immunotherapy treatments.

Discussion

- 3.2. The Subcommittee noted that the programmed cell death-1 (PD-1) inhibitors nivolumab (Opdivo) and pembrolizumab (Keytruda) are currently funded for patients with advanced melanoma, and that the access criteria for these treatments require measurement of a patient's disease response according to RECIST v1.1.
- 3.3. The Subcommittee considered that RECIST v1.1 is the standard approach within clinical trials for measuring solid tumour response to treatment.
- 3.4. The Subcommittee noted that while clinical trials continue to use RECIST v1.1, non-standardised, non-validated modification of criteria and treatment-beyond-progression were being included in clinical trials with immunotherapy agents.
- 3.5. The Subcommittee noted that many immunotherapy clinical trial protocols allow for patients to continue treatment even after RECIST v1.1 disease progression, if it is considered those patients are continuing to receive clinical benefit, but that the circumstances under which this occurs are not consistent between trials. The Subcommittee considered this differs from the way oncology clinical trials have historically been conducted, where treatment stops upon disease progression.
- 3.6. The Subcommittee noted evidence for treatment past progression from Kazandjian et al. (*Semin Oncol.* 2017;44:3-7) and Escudier et al. (*EurUrol.* 2017;72:368-76). The Subcommittee considered it was unclear if results translated to an overall survival difference. The Subcommittee noted that treatment beyond progression could differentially bias long-term results reported.
- 3.7. The Subcommittee considered that this new paradigm, based on clinician and/or patient judgment of benefit from immunotherapy treatment, introduced complexity and significant risk in terms of subjectivity when determining treatment response.
- 3.8. The Subcommittee considered that the use of immune response criteria was of particular relevance for considering treatment approaches for patients with pseudoprogression. The Subcommittee noted that pseudoprogression is the term used to describe tumour response in patients treated with immune stimulating agents who have an initial increase in tumour lesion size before demonstrating clinical objective responses and/or stable disease. The Subcommittee noted that the issues around the definition of and implementation of funding criteria to allow for pseudoprogression were discussed at its meeting in September 2016, and considered that these issues remained relevant.
- 3.9. The Subcommittee considered that currently published literature indicated that pseudoprogression only appears to be a significant phenomenon in melanoma patients as opposed to other tumour types.
- 3.10. The Subcommittee noted that alternative response criteria, the Immune Related Response Criteria (irRC) and iRECIST guidelines, have been developed for measuring the response to immune-oncology treatments.
- 3.11. The Subcommittee noted that the iRC (Wolchok et al *Clin Cancer Res* 2009;15:7412-20) and an abstract presented at ESMO 2014 regarding iRECIST (Bohnsack et al. Abstract 4958) were considered by CaTSoP at its meeting in April 2016, in the context of considering consultation feedback regarding proposed Special Authority criteria for nivolumab and pembrolizumab for advanced melanoma patients.
- 3.12. The Subcommittee noted the iRECIST guideline has recently been published in *Lancet Oncology* (Seymour et al. *Lancet Oncol* 2017;18:e143-52).

- 3.13. The Subcommittee noted that Seymour et al. conclude that although the iRECIST guideline is consensus based, it is not yet validated and therefore recommend that iRECIST criteria be used only as a secondary or exploratory endpoint in clinical trial protocols.
- 3.14. The Subcommittee considered that it was not appropriate at this time to amend the current access criteria for immunotherapy treatments.
- 3.15. The Subcommittee considered that the literature regarding immune response criteria should be reviewed at a future meeting, should further evidence become available.

4. Rituximab for CD20 positive precursor B-cell acute lymphoblastic leukaemia

Application

- 4.1. The Subcommittee considered a clinician funding application for adults with precursor B-cell acute lymphoblastic leukaemia (ALL) expressing CD20 being treated with intensive chemotherapy with curative intent.

Recommendation

- 4.2. The Subcommittee **deferred** making a recommendation on this funding application until the results of the UKALL14 trial are available for review by the Subcommittee.

