Record of the Cancer Treatment Subcommittee of PTAC meeting held at PHARMAC on 5 July 2019

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

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1. Correspondence and Matters Arising

Dexrazoxane criteria

1.1. The Subcommittee noted that in February 2018, PTAC recommended that dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults be funded with low priority subject to Special Authority criteria.

1.2. The Subcommittee noted that at its March 2017 meeting CaTSoP had considered and recommended dexrazoxane be listed on the Schedule with medium priority but had not recommended access criteria; and in February 2018, PTAC considered the proposed Special Authority should be reviewed by the Cancer Treatments Subcommittee.

1.3. The Subcommittee recommended that dexrazoxane be funded for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults subject to the following access criteria:

Restricted
Initiation
Medical oncologist, paediatric oncologist, haematologist, paediatric haematologist

All of the following:

1. Patient is to receive treatment with high dose anthracycline given with curative intent; and
2. Based on current treatment plan, patient's cumulative lifetime dose of anthracycline will exceed 250mg/m2 doxorubicin equivalent or greater; and
3. Dexrazoxane to be administered only whilst on anthracycline treatment; and
4. Either:
   4.1. Treatment to be used as a cardioprotectant for a child or young adult; or
   4.2. Treatment to be used as a cardioprotectant for secondary malignancy.

1.4. The Subcommittee noted that the Adolescent and Young Adult (AYA) definition of child or young adult was patients aged 16-24 years, however considered that it was not appropriate to specify an age in the access criteria as patients receiving cumulative lifetime doses of anthracycline in excess of 250mg/m2 with curative intent could be older than that specified by the AYA definition. The Subcommittee considered it was not appropriate to exclude patients on the basis of age when the criteria for curative intent of high dose anthracycline would be met.

1.5. The Subcommittee considered that recommended funding of dexrazoxane was not intended to include use in populations with advanced tumours for which anthracycline treatment was not administered with curative intent, such as for adult metastatic breast cancer patients, as the rationale for use of dexrazoxane was to prevent cardiac issue later in life for children and young adults. The Subcommittee considered there was no evidence for use of dexrazoxane in patients with pre-existing heart issues.

1.6. The Subcommittee considered that while secondary malignancy where further anthracycline would be administered with curative intent exceeding the specified lifetime dose threshold was rare, it would be important to include these patients.

Ibrutinib/venetoclax for chronic lymphocytic leukaemia (CLL)

1.7. The Subcommittee noted that at its meeting in February 2019, PTAC accepted CaTSoP's recommendation that venetoclax monotherapy for chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation be funded with a high priority, but also requested that CaTSoP consider the relative priorities of venetoclax and ibrutinib in this setting.

1.8. The Subcommittee noted correspondence provided by Janssen-Cilag Pty Ltd in support of reconsidering the relative priorities of venetoclax and ibrutinib for CLL with 17p deletion or TP53 mutation and for relapsed/refractory CLL. The Subcommittee considered that the information provided by Janssen-Cilag Pty Ltd was well considered and provided a useful basis for the consideration of the standing relative priorities for ibrutinib for these patient groups.

1.9. The Subcommittee considered that the evidence for the efficacy of ibrutinib for the treatment of CLL with 17p deletion or TP53 mutation and relapsed/refractory CLL is of good quality and long duration and is at least equivalent to that of venetoclax. The Subcommittee considered that the higher priority recommendations for venetoclax monotherapy were reflective of the increasing awareness of the health need for these populations relative to international treatment standards. The Subcommittee therefore considered that the recommendations for ibrutinib for CLL with 17p deletion or TP53 mutation and relapsed/refractory CLL should be upgraded to high priority.

1.10. The Subcommittee also considered that the medium priority for venetoclax monotherapy for the treatment of CLL which has relapsed within 12 to 36 months of prior therapy be upgraded to high priority based on the health need of the population. The Subcommittee noted that this makes all recommendations for ibrutinib and venetoclax monotherapy for CLL populations consistent.

1.11. The Subcommittee also reviewed the results of the recently published open-label, phase 3 CLL14 trial which investigated 12-cycle fixed-duration treatment with venetoclax plus obinutuzumab compared with chlorambucil plus obinutuzumab in patients with previously untreated CLL and co-existing conditions (Fischer et al. N Engl J Med. 2019;380:2225-36). The Subcommittee noted that this study included a small population of patients with 17p deletion (31 of 432 patients). The Subcommittee considered that while the results of this study are promising for the use of fixed-term venetoclax plus obinutuzumab for the first-line treatment of CLL in patients who are unfit for more toxic regimens, that there was not enough evidence to inform whether this would be an appropriate approach for the treatment of all previously untreated patients with 17p deletion. The Subcommittee considered that at this time, the preference would be to treat patients with previously untreated CLL and 17p deletion with ibrutinib or venetoclax monotherapy until progression.

2. Vismodegib for the treatment of metastatic or locally advance based cell carcinoma

Application

2.1. The Subcommittee reviewed a funding application for vismodegib for the treatment of locally advanced or metastatic basal cell carcinoma.

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

Recommendation

2.3. The Subcommittee recommended that vismodegib for the treatment of locally advanced or metastatic basal cell carcinoma be funded with a **medium** priority subject to the following Special Authority criteria:

> Special Authority for Subsidy – PCT only
> Initial application – only from a medical oncologist or radiation oncologist or medical practitioner on the recommendation of a medical oncologist or radiation oncologist.
> Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic basal cell carcinoma; and
> 2. Surgery is considered to be clinically inappropriate (see Note); and
> 3. Radiotherapy is considered clinically inappropriate (see Note); and
> 4. Patient is intolerant or contraindicated to platinum- or taxane-based chemotherapy.
>
> Renewal application– only from a medical oncologist or radiation oncologist or medical practitioner on the recommendation of a medical oncologist or radiation oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic basal cell carcinoma; and
> 2. There is no evidence of disease progression; and

3. The treatment remains appropriate and the patient is benefitting from treatment.

Note: “inappropriate for surgery” is defined as curative resection unlikely, would result in substantial morbidity or deformity or require complicated reconstructive surgery (removal of all or part of facial structure or requirement for limb amputation or free tissue transfer), or medical contraindication for surgery. “inappropriate for radiotherapy” is defined as hypersensitivity to radiation due to genetic syndrome such as Gorlin Syndrome, limitations due to location of tumour or cumulative prior radiotherapy dose, or progressive disease despite prior irradiation of locally advanced BCC.

Discussion

2.4. The Subcommittee noted that a funding application for vismodegib for the treatment of basal cell carcinoma (BCC) in patients with Gorlin syndrome was recommended for decline by PTAC in May 2015. The Subcommittee noted that at this meeting PTAC considered that vismodegib was a high cost medicine, that the evidence in patients with Gorlin syndrome was of weak strength and quality, that the agent is associated with significant toxicity, and that it would not be appropriate to limit funding just to patients with Gorlin Syndrome.

2.5. The Subcommittee noted that an updated application for vismodegib for the treatment of patients with metastatic or locally advanced BCC where surgery and/or radiation therapy are not appropriate was reviewed by PTAC in February 2018. The Subcommittee noted that at this meeting PTAC considered that there could be a place for vismodegib for individuals with extreme disease but noted that there was no evidence in this setting and that appropriately defining access criteria to target these patients would be difficult. The Subcommittee noted that PTAC declined the application and recommended that it be referred to CaTSoP for advice regarding alternative treatment options, defining the patient population that would benefit most from vismodegib, and the likely number of patients who would be eligible for treatment.

2.6. The Subcommittee noted that BCC is common in New Zealand, but that metastatic BCC occurs rarely. The Subcommittee considered that estimating the number of patients with locally advanced BCC is difficult as there is no widely accepted definition of locally advanced disease. The Subcommittee considered that there is likely to be a maximum of 50 patients per year with metastatic BCC, and up to 200 per year with locally advanced BCC where surgery and/or radiation therapy are not appropriate depending on how this is defined.

2.7. The Subcommittee considered that the treatment options for patients with metastatic BCC and locally advanced BCC not amenable to surgery or radiotherapy are limited to platinum- or taxane-based chemotherapy; however, the Subcommittee considered that many patients with locally advanced or metastatic BCC would not be fit enough for chemotherapy due to age or health status. The Subcommittee considered that the only treatment option for these patients would be palliative care.

2.8. The Subcommittee considered that evidence for the efficacy of platinum- or taxane-based chemotherapy is sparse but noted a review of 53 cases where patients with BCC were treated with cytotoxic therapy which reported a response rate of 77%, a complete response rate of 45%, and a median survival of 22 months (Pfeiffer et al. Eur J Cancer. 1990;26:73-7).

2.9. The Subcommittee noted that vismodegib is an inhibitor of the Hedgehog pathway which is involved in the maintenance of somatic stem cells and pluripotent cells which play an important role in tissue repair. The Subcommittee noted that the Hedgehog pathway is abnormally activated in 95% of sporadic BCCs, resulting in cell division and tumorigenesis.