Discussion

- 4.3. The Subcommittee noted that there are approximately 50 cases per year of precursor B-cell ALL in New Zealand, most frequently in childhood, but can also be seen in adults (approximately 20%). The Subcommittee noted that fit patients receive intensive multiagent chemotherapy using corticosteroids, vincristine, asparaginase and other chemotherapy agents using UKALL or HyperCVAD protocols. The Subcommittee noted that many patients are then consolidated with allogeneic haematopoietic stem cell transplant (Allo-SCT). In adults, there is a considerable unmet need for effective treatments given that despite the long and toxic course of therapy, a cure is not achieved in approximately 50% of patients.
- 4.4. The Subcommittee noted that only one-third to half of people with precursor B-cell ALL express the CD20 antigen at baseline, but the exact frequency depends on how CD20 positivity is defined. It was reasonable to suggest that approximately 10-15 adult patients per year would be CD20 positive (>20% expression) and candidates for targeted rituximab treatment given the available evidence. Rituximab would be added to existing treatment protocols and not replace any of the existing treatments.
- 4.5. The Subcommittee noted that there some evidence that CD20 expression in adults with B-cell precursor B-cell ALL is associated with a worse prognosis. In one study (Thomas et al. Blood. 2009;113:6330-7) CD20 expression of at least 20% was associated with a three year overall survival rate of 27% versus 40%. This poorer prognosis appeared to be due to a higher incidence of disease recurrence, rather than an decreased rate of response to induction therapy.
- 4.6. The Subcommittee noted the Phase II GRAALL-2005/R study (Maury et al. N Engl J Med 2016;375:1044-53) which randomised 209 eligible patients with CD20 positivity (defined as >20% expression at baseline) in a 1:1 ratio to receive a total of 16 doses of rituximab (18 in the case of salvage reinduction) over 2 years or none. The Subcommittee noted the study found no significant difference in response to

induction therapy between the groups in terms of complete remission or minimal residual disease negativity. The Subcommittee noted the study did however result in a significant improvement in event-free survival, which translated into a trend towards a small improvement in overall survival which at 4 years was 61% (95% CI, 52 to 72) and 50% (95% CI, 41 to 62) for rituximab versus no rituximab respectively. The improved event-free survival was due to reduction in the incidence rate for relapse (HR 0.52, CI, 0.31 to 0.89). The Subcommittee noted that avoiding relapses is significant as only about 20% of relapses can be salvaged and the salvage process is very resource intensive.

- 4.7. The Subcommittee noted that there was a trend towards a better response for the addition of rituximab in all ages, CNS status, or white-cell counts, and those with higher CD20 positive expression did better than those with a lower CD20 positive expression. The Subcommittee also noted that a higher proportion of patients in the rituximab group underwent transplantation during the first remission period, with event-free survival remaining longer in the rituximab group than in the control group despite censoring at the time of transplant.
- 4.8. The Subcommittee noted that transplant recommendations would not be influenced by the addition of rituximab, and any potential benefits of the rituximab would not be apparent at the time of transplant.
- 4.9. The Subcommittee noted there was a possible reduction in asparaginase reactions in the rituximab group, which could have a significant cost implication given the high comparative costs of Erwinia asparaginase, although noted that pegasparaginase is more commonly used in New Zealand and is less immunogenic compared to the Escherichia coli asparaginase used in the trial.
- 4.10. The Subcommittee noted there was weak strength but good quality evidence to suggest a benefit of adding rituximab, with no significant increase in additional adverse events in precursor B-cell ALL therapy. The Subcommittee however considered that the place in therapy of rituximab remains somewhat unclear given that the benefit appears to have been in reducing the relapse rate rather than improving the response to induction. The Subcommittee noted the small numbers of patients in the GRAALL-2005/R and considered it raised the further question about the potential benefit of a large number of rituximab doses given over a prolonged period (i.e. for late consolidation and maintenance).
- 4.11. The Subcommittee noted that CD20 increases during induction, so it is plausible that rituximab given during this period may provide a benefit, but, at this time, there is a lack of confirmatory evidence.
- 4.12. The Subcommittee noted the Phase III UKALL14 trial, which has now closed but not yet published, is seeking to determine if the addition of four doses of rituximab to standard Phase 1 induction chemotherapy results in improved event-free survival in patients with precursor B-cell lineage ALL, regardless of baseline CD20 status. The Subcommittee considered this confirmatory trial may resolve the residual uncertainty, and thus the Subcommittee considered it was appropriate to defer making a formal recommendation until the results of this trial were available.

5. Peptide Receptor Radionuclide Therapy for neuroendocrine tumours

Application

- 5.1. The Subcommittee considered two funding applications for Peptide Receptor Radionuclide Therapy (PRRT) for the treatment of patients with neuroendocrine tumours (NETs). These were a clinician application from Dr Ben Lawrence, ADHB, and a consumer application from the Unicorn Foundation, an advocacy group for patients and families affected by NETs. The Subcommittee considered that the applications received were comprehensive and well-prepared.

Recommendation

- 5.2. The Subcommittee **recommended** that Lu-tate PRRT be funded with medium priority for the treatment of unresectable or metastatic, well-differentiated NETs (irrespective of primary site) that express somatostatin receptors, subject to the following access criteria:

Initial application - only from a medical oncologist or radiation oncologist. Approvals valid for 8 months for applications meeting the following criteria:

All of the following:

1. The patient has been diagnosed with metastatic or unresectable well-differentiated* neuroendocrine tumour; and
2. Any of the following:
 - 2.1. Uncontrolled secretory syndrome despite somatostatin analogue treatment; or
 - 2.2. Progression less than 12 months since diagnosis; or
 - 2.3. Progression following chemotherapy treatment; or
 - 2.4. Extensive disease at diagnosis with no reserve for tumour progression; and
3. Patient has a Karnofsky score of 60 or more; and
4. Patient has good renal function (eGFR greater than 50 ml/min); and
5. Tumour expresses somatostatin receptors as shown on Ga68-DOTA-octreotate PET CT scan; and
6. Either:
 - 6.1. Ki-67 less than 5%; or
 - 6.2. Both:
 - 6.2.1. Ki-67 greater than 5% and less than 20%; and
 - 6.2.2. Concordant FDG expression as shown on FCG PET CT scan.

Notes: *Well-differentiated is defined as Ki-67 less than 20%

- 5.3. The Subcommittee noted that this recommendation was dependent on systems and relevant expertise being in place for the appropriate administration of PRRT.

Discussion

- 5.4. The Subcommittee noted that NETs are a heterogeneous group of tumours that differ in biologic behaviour, histologic appearance and response to treatment
- 5.5. The Subcommittee noted that some NETs are characterised anatomically by primary site, however some that secrete hormonally active substances are named by the type of hormone secreted. The Subcommittee noted that NETs are also classified according to their histologic features, which separate more indolent and well-differentiated tumours from more aggressive (high grade) poorly-differentiated tumours. The Subcommittee noted that there is currently no unified classification or grading system for NETs.
- 5.6. The Subcommittee noted that the disease course for NETs means that it is usual for retreatment with the same agent, or more than one type of treatment to be required. The Subcommittee noted that the choice of treatment depends on the tissue of origin, the grade and presence of a secretory syndrome and includes platinum-based chemotherapy, temozolomide and somatostatin analogues. The Subcommittee

considered that there was an unmet health need for effective treatments for patients with unresectable metastatic NETs.

- 5.7. The Subcommittee noted that the incidence of NETs increases with age, with patients typically around 58 years, and based on data from the Surveillance, Epidemiology, and End Results (SEER) Program registries between 1973-2004 (Yao et al. JCO 2008;26:3063-72) estimated the prevalence of NETs in 2004 was 5.25 per 100,000 cases. The Subcommittee considered there is some uncertainty regarding the incidence of NETs in New Zealand, however noted a retrospective audit of New Zealand patients is currently being undertaken. The Subcommittee noted that the applicant estimated there would be 50-60 patients in New Zealand per year diagnosed with metastatic NET, of which half would be potential candidates for PRRT, and considered this to be reasonable.
- 5.8. The Subcommittee noted that median overall survival for low grade metastatic NETs can be around 10 years (in the context of an average age of around 58 years at presentation), but varied depending on factors such as age and tumour grade, whereas survival for people with high grade NETs is measured in months. The Subcommittee considered that the systemic effects and secretory symptoms could have a significant impact on quality of life for NET patients
- 5.9. The Subcommittee noted that PRRT is a type of radioisotope therapy in which a peptide or hormone conjugated to a radionuclide or radioligand is given intravenously. The Subcommittee noted that the clinician application was specifically for Lutetium 177-DOTA-Octreotate. The Subcommittee noted that the active component of Lu-tate PRRT comprises of three parts:
 1. a radioactive lutetium moiety (the radionuclide, Lutetium (¹⁷⁷Lu)) coupled to
 2. a somatostatin analogue (the peptide, in this case octreotate) that binds to somatostatin receptors on the surface of the cancer cell, and
 3. a chelator that links the radionuclide to the peptide (in this case DOTA – 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid).
- 5.10. The Subcommittee noted that the radioactively labelled hormones enter the tumour cells which, together with nearby cells, are then damaged by radiation, and that cell death can continue for up to two years.
- 5.11. The Subcommittee noted that because of the mechanism of binding Lu-tate to the tumour cells, PRRT will only benefit patients if all tumour locations express somatostatin receptors, as shown by avidity on Ga68-DOTA-octreotate (Ga-tate) PET CT scan. For this reason, the Subcommittee considered that the primary site was not relevant in terms of defining which patients would benefit from PRRT.
- 5.12. The Subcommittee noted that for patients with higher grade NETs (Ki-67 over 5%) the somatostatin receptor expression is also cross-checked via FDG-PET CT. The Subcommittee noted that if a patient's lesion is metabolically active (FDG avid on FDG-PET CT) without a matching Ga-tate PET avidity the radiopeptide will not be delivered to that lesion.
- 5.13. The Subcommittee noted that Ga-tate scans and FDG-PET CT scans were not currently available in DHB Hospitals, but provision of these services was currently outsourced to private providers. The Subcommittee noted that this would represent an additional cost for DHBs were PRRT to be funded.
- 5.14. The Subcommittee noted that PRRT is delivered through an intravenous luer in the same way as IV chemotherapy, on 4 occasions 8 weeks apart, but may be stopped