2.10. The Subcommittee noted a systematic review of 8 studies involving 704 evaluable patients that investigated the clinical experience with the Hedgehog pathway inhibitors vismodegib and sonidegib for the treatment of locally advanced or metastatic BCC (Jacobsen et al. JAMA Dermatol. 2016;152:816-24). The Subcommittee noted that the studies included were mostly single-arm early phase trials, case series, or retrospective medical record reviews. The Subcommittee noted that the weighted average objective response rate for vismodegib was 64.7% (95% CI 63.7% to 65.6%) for patients with locally advanced BCC and 33.6% (95% CI 33.1% to 34.2%) for patients with metastatic BCC. The Subcommittee noted that the mean weighted duration of vismodegib exposure was 35.8 weeks (95% CI 35.1 to 36.5 weeks).

2.11. The Subcommittee noted the single-arm, open label, Phase 2 STEVIE trial that investigated the safety of vismodegib in 1215 patients with advanced basal cell carcinoma in a situation similar to routine practice (Basset-Seguin et al. Lancet Oncol. 2015;16:729-36; Basset-Seguin et al. Eur J Cancer. 2017;86:334-48). The Subcommittee noted that the median duration of treatment with vismodegib at the time of the primary analysis was 8.6 months. The Subcommittee noted that in patients with locally advanced disease, the response rate was 68.5% (95% CI 65.7% to 71.3%) and the median duration of response was 23.0 months. The Subcommittee noted that in patients with metastatic disease, the response rate was 36.9% (95% CI 26.6% to 48.1%) and the median duration of response was 13.9 months.

2.12. The Subcommittee noted that 98% of patients in the STEVIE trial reported a treatment-emergent adverse event; the most common being muscle spasms (66%), alopecia (62%), dysgeusia (55%), decreased weight (41%), decreased appetite (25%), and asthenia (24%). The Subcommittee noted that 31% of patients discontinued due to treatment-emergent adverse events.

2.13. The Subcommittee noted a secondary analysis of the STEVIE trial which used the Skindex-16 and MD Anderson Symptom Inventory (MDASI) instruments to assess health-related quality of life among patients with BCC treated with vismodegib (Hansson et al. Eur J Dermatol. 2018;28:775-83). The Subcommittee noted that there was a clinically meaningful improvement in emotional well-being in patients with locally advanced BCC treated with vismodegib, but no difference in symptom and functional scores. The Subcommittee noted that there was no clinically meaningful improvement or deterioration in any domain for patients with metastatic BCC receiving vismodegib.

2.14. The Subcommittee noted the single-arm, open label, PHASE 2 ERIVANCE study that investigated the long-term safety and efficacy of vismodegib in 104 patients with advanced BCC (Seculik et al. N Engl J Med. 2012;366:2171-9; Sekulic et al. J Am Acad Dermatol. 2015;72:1021-6; Sekulic et al. BMC Cancer. 2017;17:332). The Subcommittee noted that the median duration of treatment at the time of the long-term update of ERIVANCE was 12.7 months in patients with locally advanced disease and 12.9 months in patients with metastatic disease. The Subcommittee noted that in patients with locally advanced disease, the objective response rate was 60.3% (95% CI 47.2% to 71.7%) and the median duration of response was

26.2 months. The Subcommittee noted that in patients with metastatic disease, the objective response rate was 48.5% (95% CI 30.8% to 66.2%) and the median duration of response was 14.8 months.

2.15. The Subcommittee noted that all patients in ERIVANCE experienced at least one treatment-emergent adverse event, the most common being muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%), weight decrease (51.9%), fatigue (43.3%), and nausea (32.7%). The Subcommittee noted that 21.2% of patients discontinued treatment due to adverse events.

2.16. The Subcommittee considered that vismodegib is associated with some toxicity, and that this is likely to limit the duration of time patients receive treatment and has the potential to result in additional health sector costs for managing adverse events. The Subcommittee considered that patients receiving vismodegib would be seen by their treating physician routinely due to toxicity.

2.17. The Subcommittee considered that the majority of the evidence available for vismodegib is from uncontrolled single-arm early phase trials or real-world observational data from access programs, and that it is unlikely that Phase 3 trials will ever be conducted. The Subcommittee considered that the evidence is of low quality and demonstrates only a moderate benefit; however, it was also noted that advanced BCC is a mutilating disease for which there are limited treatment options available.

2.18. The Subcommittee considered that if it were funded, access to vismodegib should be restricted to patients with locally advanced or metastatic BCC for whom surgery and radiotherapy are inappropriate and platinum- or taxane-based chemotherapy is contraindicated. The Subcommittee considered that approximately ten patients per year would fit these criteria.

2.19. The Subcommittee considered there would likely be a preference for use of vismodegib over further surgery or other types of chemotherapy, even with its associated toxicities. The Subcommittee noted anecdotal reports of various alternate dosage regimens, such as intermittent treatment, being used with the aim of reducing toxicity.

2.20. The Subcommittee considered that given the previously outlined difficulty in clearly and appropriately defining a population for whom surgery, radiotherapy or other chemotherapy are contraindicated or inappropriate there would likely be a significant fiscal risk associated with funding of vismodegib.

3. Immune checkpoint inhibitors for the treatment of advanced melanoma review

Discussion

3.1. The Subcommittee noted that the immune checkpoint inhibitors (ICI), nivolumab and pembrolizumab, have been funded since July 2016 and September 2016 respectively for the treatment of metastatic or unresectable (advanced) melanoma subject to the following Special Authority criteria [note that information between square brackets denoting chemical name, dose regimen and number of cycles differs for the different chemicals]:

> Initial application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria: All of the following:

1. Patient has metastatic or unresectable melanoma stage III or IV; and
2. Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and
3. The patient has ECOG performance score of 0-2; and
4. Either:
   4.1. Patient has not received funded [nivolumab/pembrolizumab]; or
   4.2. Both:
      4.2.1. Patient has received an initial Special Authority approval for [nivolumab/pembrolizumab] and has discontinued [nivolumab/pembrolizumab] within 12 weeks of starting treatment due to intolerance; and
      4.2.2. The cancer did not progress while the patient was on [nivolumab/pembrolizumab]; and
5. [nivolumab/pembrolizumab] is to be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles); and
6. Baseline measurement of overall tumour burden is documented (see Note); and
7. Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of [nivolumab/pembrolizumab] will not be continued beyond 12 weeks ([6/4] cycles) if their disease progresses during this time.

Renewal — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Any of the following:
   1.1. Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
   1.3. Patient has stable disease according to RECIST criteria (see Note); and
2. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3. No evidence of progressive disease according to RECIST criteria (see Note); and
4. The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5. [nivolumab/pembrolizumab] will be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles).

Notes: Disease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. Target lesion measurements should be assessed using CT or MRI imaging with the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

3.2. The Subcommittee noted that in September 2016 CaTSoP had considered the access criteria for ICI for advanced melanoma following issues raised both by the Subcommittee and during consultation on the listing of these agents for advanced melanoma.

3.3. The Subcommittee noted that to date, only one of the recommendations made by CaTSoP in September 2016 has been progressed for listing (to amend the ECOG status).

3.4. The Subcommittee noted that there was now a number of years of experience with the use of ICI agents for the treatment of advanced melanoma in New Zealand and internationally; and their use had evolved and developed based on this experience.

Duration of Special Authority approval and maximum dosing requirement

3.5. The Subcommittee noted that the current duration of Special Authority approval was four months, however the criteria specify no more the 12 weeks (3 months) of treatment. Therefore, this duration of approval is resulting in a mismatch between the approval window and treatment delivery following several renewal applications.

3.6. The Subcommittee noted that the rationale for extending the approval duration soon after listing was based on consultation feedback that there is often a delay in Special Authority application and commencing treatment. However, while this may be an issue for the initial application to apply this to the renewal duration has resulted in a misaligned approval period and treatment delivery window.

3.7. The Subcommittee considered that in practice it is also difficult to manage the administrative aspects of the Special Authority renewal, in particular the scheduling of patients for imaging to determine if renewal criteria are met; and that imaging is often out of sync with both the three-monthly treatment window and the Special Authority renewal application timeframe.

3.8. The Subcommittee considered that based on usage data for ICI for advanced melanoma it may be appropriate for patients with complete response to treatment to have less frequent imaging, such as six-monthly, given the generally longer duration of treatment for these patients. However, three-monthly CT scanning would likely remain appropriate for patients with a partial response or stable disease to enable appropriate monitoring of disease response.

3.9. The Subcommittee considered that given the relatively small numbers of patients who achieve complete response, around 12% per year, the impact for DHBs as a result of reduced imaging would be very small (approximately 24 scans per year) and that this needed to be balanced with the relatively high costs of ongoing pharmaceutical beyond progression due to lack of scanning.

3.10. The Subcommittee considered that there were benefits in retaining the four-month approval duration to allow for flexibility in timing of imaging. However, recommended that specification of a maximum of 12 weeks treatment be removed from the relevant initial and renewal Special Authority criterion for ICI for advanced

melanoma (proposed changes to relevant Special Authority criterion only shown below (deletion in ~~strikethrough~~)):

> [nivolumab/pembrolizumab] is to be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] ~~for a maximum of 12 weeks ([6/4] cycles)~~; and

Special Authority prescriber restriction

3.11. The Subcommittee noted that currently Special Authority application for ICI for advanced melanoma were restricted to medical oncologist only; and that this means that other clinicians, such as registrars and nurse prescribers, are not able to make Special Authority applications.

3.12. The Subcommittee considered it would be appropriate for the Special Authority criteria for ICI for advanced melanoma be amended to allow medical practitioners to apply on the recommendation of a medical oncologist.

Pseudoprogression

3.13. The Subcommittee noted that in 2016 at the time of listing ICI for advanced melanoma, CaTSoP considered that 3% -10% of patients treated with immunotherapies had different patterns of response than are typically seen with chemotherapy agents, and who may develop progression of disease as measured by conventional WHO or RECIST criteria before later demonstrating clinically objective responses and/or stable disease - referred to as 'pseudoprogression' (an initial increase tumour lesion size with subsequent decreased tumour burden).

3.14. The Subcommittee noted that under the current Special Authority criteria for ICI, patients with advanced melanoma with signs of disease progression as measured by conventional WHO or RECIST criteria would no longer meet the criteria for ongoing funded treatment with these agents.

3.15. The Subcommittee considered that although pseudoprogression was a clinically well described phenomenon there remains no formal definition in terms of RECIST available in currently published literature. Therefore, there is no way to prospectively determine which patients have pseudoprogression.

3.16. The Subcommittee noted the pooled evidence from 8 multi-centre clinical trials investigating treatment with ICI in 2,624 patients with melanoma, of which 632 continued to receive ICI beyond disease progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria (Beaver et al. Lancet Oncol. 2018:19;229-39). The Subcommittee noted that most (86%) of the patients who remained on treatment post-progression had limited or no benefit, remaining on treatment for a short duration generally equivalent to one or two additional months of progression-free survival, and only a small proportion (14%) received a small benefit and remained on treatment for three or more months after progression.

3.17. The Subcommittee considered that there remained a significant financial impact as a result of allowing all patients who have signs of disease progression to remain on treatment for a further period of time to confirm or rule out pseudoprogression; and that widening of access to include funding of additional ICI beyond disease progression would be poorly cost-effective as the majority of patients would receive additional treatment without any further benefit.

3.18. The Subcommittee considered it would be challenging to further address this issue ahead of publication of an immune-related response criteria (irRECIST) with a prospective definition of pseudoprogression and that this may not be available for a number of years.

Acral, Mucosal and Uveal melanoma

3.19. The Subcommittee noted that the current Special Authority criteria for ICI for advanced melanoma do not specifically exclude use in acral melanoma, mucosal melanoma and uveal melanoma subtypes.

3.20. The Subcommittee noted that these populations had been excluded from the pivotal published clinical trials for ICI agents for melanoma.

3.21. The Subcommittee noted that in 2016 CaTSoP noted evidence for ICI treatment of patients with acral (N=25) and mucosal (N=35) melanoma from a retrospective multi-centre cohort study in the United States (Shoushtari et al. Cancer. 2016:15;3354-3362). The Subcommittee considered that the results demonstrated small benefits in patients with acral melanoma (objective response in 32% with ICI) and in patients with mucosal melanoma (objective response in 23% with ICI).

3.22. The Subcommittee noted recent published evidence for immune checkpoint inhibitor (ICI) treatment compared with chemotherapy for patients with uveal (N=210) or mucosal (N=229) melanoma from a retrospective study of 25 centres in France (Mignard et al. J Oncol. 2018:1908065). The Subcommittee noted the 12-week results demonstrated no benefit from ICI in patients with uveal melanoma (objective response in 0% with ICI compared to 3.6% with chemotherapy) and only a small benefit in mucosal melanoma (objective response in 12% with ICI compared to 14% with chemotherapy).

3.23. The Subcommittee considered that, the current evidence for *acral* and *mucosal* melanoma response to ICI is of poor-to-moderate quality only, and that no amendment should be made to access criteria with regards to these types of melanoma at this time.

3.24. The Subcommittee **recommended** that the initial Special Authority criteria for ICI for advanced melanoma be amended to exclude patients with *uveal* melanoma due to poor-to-moderate quality evidence of no response (proposed changes to relevant Special Authority criterion only are shown below (additions in **bold**)):

> Patient has metastatic or unresectable melanoma **(excluding uveal)** stage III or IV;

3.25. The Subcommittee considered that there would likely be around 3-4 patients with uveal melanoma per year in New Zealand.

Evaluable but not radiologically measurable disease

3.26. The Subcommittee noted that, in 2016, CaTSoP had recommended that the Special Authority criteria for ICI be amended to facilitate non-radiological assessment using RECIST v1.1 criteria, an objective measurement of tumour burden and defines ‘measurable’ as having a caliper measurement 10 mm or more.

3.27. The Subcommittee considered that this proposed change to the Special Authority criteria remains appropriate and considered that caliper measurement and physical examination (with or without medical photography) would inform the

assessment of disease status and treatment response according to RECIST criteria v1.1.

3.28. The Subcommittee considered that some patients with advanced melanoma can have a large number of small cutaneous lesions (eg 200 affecting an entire limb). The Subcommittee considered that such a tumour burden is not amenable to measurement and evaluation according to RECIST v1.1 criteria due to administrative and logistic difficulties with lesion measurement, and challenges with identifying representative lesions suitable for reproducible, repeated evaluation of treatment response over time.

3.29. The Subcommittee considered that, for the small proportion of patients with advanced melanoma with a significant tumour burden (size and/or number of lesions) that is not amenable to evaluation by RECIST v1.1, but for whom response to treatment can be clinically evaluated (eg visual assessment on physical examination for extensive cutaneous melanoma), funding of ICI should be managed via the Exceptions Framework on an individual assessment basis.

3.30. The Subcommittee reiterated its 2016 **recommendation** that the Special Authority for ICI for advanced melanoma be amended to allow clinical (non-radiological) assessment of disease according to RECIST version 1.1 criteria (proposed changes to relevant Special Authority criteria are shown below in **bold** and ~~strikethrough~~ as applicable):

Initial application — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has metastatic or unresectable melanoma stage III or IV; and
2. Patient has measurable disease as defined by **RECIST version 1.1** ~~the presence of at least one CT or MRI measurable lesion~~**,** and
3. The patient has ECOG performance score of 0-2; and
4. Either:
   - 4.1. Patient has not received funded [nivolumab/pembrolizumab]; or
   - 4.2. Both:
     - 4.2.1. Patient has received an initial Special Authority approval for [nivolumab/pembrolizumab] and has discontinued [nivolumab/pembrolizumab] within 12 weeks of starting treatment due to intolerance; and
     - 4.2.2. The cancer did not progress while the patient was on [nivolumab/pembrolizumab]; and
5. [nivolumab/pembrolizumab] is to be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles); and
6. Baseline measurement of overall tumour burden is documented (see Note); and
7. Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of [nivolumab/pembrolizumab] will not be continued beyond 12 weeks ([6/4] cycles) if their disease progresses during this time.

Renewal — (unresectable or metastatic melanoma) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Any of the following:
   - 1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
   - 1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
   - 1.3 Patient has stable disease according to RECIST criteria (see Note); and

2. **Either:**
   2.1 Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; ~~and~~ **or**
   2.2 **Both:**
      2.2.1 **Patient has measurable disease as defined by RECIST version 1.1; and**
      2.2.2 Patient's disease has not progressed clinically and disease response to treatment has been clearly documented in patient notes; and

3. No evidence of progressive disease according to RECIST criteria (see Note); and
4. The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
5. [nivolumab/pembrolizumab] will be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles).

Notes:
Baseline assessment and d~~D~~isease responses to be assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47). Assessments of overall tumour burden and measurable disease to be undertaken on a minimum of one lesion and maximum of 5 target lesions (maximum two lesions per organ). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and suitable for reproducible repeated measurements. **Measurable disease includes by CT or MRI imaging and caliper measurement by clinical exam.** Target lesion measurements should be assessed using ~~CT or MRI imaging with~~ the same method of assessment and the same technique used to characterise each identified and reported lesion at baseline and every 12 weeks. Response definitions as follows:

- Complete Response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- Stable Disease: Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

Fixed dose regimens

3.31. The Subcommittee noted that the current Special Authority criteria for ICI for advanced melanoma specified administration subject to weight-based dose regimens, 3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks for nivolumab and pembrolizumab respectively.

3.32. The Subcommittee noted that there are now also fixed-dose regimens for these agents 240 mg every two weeks or 480 mg every four weeks for nivolumab and 200 mg every three weeks or 400 mg every 6 weeks for pembolizumab.

3.33. The Subcommittee noted evidence suggesting that there are cost differences but not necessarily better outcomes associated with different fixed dose and weight-

based dose regimens of nivolumab and pembrolizumab (Ogungbenro et al. Clin Pharmacol Ther. 2018:103;582-90).

3.34. The Subcommittee noted that fixed dose regimens resulted in a higher number of milligrams per dose being administer for the majority of patients and therefore was associated with higher pharmaceutical costs as compared to the current weight-based dosing regimens.