early if tumour load is significantly reduced and it is judged there is insufficient tumour load to absorb another dose. The Subcommittee noted that SPECT CT is used to monitor response to treatment, which is available in most existing DHB nuclear medicine facilities.

- 5.15. The Subcommittee noted that the infusions are administered in a nuclear medicine department, with appropriate lining and facility for safe collection of radioactive urine excreted during and immediately after therapy. The Subcommittee considered that while multiple DHBs currently have appropriate nuclear medicine facilities, there was a lack of clinical staff in all centres currently who had the relevant expertise to administer PRRT in New Zealand, particularly appropriately trained radiopharmacists and suitably experienced nuclear medicine physicians.
- 5.16. The Subcommittee noted that the applicants had proposed that PRRT could be delivered at a single New Zealand site, to provide sufficient treatments so that operating expenditure could be reduced; and that this could be achieved by reorganisation of suitable space and rebalancing of the nuclear medicine workforce. The Subcommittee considered a single site may not be required if the required specialist scanning facilities were able to be provided locally, as expertise could be shared virtually.

Evidence

- 5.17. The Subcommittee noted that the primary evidence for the use of Lu-tate PRRT is from the NETTER-1 trial (Strosberg et al. N Engl J Med. 2017;376:125-35), an open-label prospective phase 3, randomised, controlled trial of PRRT in 229 patients with metastatic or locally advanced, unresectable, midgut NETS who received either four infusions of ¹⁷⁷Lu-Dotatate (n=116) at a dose of 7.4GBq (200mCi) every 8 weeks administered with best supportive care including octreotide LAR (30mg every 4 weeks for symptom control) or octreotide LAR alone (n=113, 60mg every 4 weeks approximately 24 hours after each Lu-Dotatate infusion then monthly after completion of all four treatments).
- 5.18. The Subcommittee noted that an intravenous amino acid solution was administered concomitantly for at least 4 hours, starting 30 minutes before infusion of the radiopharmaceutical, to reduce renal toxicity by preventing reabsorption of radionuclide in the kidney. The Subcommittee noted that there did not appear to be an appropriate amino acid solution currently registered in New Zealand.
- 5.19. The Subcommittee noted eligibility criteria included disease progression as per RECIST v1.1 on CT or MRI over a maximum period of 3 years during treatment with octreotide LAR (20-30mg every 3-4 weeks for at least 12 weeks prior to randomisation), Karnofsky score of at least 60, somatostatin receptors present on all target lesions, and well-differentiated histologic features as defined by the Ki67 index of 20% or less.
- 5.20. The Subcommittee noted that the key exclusion criteria were serum creatinine >150umol/L or creatinine clearance of less than 50ml/min; Hb <8.0g/dl; white cell count <2000/mm³; platelet count 75,000/mm³; treatment with more than 30mg octreotide LAR within 12 weeks; previous PRRT at any time; chemotherapy within last 12 weeks.
- 5.21. The Subcommittee noted that in the Lu-Dotatate group, patients received four infusions every 8 weeks unless unacceptable toxic effects occurred, disease

progression as per RECIST v1.1 on imaging, patient was unwilling or unable to adhere to trial procedures, patient withdrew consent or died.