3.35. The Subcommittee noted that adoption of fixed dose regimens would provide benefits for DHBs in terms of reduced infusion requirements, due to the less frequent administration schedule, and pharmacy compounding efficiencies for both time to compound and potentially reduced wastage (as pre-prepared doses could be used to treat any eligible patient). The Subcommittee considered there were also benefits for patients from the reduced frequency of infusion administration with fixed dosing regimens.

3.36. The Subcommittee considered that it appeared clinically appropriate for ICI for advanced melanoma to be administered either on weight based on fixed dosing regimens; and that dose regimens with lower administration frequencies would be preferred from a health system and patient point of view.

3.37. The Subcommittee considered that it would be important for the clinical community to understand that the timing of any amendment to the Special Authority criteria to allow for fixed dosing, given the fiscal impact, would likely need to be made as a result of reaching a suitable commercial arrangement with the suppliers of ICI.

Treatment duration and treatment break for long-term responders

3.38. The Subcommittee noted that, given that ICI were listed in 2016, there are now a number of patients who are long-term responders (with stable disease or better) who have been receiving treatment with ICI for 2 years or more.

3.39. The Subcommittee noted that there were a number of interrelated issues for the Special Authority criteria and long-term treatment including:

- Whether a finite duration of treatment should be specified,
- What appropriate monitoring requirements for long-term responders are, and
- Whether patients should be able to restart ICI treatment upon signs of progression (following discontinuation for reasons other than disease progression or toxicity).

3.40. The Subcommittee noted that in 2016 the duration of long-term responding advanced melanoma patients (those with stable disease response or better) was uncertain and that given the current Special Authority criteria there was the potential for patients to remain on treatment indefinitely as long as they can still tolerate treatment.

3.41. The Subcommittee noted that while trials for pembrolizumab limited the treatment duration to 96 weeks or 2 years the trial protocols for nivolumab was for use until disease progression.

3.42. The Subcommittee noted that in 2016 CaTSoP had considered that it may be appropriate for the maximum duration of treatment to be limited to 96 weeks or 2 years (as this was the maximum duration reported in the literature at the time) and that the appropriate duration of treatment should be reviewed following publication of extended follow up data.

3.43. The Subcommittee noted the four-year survival and outcome data for pembrolizumab from the randomised (1:1:1), phase III Keynote-006 trial in advanced melanoma (N = 834) which provides evidence for up to two years of pembrolizumab (10 mg per kg every 2 weeks or every 3 weeks) compared to four doses of ipilimumab 3 mg per kg (Long et al. J Clin Oncol. 2018:36;15(suppl.9503). The Subcommittee noted that 19% (N = 103) of pembrolizumab patients completed two years of pembrolizumab and after median post pembrolizumab follow-up of 20.3 months, 86% (N = 89) remained without progression.

3.44. The Subcommittee considered that a treatment break in the first course of ICI treatment (electively discontinuing for reasons other than toxicity or disease progression eg overseas travel or due to good response to treatment) would appeal to patients if there was certainty of the option to restart treatment to undertake a second course. The Subcommittee noted that the current Special Authority renewal criteria, which require no signs of disease progression, mean that for patients who electively cease ICI treatment in this way they are not eligible to restart treatment once their disease relapses.

3.45. Members considered that international practice is moving to patients stopping treatment after a complete response to treatment for 6 months, however, it was noted that practice in New Zealand appears to be for patients to remain on treatment for at least 12 months before considering a break.

3.46. The Subcommittee noted that Long et al. report that 8 of the pembrolizumab patients who had disease progression were eligible for a second course of up to one year of pembrolizumab (200 mg every 3 weeks) and had a median of 9.7 months on second-course of treatment with disease progression occurring in 1 patient. The Subcommittee considered this was a relatively small proportion of patients at risk of progression on second-course treatment and that patients who had a complete response to their first course of pembrolizumab treatment received the most benefit (response) on retreatment.

3.47. The Subcommittee noted data from a real-world cohort study of advanced melanoma patients who electively discontinued nivolumab (N = 18) or pembrolizumab (N = 167) without disease progression or treatment-limiting toxicity after a median of 12 months on treatment (Jansen et al. Ann Oncol. 2019:30;1154-61). The Subcommittee noted that patients who had complete response at baseline were the least likely to have disease progression (occurring in 14%) compared to patients with partial response (32%) or stable disease (50%) at baseline.

3.48. The Subcommittee noted that the nivolumab and pembrolizumab data reported by Jansen et al. shows that of the patients who restarted treatment after a break, the patients with a previous complete response were most likely to have a response to this second course of treatment, followed by those with previous partial response, and those with previous stable disease were the least likely to have a second response.

3.49. The Subcommittee considered that, based on current evidence, a second course of treatment is most beneficial for patients who had a complete response (CR) to their previous course of treatment with nivolumab or pembrolizumab.

3.50. The Subcommittee considered that patients whose best response to a first course was stable disease were the most likely to have disease progression off-treatment and least likely to obtain a second response. The Subcommittee considered it would be important for patients who received a partial response (PR) or had stable disease (SD) from the first course of pembrolizumab treatment to be well informed of the potential risks of a lack of response to second-course treatment as well as the potential benefits of a treatment break and subsequent second course of treatment,

3.51. The Subcommittee considered that the Special Authority criteria should not be amended for a limited, finite treatment duration for initial approvals and renewals of nivolumab and pembrolizumab for unresectable or metastatic melanoma because treatment beyond 96 weeks or 2 years remains appropriate. However, considered that clinicians and patients should be able to make an informed decision to stop long-term treatment (take a treatment break) for reasons other than disease progression or toxicity with the option to restart treatment upon signs of disease progression.

3.52. The Subcommittee considered that it was important for the decision to take a treatment break or not to be made at the clinician's and patient's discretion and as such it was not appropriate for a minimum duration or level of response to the first course of treatment to be mandated.

3.53. The Subcommittee considered it unlikely that there would be a financial risk of treatment cessation and re-start because the total duration of treatment would either be the same or less, as compared to continuous treatment, with the duration of total treatment dependent on the individual's response to a second course of treatment.

3.54. The Subcommittee **recommended** that the Special Authority renewal criteria for ICI for advanced melanoma be amended to allow a second course of treatment for patients for patients who have stopped ICI treatment for reasons other than disease progression or toxicity as follows (proposed changes to relevant Special Authority criteria are shown below in **bold** and ~~strikethrough~~ as applicable):

Renewal — (unresectable or metastatic melanoma) only from a medical oncologist.
Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. **Either:**
    - 1.1. **All of the following:**
        - 1.1.1. Any of the following:
            - 1.1.1.1. Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
            - 1.1.1.2. Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
            - 1.1.1.3. Patient has stable disease according to RECIST criteria (see Note); and
        - 1.1.2. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and or
        - 1.1.3. No evidence of progressive disease according to RECIST criteria (see Note); and

1.1.4. The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
1.1.5. [nivolumab/pembrolizumab] will be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles)**; or**

2. All of the following:
- **2.1. Patient has previously discontinued treatment with [nivolumab/pembrolizumab] for reasons other than severe toxicity or disease progression; and**
- **2.2. Patient has signs of disease progression; and**
- **2.3. Disease has not progressed during previous treatment with [nivolumab/pembrolizumab]; and**
- **2.4. [nivolumab/pembrolizumab] will be used at a maximum dose of [3 mg/kg every 2 weeks / 2 mg/kg every 3 weeks] for a maximum of 12 weeks ([6/4] cycles).**

3.55. The Subcommittee considered that given the above recommendation regarding amendment to the Special Authority criteria to allow a treatment break for patients who are long-term responders, that it would not be appropriate to amend the criteria as recommended in 2016 with regards to monitoring requirements for those on long term treatment.

4. Evidence appraisal discussion

Discussion

4.1. The Subcommittee considered that large, randomised controlled trials are becoming less common. The Subcommittee considered that medicine funding applications are increasingly based on limited or early-phase clinical data, primarily phase I or phase II trial data, and that often these are not followed up with further data from a phase III trial.

4.2. The Subcommittee considered that there was also a trend for increased complexity of clinical trials overall and an increased use of novel, adaptive and real-world clinical trial designs. The Subcommittee considered that there appeared to be few guidelines available to direct how to approach interpretation of this type of trial evidence.

4.3. The Subcommittee considered that many newer clinical trials involve small patient groups, often molecularly defined niche subgroups. The Subcommittee considered that the data from such niche groups often has too few patients to use for determination of survival outcomes.

4.4. The Subcommittee considered that new agents are developing rapidly and are often partnered with diagnostic technology; a recent example of this being PD-L1 testing. The Subcommittee considered that partnered technology brings challenges due to validation and implementation requirements.

Surrogate endpoints

4.5. The Subcommittee considered that clinical trial evidence is increasingly using surrogate endpoints (such as objective response rate, progression-free survival, disease-free survival) making it difficult to obtain ‘gold-standard’ phase III, randomised controlled trial providing overall survival data to support funding decisions. Members considered that future clinical trial evidence would continue to evolve and would likely mean increased need to rely on surrogate outcome

data such as patient-reported outcome endpoints, or molecularly defined endpoints.