- 5.22. The Subcommittee noted that the estimated rate of progression-free survival (PFS), the primary outcome measure, at month 20 was 65.2% (95% CI, 50.0 to 76.8) in the Lu-Dotatate group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The median PFS had not yet been reached in the Lu-Dotatate group and was 8.4 months (95% CI, 5.8 to 9.1) in the control group (hazard ratio for disease progression or death with Lu-Dotatate vs. control, 0.21; 95% CI, 0.13 to 0.33; $p < 0.001$).
- 5.23. The Subcommittee noted that at data cut-off, there had been 26 deaths in the control group and 14 in the Lu-Dotatate group; and that while the survival data awaits maturation, a planned interim analysis of overall survival showed borderline significance (HR 0.40: $p = 0.004$ with a required O'Brien-Fleming threshold p -value of 0.000085).
- 5.24. The Subcommittee noted that most common adverse events among patients in the Lu-Dotate group were nausea (59%), and vomiting (47%) and that for 73% of these patients were attributable to the amino acid infusions with events resolving once infusions were completed. The Subcommittee noted that grade 3 or greater adverse events were only reported in the Lu-Dotate group: neutropenia (1%), thrombocytopenia (2%), and lymphopenia (9%).

General Comments

- 5.25. The Subcommittee considered that there was good quality evidence of benefit from treatment with PRRT, particularly in functional NETs, although the magnitude of benefit was uncertain. The Subcommittee considered that while survival data is immature it appears promising.
- 5.26. The Subcommittee considered that, from currently published evidence, PRRT had a significant effect on tumour size, however it was unclear whether PRRT improved quality of life overall, but that there would likely be benefit in terms of symptom control and possibly reduced octreotide use (Khan et al. J Nucl Med 2011;52:1361-8).
- 5.27. The Subcommittee noted that there was a 12-month difference between baseline clinical characteristics of the NETTER-1 trial arms in the time since diagnosis and starting treatment. The Subcommittee considered these differences between the groups were clinically significant, and maturity of the data was going to be important.
- 5.28. The Subcommittee noted that the evidence was limited to patients with mid-gut NETs, but considered that there was no evidence to suggest that benefit is determined by primary site but rather somatostatin receptor expression.
- 5.29. The Subcommittee considered that funding for PRRT was requested for the treatment of unresectable or metastatic, well-differentiated NETs (irrespective of primary site) that express somatostatin receptors, and if Ki-67 $> 5\%$ also show concordant FDG expression. The Subcommittee considered that this represented a very targeted group of patients with well-differentiated low grade tumours.
- 5.30. The Subcommittee noted that octreotide LAR is currently only funded for NET patients with secretory syndromes, and therefore New Zealand patients with non-secretory NETs differ from the NETTER-1 trial population; however, the Subcommittee considered it likely that likely both groups would derive a similar level

of benefit from PRRT. The Subcommittee considered it was not reasonable to exclude these patients from treatment eligibility should PRRT be funded.

- 5.31. The Subcommittee considered that the regulatory requirements and handling of the PRRT radionuclide would be no different than for other currently used radionuclide treatments.
- 5.32. The Subcommittee noted that NICE in the UK had not recommend PRRT based on an unfavourable cost-benefit analysis by comparison with everolimus, but noted that everolimus is not funded for NETs in the New Zealand setting. The Subcommittee noted that, from publicly-available information, the costs of PRRT considered by NICE was unknown.
- 5.33. The Subcommittee noted that the Northern Regional Cancer Network Clinical Practice Committee had reviewed PRRT, and considered it would be useful to request a copy of that group's assessment.
- 5.34. The Subcommittee considered that, if PRRT were to be funded, there were significant implementation issues that would need to be addressed, particularly in terms of having the appropriate facilities and expertise required for the administration of PRRT.
- 5.35. The Subcommittee considered a national multi-disciplinary team would be useful to ensure stewardship of resources and aid in patient selection and treatment management of patients undergoing PRRT.