4.6. The Subcommittee noted that the reason surrogate endpoints are used is to provide an indirect measure of a clinical effect (such as how a patient feels, functions or survives) that is not feasible or practical to be observed in a trial setting. The Subcommittee noted that surrogate endpoints can reduce the time for clinical trial results to accrue and therefore accelerate drug approval timeframes. The Subcommittee questioned whether these surrogate endpoints were predictive of clinically significant endpoints such as increased survival and noted the current debate in the literature.

4.7. 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. The Subcommittee considered this relationship was also further complicated by the evolution of treatment paradigms meaning the relationship could change over time. For these reasons, the Subcommittee considered it was important for the validity of surrogate endpoints that correlate with clinically meaningful outcomes to be confirmed in each disease setting.

4.8. The Subcommittee considered that surrogate endpoint data may be misleading in regard to the benefit of a medicine and that the shorter timeframe of surrogate outcome data collection (compared to duration of data collection for a desired long-term outcome) may not be sufficient to identify potentially significant adverse events associated with the medicine. While the Subcommittee considered that surrogate endpoint data should be interpreted with caution, it was considered that endpoints such as progression-free survival were less likely than overall survival to be confounded by treatment crossover and post-progression treatment.

4.9. The Subcommittee noted that the majority (two thirds) of FDA-approved cancer medicines from 2009 to 2014 were based upon improvements in surrogate outcome endpoints (Kim et al. Mayo Clin Proc. 2016:91;713-25). The Subcommittee also noted data for FDA-approved cancer medicines from 2005 to 2012, in which 84% of pivotal trials used surrogate outcomes as the primary study endpoint (Downing et al. JAMA. 2014:311;368-77).

4.10. The Subcommittee considered that, where a medicine is funded based upon surrogate endpoint evidence, there is a risk subsequent data may show reduced, or a lack of, benefit (in terms of desired clinical outcome) than was predicted by the surrogate endpoint. The Subcommittee noted as an example olaratumab for soft tissue sarcoma, granted accelerated approval by the FDA in 2016 (and over 40 other countries) based on limited phase II data with small patient numbers, but shown in the recently published confirmatory phase III ANNOUNCE study not to improve overall survival.

4.11. The Subcommittee considered, however, that in many cases it would be difficult for a funding decision to be delayed until mature phase III data is available as this may not be forthcoming nor provide the overall survival endpoints previously relied upon.

4.12. The Subcommittee noted that many of the international regulatory authorities (such as the FDA, CADTH, EMA, NICE and TGA) acknowledge the need to recognise surrogate outcomes in their accelerated drug approval programs and

that these programs require some link between the surrogate outcome and the desired clinical outcome in different diseases.

4.13. The Subcommittee noted that a review of meta-analyses of randomised controlled trials in oncology identified strong correlation between surrogate outcomes and overall survival in about 18% of the studies, with the remaining 82% of studies demonstrating low or moderate correlation (Haslam et al. Eur J Cancer. 2019:106;196-211).

4.14. The Subcommittee noted that reviews show correlation between surrogate outcomes and desired clinical outcomes in certain cancer types, such as gastro-intestinal cancers and melanoma, but not in other cancers such as breast cancer and non-small cell lung cancer. The Subcommittee noted that in other cancer settings, correlations between surrogate outcomes and desired clinical outcomes were poor across multiple, later lines of therapy (Hashim et al. Value Health. 2018:21;9-17).

4.15. The Subcommittee considered that, given the high cost generally associated with oncology treatments and, in order for clinical advisors to continue to provide high quality advice to PHARMAC regarding funding applications, there would be value in the development of a framework for considering the indications/situations surrogate endpoints would be considered acceptable as predictive of health outcomes in funding decisions. The Subcommittee considered that a framework would ideally also provide tools to appraise and weight different types of evidence.

Critical appraisal tools

4.16. The Subcommittee noted that there are different assessment techniques used internationally for either physician-patient decision making, funding agency decision-making or evidence quality assessment of oncology medicines.

4.17. The Subcommittee considered that the tools identified as most relevant and which could be considered for adaption to a New Zealand context, alongside the Factors for Consideration, to help with assessment and appraisal of medicine funding applications are the ESMO Magnitude of Clinical Benefit Scale, ASCO Value Framework, and the GRADE assessment of clinical evidence.

4.18. The Subcommittee considered that the ASCO Value Framework was a complex form which assessed clinical benefit, toxicity, quality of life (QOL) and balanced these aspects against the cost of the medicine. The Subcommittee considered that scores were weighted within the form and a value figure was generated out of a wide range with cut-off at about 45. The Subcommittee noted that this tool was designed primarily to guide patient-clinician decision making but considered it was useful and versatile due to the wide range of output values. Members considered that it was a useful tool with a number of components.

4.19. The Subcommittee noted that the ESMO-MCBS was designed to inform healthcare policy in Europe but considered it relevant to New Zealand. The Subcommittee noted that the assessment is scored by a panel independently and that the scale is limited (1 to 5 for most assessments, or 1 to 4 if there is no OS data) and that assessments completed by ESMO are available online. The Subcommittee noted that the ESMO-MCBS is generally used for single trials but also meta-analyses, and that different forms are available for different study

designs. Members considered that a downside of this tool is that the output is usually a 3 or 4 despite using a variety of different assessment forms.

4.20. The Subcommittee considered that the ASCO Value Framework and the ESMO-MCBS measure the same factors using different scales and factors; and considered that at this stage it was uncertain what the impact, if any, of the use of these tools may have on medicine funding decisions. Members considered that the wider scale of the ASCO Value Framework provided a broader picture of the assessment and reduced the impact of an individual reviewer. Members noted the evidence supporting the ASCO and ESMO tools is for use in solid tumours and therefore consideration would need to be given regarding their applicability for use in assessment of blood cancers.

4.21. The Subcommittee noted that the GRADE Handbook was designed to assess the quality of evidence and it is primarily used for Cochrane analysis and development of guidelines. Members noted that the Cochrane Collaboration offers training on the use of GRADE for evidence assessment.

5. Cetuximab and bevacizumab for treatment of metastatic colorectal cancer (mCRC) left-sided CRC and bevacizumab right-sided CRC

Application

5.1. The Subcommittee reviewed a funding application from Merck Serono for cetuximab for the first-line treatment of RAS wild-type, left-sided metastatic colorectal cancer.

5.2. The Subcommittee reviewed a funding application from the Gastrointestinal Tumour Specialist Interest Group for bevacizumab for the first- and second-line treatment of metastatic colorectal cancer.

5.3. The Subcommittee reviewed correspondence from the Gastrointestinal Tumour Specialist Interest Group, which provided an overview of the treatment landscape for colorectal cancer.

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

Recommendation

5.5. The Subcommittee **recommended** that cetuximab for the first-line treatment of left-sided metastatic colorectal cancer be funded with a **medium** priority subject to the following Special Authority criteria:

Special Authority for Subsidy
Initial application – (colorectal cancer) only from a medical oncologist or medical practitioner on the recommendation of medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has metastatic colorectal cancer located on the left side of the colon (see Note); and
2. There is documentation that confirming disease is RAS and BRAF wild-type; and
3. Cetuximab is to be used as first-line treatment in conjunction with FOLFIRI or FOLFOX chemotherapy; and
4. Cetuximab to be discontinued at disease progression.

Renewal application – (colorectal cancer) only from a medical oncologist or medical practitioner on the recommendation of medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has no evidence of disease progression; and
2. Cetuximab remains appropriate and the patient is benefitting from treatment; and
3. Cetuximab is to be used in conjunction with FOLFIRI or FOLFOX chemotherapy.

Note: Left-sided colorectal cancer comprises cancer of the distal one-third of the transverse colon, the splenic flexure, the descending colon, the sigmoid colon, or the rectum.

5.6. The Subcommittee **recommended** that bevacizumab for the first- and second-line treatment of metastatic colorectal cancer be **declined**.

Discussion

5.7. The Subcommittee noted that the application for cetuximab for the first-line treatment of RAS wild-type, left-sided metastatic colorectal cancer (mCRC) was reviewed by PTAC in August 2018. At this time, PTAC recommended that cetuximab be declined and referred the application to CaTSoP for advice regarding EGFR-inhibition in mCRC (including for anatomically defined sub-populations).

5.8. The Subcommittee noted that colorectal cancer is an area of high health need in New Zealand. The Subcommittee noted that there are 3000 new cases of colorectal cancer diagnosed each year in New Zealand and that approximately 20% of individuals present with metastatic disease. The Subcommittee noted that data from the United States Surveillance, Epidemiology, and End Results (SEER) program indicating mCRC 5-year survival of 14%. The Subcommittee noted that Māori and Pacific Peoples are diagnosed at younger ages, are more likely to have metastatic disease at diagnosis, and are more likely to have left-sided colorectal cancer (Jackson et al. The PIPER project final report. 2015).

5.9. The Subcommittee noted that the left and right side of the colon are derived from different embryologic origins, and that left- and right-sided colorectal cancers exhibit differences in incidence, pathogenesis, genetic and molecular signatures, and immunological profile. The Subcommittee noted that primary tumour location, or 'sidedness' has been recognised as a prognostic factor in mCRC for some time, but that it has only recently been suggested that 'sidedness' may also be predictive of response to treatment (Holch et al. Eur J Cancer. 2017;70:87-98).

5.10. The Subcommittee noted that mutations in EGFR, RAS, and BRAF are widely accepted as prognostic and predictive markers in colorectal cancer. The Subcommittee considered that testing for EGFR is not normally conducted in New Zealand as it is assumed that most patients with CRC overexpress EGFR. The Subcommittee considered that access to RAS and BRAF testing in New Zealand is highly variable depending on region and that should eligibility for funding be determined in part by the presence or absence or mutations it would be important for this to be accompanied by an equitable approach to access to mutation testing across the country.

5.11. The Subcommittee noted that chemotherapy is the standard of care for patients with mCRC for whom surgery is not adequate or appropriate. The Subcommittee

noted that single-agent chemotherapies used for mCRC include capecitabine and 5-fluorouracil and combination regimens include FOLFIRI (leucovorin + 5-fluorouracil + irinotecan), FOLFOX (leucovorin + 5-fluorouracil + oxaliplatin), and XELOX (capecitabine + oxaliplatin).

5.12. The Subcommittee noted that the treatment paradigm suggested by the Gastrointestinal Tumour Specialist Interest Group and the applications being reviewed propose that cetuximab plus chemotherapy should be used for the first-line treatment of RAS wild-type, left-sided mCRC; bevacizumab plus chemotherapy should be used for the first-line treatment of RAS wild-type, right-sided mCRC and first-line treatment for all RAS mutant mCRC; and bevacizumab plus chemotherapy should be used for the second line treatment of all mCRC.

Cetuximab

5.13. The Subcommittee noted that cetuximab is a monoclonal antibody that prevents the binding of endogenous ligands to EGFR, resulting in the internalisation and down-regulation of the receptor. The Subcommittee considered that the involvement of the EGFR signalling pathway in the development of malignancies such as CRC has been extensively documented.

5.14. The Subcommittee noted that cetuximab is approved by Medsafe for the treatment of EGFR-expressing, RAS wild-type mCRC and squamous cell cancer of the head and neck.

5.15. The Subcommittee noted that cetuximab is funded for the treatment of locally advanced, non-metastatic squamous cell cancer of the head and neck in patients contraindicated or intolerant to cisplatin.

5.16. The Subcommittee noted the randomised, open-label, Phase 3 CRYSTAL trial that investigated the efficacy of cetuximab plus FOLFIRI compared with FOLFIRI alone for the first-line treatment of 599 individuals with EGFR-positive mCRC (van Cutsem et al. N Engl. J Med. 2009;360:1408-17). The Subcommittee noted that after a median follow-up of approximately 30 months, the progression-free survival (PFS) in the primary analysis population was 8.9 months with cetuximab plus FOLFIRI compared with 8.0 months with FOLFIRI alone (HR 0.85; 95% CI 0.72 to 0.99; P=0.048) and the overall survival [OS] was 19.9 months vs 18.6 months (HR 0.93; 95% CI 0.81 to 1.07; P=0.31). The Subcommittee noted that in KRAS wild-type patients, the PFS was 9.9 months with cetuximab plus FOLFIRI compared with 8.7 months with FOLFIRI alone (HR 0.68; 95% CI 0.50 to 0.94; P=0.02) and the OS was 24.9 months vs 21.0 months (HR 0.84; 95% CI 0.64 to 1.11).

5.17. The Subcommittee noted a retrospective analysis of the phase 3 CRYSTAL and FIRE-3 trials that investigated the prognostic and predictive value of primary tumour location in patients with RAS wild-type mCRC treatment with first-line cetuximab plus FOLFIRI (Tejpar et al. JAMA Oncol. 2017;3:194-201). The Subcommittee noted that cetuximab plus FOLFIRI significantly improved OS for patients with left-sided tumours relative to the trial comparators, whereas limited benefits were observed in patients with right-sided tumours. The Subcommittee noted that in both trials, a significant interaction was observed between primary tumour location and treatment for OS (CRYSTAL: HR 1.95; 95% CI 1.09 to 3.48; FIRE-3: HR 0.40; 95% CI 0.23 to 0.70).

5.18. The Subcommittee noted that a number of systematic reviews and meta-analyses have been performed to investigate the prognostic and predictive value of CRC sidedness in response to EGFR inhibition (Arnold et al. Ann Oncol. 2017;28:1713-29; Boeckx et al. Ann Oncol. 2017;28:1862-68; Holch et al. Eur J Cancer. 2017;70:87-98; Chen et al. Medicine [Baltimor]. 2018;97:e0097; Tejpar et al. JAMA Oncol. 2017;3:194-201; Cao et al. Oncotarget. 2017;8:53631-41; Ottaiano et al. Front Pharmacol. 2018;9:441). The Subcommittee considered that these studies all came to a similar conclusion; that a significant benefit was seen in patients with RAS wild-type, left-sided tumours when EGFR inhibitors were added to chemotherapy.

5.19. The Subcommittee noted a systematic review and meta-analysis that investigated the predictive value of KRAS, NRAS, BRAF, PIK3CA, and PTEN for anti-EGFR treatment in mCRC (Therkildsen et al. Acta Oncol. 2014;53:852-64). The Subcommittee noted that the study concluded that mutations in KRAS, NRAS, BRAF, PIK3CA, and non-functional PTEN predicted resistance to anti-EGFR therapies. The Subcommittee considered that this should be taken into account when considering potential criteria for access to cetuximab, if it were to be funded.

5.20. The Subcommittee considered that the safety profile for cetuximab is manageable, but that it is associated with significant skin toxicities such as acneiform rash that often require treatment (van Cutsem et al. N Engl. J Med. 2009;360:1408-17).

5.21. The Subcommittee noted four studies that included analysis of quality of life in patients with CRC receiving cetuximab (Sommeijer et al. Acta Oncol. 2014;53:877-84; Iwamoto et al. Cancer Med. 2018;7:4217-27; Pinto et al. Cancer Med. 2016;5:3272-81; Rosati et al. J Geriatr Oncol. 2018;9:243-248). The Subcommittee noted that these studies generally indicated that cetuximab in combination with chemotherapy does not have a substantial impact on quality of life, provided skin reactions were adequately managed.

5.22. The Subcommittee considered that if cetuximab were to be funded, there would be costs associated with administration (weekly or depending of clinician comfort fortnightly infusion) and the management of adverse events.

5.23. The Subcommittee considered that if cetuximab were funded for patients with RAS and BRAF wild-type, left-sided mCRC, that only 30% of individuals would be fit enough and eligible for treatment. The Subcommittee considered that this would be approximately 70 patients per year.

5.24. The Subcommittee considered that although the data for the use of cetuximab in left-sided mCRC is largely from post hoc analyses, that the signal of a benefit is consistent. The Subcommittee further considered that it is unlikely that prospective trials powered to investigate the use of anti-EGFR therapies in left vs right-sided mCRC will be conducted. The Subcommittee considered that the body of evidence available to date indicates that cetuximab provides a moderate survival benefit for patients with RAS and BRAF wild-type, left-sided mCRC with manageable toxicity and no significant effect on quality of life.

Bevacizumab

5.25. The Subcommittee noted that bevacizumab is a monoclonal antibody that inhibits the binding of VEGF to its receptors on endothelial cells, resulting in reduced tumour angiogenesis.

5.26. The Subcommittee noted that bevacizumab is approved by Medsafe for the treatment of mCRC; advanced or metastatic renal cell cancer; advanced or metastatic non-small cell lung cancer; metastatic breast cancer; relapsed high-grade malignant glioma; epithelial ovarian, fallopian tube, or primary peritoneal cancer; and cervical cancer. The Subcommittee noted that bevacizumab is not currently funded for use in any cancer indication.

5.27. The Subcommittee noted a systematic review and meta-analysis that evaluated the additive effect of bevacizumab in combination with chemotherapy for the first-line treatment of mCRC (Baraniskin et al. Eur J Cancer. 2019;106:37-44). The Subcommittee noted that overall, the analysis of PFS and OS favoured bevacizumab plus chemotherapy compared with chemotherapy alone. The Subcommittee considered that the benefit was more pronounced when bevacizumab was combined with fluoropyrimidine monotherapy compared with combination therapies such as 5-FU plus irinotecan or oxaliplatin. The Subcommittee also considered that the studies included were relatively old and most were only powered to detect a PFS benefit. Members considered that bevacizumab likely provides more of a benefit when used in combination with less effective chemotherapy regimens, but that the standard of care combinations in New Zealand (FOLFIRI, FOLFOX, CAPOX) are relatively effective.

5.28. The Subcommittee noted an analysis of an observational cohort study (BRiTE) that investigated the association between various pre- and post-treatment factors and survival in patients with mCRC treated with bevacizumab beyond first-line (Grothey et al. J Clin Oncol. 2008;26:5326-34). The Subcommittee noted that this study reported that bevacizumab treatment beyond progression was associated with improved survival compared with no bevacizumab beyond progression (HR 0.48; P<0.001).