6. Axitinib for the second-line treatment of metastatic renal cell carcinoma

Application

- 6.1. The Subcommittee considered a noting paper from PHARMAC staff seeking updated advice from the Subcommittee regarding axitinib (Inlyta) for the second-line treatment of metastatic clear cell renal cell carcinoma (RCC), in the light of updated proposed pricing provided by the supplier, Pfizer (NZ) Ltd; and updated advice regarding previously considered unfunded second-line treatments for RCC – everolimus and sorafenib.

Recommendation

- 6.2. The Subcommittee **recommended** that axitinib for the second-line treatment of metastatic renal cell carcinoma (mRCC) be funded with a low priority, subject to the following Special Authority criteria:

AXITINIB – Special Authority for Subsidy – Retail pharmacy

Initial application - only from a medical oncologist. 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. The disease is of predominant clear cell histology; and
3. The disease has progressed following prior treatment with sunitinib or pazopanib; and
4. The patient has good performance status (WHO/ECOG grade 0-1).

Renewal 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: axitinib treatment should be stopped if disease progresses.

Discussion

- 6.1. The Subcommittee noted that in New Zealand the currently funded pharmaceutical treatments for advanced clear cell RCC are interferon alpha and the tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib.
- 6.2. The Subcommittee noted that there are currently no funded second-line treatment options for patients with disease refractory to sunitinib or pazopanib. The Subcommittee considered that the median survival for advanced RCC patients following first line TKI treatment with best supportive care was 4-11 months.
- 6.3. The Subcommittee considered that there is a significant group of advanced clear cell RCC patients, with good performance status and limited disease burden on current first-line treatment, who have had good control over several years. The Subcommittee considered that once these patients stop first line tyrosine kinase inhibitor treatment, progression of their disease is generally rapid, due to multifocal acquired resistance that develops under treatment-induced selection pressure. The Subcommittee considered there was an unmet health need for an effective second-line treatment option for advanced clear cell RCC.

Axitinib

- 6.4. The Subcommittee noted that the application from Pfizer (NZ) Ltd for the funding of axitinib (Inlyta) on the Pharmaceutical Schedule was for patients with metastatic clear cell renal cell carcinoma (RCC) where disease progression or intolerance has occurred following prior tyrosine kinase inhibitor treatment, and that this setting had been considered by PTAC at its meeting in November 2013. The Subcommittee noted that PTAC had recommended the application be declined.
- 6.5. The Subcommittee noted that PTAC's recommendation was based on evidence from the AXIS study (Rini B. Lancet. 2011;378(9807):931-9 and Motzer RJ et al. Lancet Oncology, 2013;14:552-62), a phase III, randomised, open-label study of comparing axitinib with sorafenib in 723 patients with mRCC progressing after first line treatment; and an indirect comparison of axitinib with best supportive care.
- 6.6. The Subcommittee noted that in November 2013 PTAC had considered overall the evidence base for axitinib in the requested population was weak and that members considered the strength of evidence supporting the use of axitinib did not justify its very high cost.
- 6.7. The Subcommittee noted that the supplier of axitinib had since provided an updated commercial proposal for funding of axitinib as a second-line clear cell RCC treatment, which improved the estimated cost-effectiveness of axitinib treatment.
- 6.8. The Subcommittee noted that a sub-analysis by prior therapy from a randomised phase III AXIS study (Escudier et al. Br J Cancer 2014;110:2821-8) had been published since PTAC's review of the application. However, the Subcommittee considered this post hoc analysis to be limited by the small subgroups under consideration and that it did not significantly add to the quality of evidence for the use of axitinib in the second-line setting for clear cell RCC.
- 6.9. The Subcommittee considered that axitinib provided limited benefit as a second-line treatment for clear cell RCC. The Subcommittee recommended that axitinib be funded with low priority for the second-line treatment for relapsed metastatic clear

cell RCC, noting the unmet health need in this population but also that the price sought by the supplier remained high.

Everolimus

- 6.10. The Subcommittee noted that an application for everolimus (Afinitor, Novartis) for second-line mRCC was considered by PTAC at its meeting in November 2011 and CaTSoP in the same month. The Subcommittee noted that both committees had recommended the application be declined primarily due to the high cost and marginal benefit.
- 6.11. The Subcommittee noted that these recommendations were primarily based on evidence from the RECORD1 trial, a randomised phase III comparing everolimus with placebo both in conjunction with best supportive care (Motzer et al. Lancet 2008;372:449-56, and Motzer et al. Cancer 2010;116:4256-65).
- 6.12. The Subcommittee noted that the phase III RECORD-3 and RECORD-4 studies were now published, but considered however that these did not significantly improve the evidence base for the use of everolimus in this setting.
- 6.13. The Subcommittee considered the previous recommendation to decline the application remained appropriate.