5.29. The Subcommittee noted a meta-analysis that investigated whether continuation of antiangiogenic drugs beyond progression provided clinical benefit in patients with mCRC (Hoffheinz et al. Gastroenterol Res Pract. 2016;2016:9189483). The Subcommittee noted that this study reported that continuing antiangiogenic treatment beyond progression significantly improved PFS (HR 0.64; 95% CI 0.55 to 0.75) and OS (HR 0.83; 95% CI 0.76 to 0.89); however, it was also noted that the test for heterogeneity of study results was significant for both OS and PFS (primarily due to the FOSCO trial).

5.30. The Subcommittee noted the findings of two studies that investigated whether primary tumour location affected outcomes in patients with left- and right-sided mCRC treated with cetuximab or bevacizumab plus chemotherapy (Tejpar et al. JAMA Oncol. 2017;3:194-201; Venook. J Clin Oncol. 2016;34:3504-04). The Subcommittee considered that these studies suggest that patients with right-sided mCRC have a poorer prognosis than patients with left-sided mCRC, and that patients with right-sided mCRC derived limited incremental benefit from treatment with bevacizumab.

5.31. The Subcommittee considered that the major safety concerns with bevacizumab are hypertension, proteinuria, bleeding, thromboembolic events, and fistulae.

5.32. The Subcommittee considered that the evidence currently available, noting it is unlikely that further prospective studies would be conducted, was modest and indicates that bevacizumab provides only a marginal incremental survival benefit when used in combination with standard of care chemotherapy combinations such as FOLFIRI and FOLFOX. The Subcommittee therefore considered that given the marginal benefit the application for bevacizumab for the first- and second-line treatment of mCRC should be declined and particularly noting the relatively high current price of bevacizumab.

6. Abiraterone acetate for the treatment of hormone naïve and hormone sensitive metastatic prostate cancer

Application

6.1. The Subcommittee reviewed a funding application for abiraterone acetate to be used in combination with prednisone and androgen deprivation therapy for the treatment of high-risk metastatic hormone-naïve prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC).

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** that abiraterone acetate in combination with prednisone or prednisolone and androgen deprivation therapy for the treatment of newly diagnosed high risk metastatic hormone-naïve prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) be funded with a high priority subject to the following Special Authority criteria:

Special Authority for Subsidy – Retail Pharmacy - Specialist
Initial application - (hormone-naïve or hormone-sensitive) only from a medical oncologist or radiation oncologist, or any medical practitioner on the recommendation of a medical oncologist or radiation oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has metastatic prostate cancer documented by a positive bone scan or metastatic lesions on CT or MRI; and
2. Patient was diagnosed with metastatic prostate cancer within the last three months; and
3. Patient does not have neuroendocrine differentiation or small-cell histologic features; and
4. Patient has an ECOG performance score of 0-2; and
5. At least two of the following:
    5.1. Patient has measurable visceral metastases on CT or MRI (excluding nodes); or
    5.2. Patient has three or more lesions by bone scan, CT or MRI; or
    5.3. Patient has a Gleason score of eight or more (International Society of Urological Pathologists [ISUP] Grade 4 or 5); and
6. Any of the following:
    6.1. Patient has not previously received treatment for metastatic prostate cancer; or
    6.2. Patient has received only one course of palliative radiation or surgical therapy to treat symptoms associated with metastatic disease; or
    6.3. Patient has received up to three months of androgen deprivation therapy and is continuing to respond to treatment; and
7. Abiraterone not to be given with taxane chemotherapy.

Renewal application – (hormone-naïve or hormone-sensitive) only from a medical oncologist or radiation oncologist, or any medical practitioner on the recommendation of a medical oncologist

or radiation oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. No evidence of clinical disease progression; and
2. No initiation of taxane chemotherapy with abiraterone; and
3. The treatment remains appropriate and the patient is benefitting from treatment.

6.4. The Subcommittee **deferred** making a recommendation regarding other metastatic prostate cancer populations pending further evidence for use in these settings.

6.5. The Subcommittee **recommended** that were abiraterone acetate be funded for patients with hormone-naïve/sensitive metastatic prostate cancer, that the Special Authority criteria for abiraterone acetate for patients with castration-resistant disease be amended to exclude patients who have had prior abiraterone therapy whether or not they had received prior taxane chemotherapy.

Discussion

6.6. The Subcommittee noted that the application for abiraterone acetate in combination with prednisone and androgen deprivation therapy (ADT) for the treatment of newly diagnosed high-risk metastatic hormone-naïve prostate cancer (mHNPC) and newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) was reviewed by PTAC in November 2018. At this time, PTAC recommended that:

- abiraterone acetate in combination with prednisone and ADT be funded with low priority for the treatment of mHNPC and mHSPC subject to the eligibility criteria for the LATITUDE trial
- abiraterone acetate for use in combination with prednisone and ADT in a wider group of patients than those meeting the eligibility criteria for the LATITUDE trial be deferred until additional data in these settings is available
- the application be referred to CaTSoP for advice regarding the current use of, and benefit of ADT plus docetaxel in the treatment of prostate cancer; appropriate Special Authority criteria for abiraterone acetate (including whether amendment to the current metastatic castration-resistant prostate cancer criteria would be required); and the potential benefit of abiraterone acetate in a wider group of prostate cancer patients than those included in the LATITUDE trial.

6.7. The Subcommittee noted that the current standard of care for patients with newly diagnosed metastatic prostate cancer is ADT, either alone or in combination with docetaxel in patients fit enough to receive chemotherapy. Members considered that medical oncologists may use tumour burden to consider who would benefit from docetaxel chemotherapy.

6.8. The Subcommittee considered that there is a need for an alternative treatment option for individuals with newly diagnosed metastatic prostate cancer who are not candidates for chemotherapy or who would not consider chemotherapy because its tolerability and impact on daily life. The Subcommittee considered that the average age at the time of diagnosis is 66 years, and that individuals of this age are often still working and living full lives. The Subcommittee considered

that this cohort may also be less likely to receive docetaxel due to its side effect profile.

6.9. The Subcommittee noted that abiraterone acetate is a selective irreversible inhibitor of CYP17A1, which is an enzyme required for androgen biosynthesis in testicular, adrenal, and prostatic tumour tissue.

6.10. The Subcommittee noted that a consequence of inhibiting CYP17A1 is an increase in mineralocorticoid levels; therefore, patients treated with abiraterone acetate also receive prednisone or prednisolone in order to avoid mineralocorticoid toxicities.

6.11. The Subcommittee noted that abiraterone acetate is approved by Medsafe for use in combination with ADT and prednisone or prednisolone for the treatment of mHNPC and mHSPC, and for selected patients with metastatic castration resistant prostate cancer. The Subcommittee noted that abiraterone acetate has been funded for the treatment of metastatic castration resistant prostate cancer since 2015.

6.12. The Subcommittee noted that the recommended dosage of abiraterone acetate is 1000 mg orally as a single daily dose in combination with 10 mg (either once daily or as 5 mg twice daily) prednisone or prednisolone.

6.13. The Subcommittee noted that the key clinical evidence for abiraterone acetate in mHNPC and mHSPC is provided by the double-blind, placebo-controlled, Phase 3 LATITUDE trial, which investigated the efficacy of abiraterone acetate plus prednisone with ADT in 1199 patients with newly diagnosed, hormone naïve castration sensitive metastatic prostate cancer. The Subcommittee noted that high risk was defined as two or more of the following: Gleason Score ≥ 8, 3 or more lesions on bone scan, and/or visceral metastases (excluding nodes). The Subcommittee noted the design of the LATITUDE trial and the results of the interim analysis (Fizazi et al. N Engl J Med. 2017;377:352-60). The Subcommittee noted that the trial was unblinded, to allow crossover, as a result of the findings of the interim analysis.

6.14. The Subcommittee noted the final overall survival analysis of the LATITUDE trial, which was not available at the time PTAC reviewed the application in November 2018 (Fizazi et al. Lancet Oncol. 2019;20:686-700). The Subcommittee noted that after a median follow-up of 51.8 months, the median overall survival was 53.3 months in the abiraterone acetate plus prednisone group, compared with 36.5 months in the placebo group (HR 0.66; 95% CI 0.56 to 0.78; *P*<0.0001). The Subcommittee noted that 275 deaths (46%) had occurred in the abiraterone acetate plus prednisone group, compared with 343 (57%) in the placebo group. The Subcommittee noted that compared with placebo, abiraterone acetate plus prednisone improved time to skeletal related events (HR 0.75; 95% CI 0.60 to 0.95; *P*=0.0181), time to chemotherapy initiation (HR 0.51; 95% CI 0.41 to 0.63; *P*<0.0001), time to subsequent prostate cancer therapy (HR 0.45; 95% CI 0.38 to 0.53; *P*<0.0001), and time to prostate-specific antigen progression (HR 0.31; 95% CI 0.27 to 0.36; *P*<0.0001). The Subcommittee noted that at the time of the final analysis, 72 patients had crossed over from placebo to abiraterone acetate plus prednisone.