Sorafenib

- 6.14. The Subcommittee noted that an application for sorafenib (Nexavar, Bayer) for first-line mRCC had been considered by both PTAC and CaTSoP in 2008 and 2011 respectively. The Subcommittee noted that both committees had recommended that the application be declined due to no demonstrable benefit, its high cost, and significant toxicity. The Subcommittee noted that it appeared no further evidence for the use of sorafenib in this setting had been published, and considered that the previous recommendations to decline the application remained appropriate.

General comments

- 6.15. The Subcommittee noted that there were currently a number of agents being investigated in late stage clinical trials for the treatment of advanced RCC. The Subcommittee considered that these included head-to-head trials that would help address the question of second-line sequencing.
- 6.16. The Subcommittee noted that, based on currently available phase III trial evidence, it appeared that the two most active agents for the treatment of relapsed clear cell RCC are nivolumab, an antiPD1 inhibitor, and cabozantinib, a combined VEGFR2 and MET inhibitor. Members noted that these agents appeared to provide overall survival benefits over everolimus treatment in a second-line setting of 5.4 months and 4.9 months respectively (CHECKMATE025: Motzer et al. N Engl J Med. 2015;373:1803-13, and METEOR trial: Choueiri et al. Lancet Oncology 2016;17:917-27).
- 6.17. The Subcommittee noted that a clinician funding application for the use of nivolumab in the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy was on the agenda for consideration at this meeting.

7. Nivolumab for Relapsed Clear Cell Renal Cell Carcinoma

Application

- 7.1. The Subcommittee considered a clinician funding application for the use of nivolumab (Opdivo) for the second-line treatment of relapsed clear cell renal cell carcinoma (RCC) following prior angiogenic therapy.

Recommendation

- 7.2. The Subcommittee **recommended** that nivolumab (Opdivo) for the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy be funded with a medium priority, but also considered that its priority rating would decrease if the cost-effectiveness of nivolumab in this setting was poor.

Discussion

- 7.3. The Subcommittee noted that in 2012 the New Zealand Cancer Registry data recorded 897 registrations for cancers of the kidney and 168 deaths. The Subcommittee noted that the age standardised rate of renal cell cancer mortality is significantly higher in Māori (3.8 per 100,000 person years) compared with non-Māori (2.5 per 100,000).
- 7.4. The Subcommittee noted that in New Zealand the currently funded pharmaceutical treatments for advanced clear cell RCC are interferon alpha and the VEGF tyrosine kinase inhibitors (TKIs) pazopanib and sunitinib.
- 7.5. The Subcommittee noted that there are currently no funded second-line treatment options for patients with disease refractory to sunitinib or pazopanib. The Subcommittee considered that the median survival for advanced RCC patients following TKI treatment with best supportive care was 4-11 months.
- 7.6. The Subcommittee considered that there is a significant group of advanced clear cell RCC patients with good performance status and limited disease burden on current first-line treatment. The Subcommittee considered that once these patients stop tyrosine kinase inhibitor treatment, progression of their disease is generally rapid. The Subcommittee considered there was an unmet health need for an effective second-line treatment option for advanced clear cell RCC.
- 7.7. The Subcommittee noted that other funding applications for the second line treatment of metastatic RCC for axitinib, sorafenib and everolimus have previously been considered by PTAC and CaTSoP, and that all of these applications had been recommended for decline. The Subcommittee noted that funding of these agents had been reconsidered by CaTSoP at this August 2017 meeting and while it had not changed its previous recommendation regarding sorafenib and everolimus for RCC, it had recommended axitinib be funded with low priority for the second-line treatment of metastatic RCC subject to clinical criteria being met.
- 7.8. The Subcommittee noted that the key clinical evidence for the use of nivolumab in the second-line treatment of advanced RCC comes from CHECKMATE-025, a randomised, open-label, phase 3 study of nivolumab in comparison with everolimus in 821 patients with metastatic clear-cell renal cell carcinoma who had received previous antiangiogenic therapy. (Motzer et al. N Engl J Med. 2015;373:1803–13).
- 7.9. The Subcommittee noted that eligibility criteria included no more than three previous regimens of systemic therapy, disease progression during or after the last treatment regimen, and a Karnofsky performance status of at least 70 at the time of study entry. The Subcommittee noted that patients previously treated with an mTOR inhibitor, or a condition requiring treatment with glucocorticosteroids, were excluded.

- 7.10. The Subcommittee noted that at a minimum follow-up of 14 months median overall survival (OS), the primary end-point, was 25.0 months (95% CI, 21.8-not estimable) with nivolumab and 19.6 months (95% CI, 17.6-23.1) with everolimus (hazard ratio (HR) for death, 0.73; 98.5% CI, 0.57-0.93; P = 0.002); a 5.4 month gain in overall survival.
- 7.11. The Subcommittee noted that median progression-free survival was 4.6 months (95% CI, 3.7-5.4) with nivolumab and 4.4 months (95% CI, 3.7-5.5) with everolimus (HR, 0.88; 95% CI, 0.75-1.03; P = 0.11).
- 7.12. The Subcommittee noted that grade 3 or 4 treatment-related adverse events occurred in 19% of the patients receiving nivolumab and in 37% of the patients receiving everolimus; the most common event with nivolumab being fatigue (in 2% of those patients) and with everolimus being anemia (8%).
- 7.13. The Subcommittee noted that of the 821 patients who underwent randomisation, 756 (92%) had quantifiable tumour PD-L1 expression in pre-treatment samples; and that the authors concluded that the data did not support PD-L1 as a marker of treatment benefit in RCC.
- 7.14. The Subcommittee noted that among the 821 patients who underwent randomisation, 227/410 patients (55%) in the nivolumab group and 260/411 patients (63%) in the everolimus group received subsequent systemic therapy. The Subcommittee noted that the most common subsequent therapeutic agents used after nivolumab were everolimus (105 patients, 26%), axitinib (99 patients, 24%), and pazopanib (37 patients, 9%).
- 7.15. The Subcommittee considered that quality of life data from CHECKMATE025 indicated there were quality of life improvements during treatment with nivolumab from around 16 weeks.
- 7.16. The Subcommittee noted unpublished updated overall survival data from CHECKMATE025 provided by the supplier of nivolumab. The Subcommittee noted that at a median follow-up of 33.6 months the median OS was 6.3 months longer with nivolumab than with everolimus (HR 0.73, 95.45% CI 0.61-0.88). The Subcommittee considered that, based on this data, the survival gain with nivolumab appeared to be maintained with longer follow-up.
- 7.17. The Subcommittee noted that in November 2016 the National Institute for Health Care Excellence (NICE) had recommended nivolumab as an option for previously treated advanced RCC in adults. The Subcommittee noted that NICE concluded that nivolumab extended OS compared with everolimus (which is funded in the UK as a second-line RCC treatment), but NICE had noted there was uncertainty about the extent of the survival benefit when measured over the long term.
- 7.18. The Subcommittee noted, that in November 2016, the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia did not recommend the listing of nivolumab for the treatment of advanced or metastatic clear cell variant RCC, on the grounds of unfavourable and uncertain cost-effectiveness when compared to everolimus. The Subcommittee noted that the PBAC had not reviewed the unpublished updated survival data.
- 7.19. The Subcommittee considered that based on current pricing for PD-1 inhibitors it was likely that funding of nivolumab for the second-line treatment of advanced clear cell RCC may be associated with a significant budget impact. The Subcommittee

considered that if nivolumab were to be funded in this setting it would have a significant impact on DHB infusion services and outpatient treatment resources.

- 7.20. The Subcommittee considered that, of the second-line advanced RCC treatments, nivolumab would be the preferred option based on the quality of evidence.
- 7.21. The Subcommittee recommended that nivolumab be funded with medium priority for the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy, but considered however that its priority rating would decrease if the cost-effectiveness of nivolumab in this setting was poor.
- 7.22. The Subcommittee noted that there were a number of ongoing clinical trials investigating the use of immune checkpoint inhibitors in the treatment of advanced RCC, but that it appeared mature data for use of other agents as second-line monotherapy was not yet available, and all new trials are for combination regimens with tyrosine kinase inhibitors or in a first-line setting. .