6.15. The Subcommittee noted safety data from the final overall survival analysis of the LATITUDE trial (Fizazi et al. 2019). The Subcommittee noted that the most common grade 3 or 4 adverse events were hypertension (abiraterone acetate

plus prednisone 21% [n = 125], placebo 10% [n = 60], crossover 4% [n = 3]) and hypokalaemia (abiraterone acetate plus prednisone 12% [n = 70], placebo 2% [n = 10], crossover 3% [n = 2]). The Subcommittee noted that treatment-related serious adverse events were reported in 5% (n = 30) of patients in the abiraterone acetate plus prednisone group, 2% (n = 13) in the placebo group, and 1% (n = 1) in the crossover group. The Subcommittee noted that treatment-related adverse events leading to discontinuation were reported in 4% (n = 24) of patients in the abiraterone acetate plus prednisone group, 2% (n = 11) in the placebo group, and 1% (n = 1) in the crossover group. The Subcommittee considered that no new safety signals were identified.

6.16. The Subcommittee noted the results of the patient-reported outcome and health-related quality of life analysis of the LATITUDE trial after a median follow-up of 30.9 months (Chi et al. Lancet Oncol. 2018;19:194-206). The Subcommittee noted that the analysis included the Brief Pain Inventory – Short Form, the Brief Fatigue Inventory, the Functional Assessment of Cancer Therapy Prostate scale (FACT-P), and the EuroQoL questionnaire. The Subcommittee noted that adherence was 90% or higher for all patient reported outcome measurement tools. The Subcommittee noted that the median time to deterioration of functional status according to FACT-P was 12.9 months in the abiraterone acetate plus prednisone group, compared with 8.3 months in the placebo group (HR 0.85; 95% CI 0.74 to 0.99; *P*=0.032). The Subcommittee noted that the median time to pain interference progression was not reached in the abiraterone acetate plus prednisone group compared with 18.4 months in the placebo group (HR 0.67; 95% CI 0.56 to 0.80; *P*<0.0001).

6.17. The Subcommittee noted that additional evidence for the use of abiraterone acetate with prednisolone and ADT is provided by Arm G of the open-label, multi-arm, multi-stage, Phase 2-3 STAMPEDE trial (James et al. N Engl J Med. 2017;377:338-51). The Subcommittee noted that ARM G contained four groups of patients: 50% of patients were those with newly diagnosed metastatic prostate cancer, approximately 20% were men with newly diagnosed node positive but not otherwise metastatic prostate cancer, approximately 27% were those with newly diagnosed but node negative high risk locally advanced prostate cancer (high risk defined as T3,4 disease; Gleason 8 – 10, PSA ≥ 40 nG/mL); and a final group of men previously treated with radical surgery or brachytherapy no longer receiving therapy and newly relapsing with high risk features and that this was the smallest group (<5% in both arms).

6.18. The Subcommittee noted that for the whole study population the 3-year survival was 83% in the abiraterone acetate with prednisolone and ADT arm (Arm G), compared with 76% in the ADT-alone arm (HR 0.63; 95% CI 0.52 to 0.76; *P*<0.001). The Subcommittee noted that failure free survival time in the abiraterone acetate with prednisolone and ADT arm was 43.9 months, compared with 30.0 months in the ADT-alone arm, that the 3-year progression-free survival was 80% compared with 62% (HR 0.40; 95% CI 0.34 to 0.47; *P*<0.001), and that the 3-year rate without symptomatic skeletal events was 88% compared with 78% (HR 0.46; 95% CI 0.34 to 0.47; *P*<0.001).

6.19. The Subcommittee noted that among the 1476 patients in the safety population in the relevant sub-analysis of STAMPEDE in whom progression had not occurred within the first year, the prevalence of grade 3 or higher adverse events was 15% among patients who received abiraterone acetate plus prednisolone and ADT, compared with 11% in the ADT alone group. The Subcommittee noted that the main adverse events that occurred over and above the control therapy were

hypertension, mild increases in aminotransferase levels, and respiratory disorders.

6.20. The Subcommittee considered that the patient population in STAMPEDE differed from the patients in LATITUDE; STAMPEDE included patients with non-metastatic disease and patients with high-risk disease defined by different criteria. The Subcommittee considered that this limits the value of direct comparison between the trials.

6.21. The Subcommittee noted that there is no head-to-head trial comparing abiraterone plus ADT with docetaxel plus ADT, but did identify three network meta-analyses that indirectly compared the agents (Feyerabend et al. Eur J Cancer. 2018;103:78-87; Wallis et al. Eur Urol. 2018;73:834-44; Vale et al. Ann Oncol. 2018;29:1249-57). The Subcommittee noted that Feyerabend et al (2018) reported that abiraterone plus prednisone and ADT is at least as effective in reducing the risk of death as docetaxel plus ADT; and was reportedly better at preventing disease progression and improving quality of life. The Subcommittee noted that Wallis et al (2018) reported that there was no significant difference in overall survival between abiraterone acetate plus prednisone/prednisolone and ADT and docetaxel plus ADT. The Subcommittee noted that Vale et al (2018) reported that abiraterone acetate plus prednisone/prednisolone appears to be the most effective treatment, although considered it was not clear whether this is due to an increased benefit or variation in the trials included.

6.22. The Subcommittee noted that a direct, randomised comparison of abiraterone acetate plus prednisolone and ADT with docetaxel plus ADT was conducted as part of the STAMPEDE trial (Sydes et al. Ann Oncol. 2018;29:1235-1248). The Subcommittee noted that this was not a formally powered comparison. The Subcommittee noted that after a median follow-up of 4 years, there were 44/189 (23%) deaths in the docetaxel arm and 105/377 (28%) deaths in the abiraterone acetate arm (all patients: overall survival HR 1.16; 95% CI 0.82 to 1.65; patients with metastatic disease: overall survival HR=1.13; 95% CI 0.77 to 1.66).

6.23. The Subcommittee noted that guidelines from NCCN, ESMO, and ASCO recommend that abiraterone acetate plus prednisone and ADT are appropriate for patients with metastatic hormone-sensitive disease who are fit enough to receive these agents.

6.24. The Subcommittee noted that metastatic prostate cancer in New Zealand is primarily diagnosed by a positive bone scan or metastatic lesions on CT or MRI, and that these were the criteria used for eligibility in the LATITUDE trial. The Subcommittee noted that gallium-labelled prostate-specific membrane antigen ligand (PSMA) PET imaging is a diagnostic tool available privately in New Zealand that has better specificity and sensitivity than standard imaging modalities for detecting metastatic prostate cancer. The Subcommittee considered that there is pressure to more widely introduce PSMA PET technology, and that this has potential consequences for equity due to variable access as patients who are able to access PSMA-PET could qualify for treatment earlier in their disease course. The Subcommittee also considered that it is unclear at this time whether metastatic disease diagnosed using PSMA PET imaging is comparable with metastatic disease diagnosed using conventional imaging modalities.

6.25. The Subcommittee noted PTAC's recommendation that abiraterone acetate, for use in combination with prednisone and ADT in a wider group of patients than

those meeting the eligibility criteria for the LATITUDE trial, be deferred until additional data in these settings is available. The Subcommittee considered that the data from the STAMPEDE trial suggests that there is potential for abiraterone acetate to have health benefits in a population wider than that described by LATITUDE, but agreed that this evidence is not yet mature enough to make a positive recommendation.

6.26. The Subcommittee noted that the existing Special Authority criteria for abiraterone acetate for metastatic castration-resistant prostate cancer stipulates that where patients are previously treated with chemotherapy containing a taxane they must have had prior treatment with abiraterone. The Subcommittee considered that if abiraterone were funded for newly diagnosed castrate sensitive or hormone naive metastatic prostate cancer, that this criterion should not be changed. However, the Subcommittee considered that amendment should be made to preclude prior abiraterone treatment for patients who have not received prior taxane chemotherapy. The Subcommittee considered that patients should be eligible to receive abiraterone acetate only once, either for newly diagnosed high risk mHNPC/mHSPC or for metastatic castration-resistant prostate cancer, as there is a lack of evidence to support a further line of abiraterone treatment following relapse.

6.27. The Subcommittee considered that if abiraterone acetate was to be funded for newly diagnosed high risk mHNPC and mHSPC that there would likely be a decrease in the use of docetaxel and bicalutamide.

6.28. The Subcommittee considered that if abiraterone acetate was to be funded for newly diagnosed high risk mHNPC and mHSPC subject to the eligibility criteria in LATITUDE, that the patient number estimates provided by the supplier were reasonable (n = 113 in year 1, increasing to n = 520 in year 5). The Subcommittee considered that uptake of abiraterone acetate in these populations would be high as there would likely be a preference for abiraterone plus prednisone/prednisolone and ADT over ADT and docetaxel.

6.29. The Subcommittee considered that the evidence for the efficacy and safety of abiraterone acetate, in combination with prednisone and ADT, for the treatment of newly diagnosed high risk mHNPC and mHSPC provided by LATITUDE, was of moderate to high quality, and that there is a need for an alternative treatment option for these patients. The Subcommittee considered that if abiraterone acetate was to be funded for newly diagnosed high risk mHNPC/mHSPC, that the Special Authority criteria should reflect the eligibility criteria of the LATITUDE trial.