Record of the Cancer Treatment Subcommittee of PTAC meeting held at PHARMAC on 5 April 2019 (record for web publishing)

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

The Cancer Treatments Subcommittee may:

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

The record of this Subcommittee meeting will be reviewed by PTAC at its August 2019 meeting.

Present from CaTSoP:
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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Summary of recommendations

4.7. The Subcommittee recommended that nivolumab for the second-line treatment of relapsed clear cell RCC be funded subject to the following Special Authority criteria:

> Initial application — only from a medical oncologist or from a relevant specialist on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has metastatic renal-cell carcinoma; and
> 2. The disease is of predominant clear-cell histology; and
> 3. Patient has a Karnofsky performance status of 70 or greater; and
> 4. Patient has documented measurable disease according to RECIST; and
> 5. Patient has had received one or two previous regimens of antiangiogenic therapy; and
> 6. Patient has had no more than three total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy drugs; and
> 7. Disease progression has occurred following previous treatment; and
> 8. Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks and discontinued at disease progression.
>
> Renewal application — only from a medical oncologist or from a relevant specialist on the recommendation of 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; or
> 1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
> 1.3. Patient has stable disease according to RECIST criteria; and
> 2. No evidence of disease progression according to RECIST criteria; and
> 3. Response to treatment in target lesions has been determined by radiologic assessment following the most recent treatment period; and
> 4. The treatment remains clinically appropriate and the patient is benefitting from treatment and tolerating treatment; and
> 5. Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks and discontinued at disease progression.

4.12. The Subcommittee recommended that the appropriate clarification to the definition in the olaparib Special Authority criteria was 'pathogenic germline BRCA1 or BRCA2 gene mutation' as this was the intent of the population to be treated.

5.5. The Subcommittee recommended that palbociclib for use in combination with fulvestrant for the second-line treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer be funded with a medium priority subject to the following Special Authority criteria:

> Initial application **-** only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has unresectable locally advanced or metastatic breast cancer; and
> 2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
> 3. Patient has relapsed or progressed during prior endocrine therapy; and
> 4. Patient has an ECOG performance score of 0-2; and
> 5. Palbociclib must be used in combination with an endocrine partner.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:

All of the following:

1. Palbociclib must be used in combination with an endocrine partner; and
2. No evidence of progressive disease; and
3. The treatment remains appropriate and the patient is benefitting from treatment.

5.7. The Subcommittee recommended that a CDK4/6 inhibitor for use in combination with an endocrine partner for the first-line treatment of HR-positive, HER2 negative locally advanced or metastatic breast cancer be funded with a high priority.

5.8. The Subcommittee recommended that a CDK4/6 inhibitor for use in combination with an endocrine partner for the second-line treatment of HR-positive, HER2 negative locally advanced or metastatic breast cancer in patients with hormone-sensitive disease be funded with a high priority.

5.9. The Subcommittee recommended that a CDK4/6 inhibitor for use in combination with an endocrine partner for the second-line treatment of all HR-positive, HER2 negative locally advanced or metastatic breast cancer be funded with a medium priority.

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

8.8. The Subcommittee recommended that pembrolizumab be funded in a first-line setting for advanced NSCLC patients subject to the following access criteria:

Initial application - (NSCLC first-line) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Patient has not received prior treatment with an immune checkpoint inhibitor for NSCLC; and
2. Either:
   - 2.1. All of the following:
     - 2.1.1. Patient has locally advanced or metastatic, unresectable, non-small cell lung cancer; and
     - 2.1.2. The patient has not had prior chemotherapy treatment for their disease; and
     - 2.1.3. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase; and
     - 2.1.4. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 50% as determined by a validated Dako-based diagnostic test; and
     - 2.1.5. Patient has an ECOG 0-1; and
     - 2.1.6. Pembrolizumab to be used as monotherapy at a maximum dose of 200 mg every 3 weeks (or equivalent) for a maximum of 12 weeks; and
     - 2.1.7. Baseline measurement of overall tumour burden is documented; or
   - 2.2. All of the following:
     - 2.2.1. Patient has metastatic, unresectable, non-small cell lung cancer; and
     - 2.2.2. The patient has not had prior treatment for their metastatic disease; and
     - 2.2.3. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase; and
     - 2.2.4. Patient has an ECOG 0-1; and
     - 2.2.5. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks (or equivalent); and
     - 2.2.6. Pembrolizumab to be used in combination with platinum-pemetrexed or carboplatin-paclitaxel; and
     - 2.2.7. Baseline measurement of overall tumour burden is documented.

Renewal – (NSCLC first line) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

1. Patient has received prior funded pembrolizumab treatment for NSCLC; and
2. Any of the following:

2.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
2.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
2.3. Patient has stable disease according to RECIST criteria; and
3. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
4. No evidence of disease progression according to RECIST criteria; and
5. The treatment remains clinically appropriate and patient is benefitting from treatment; and
6. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks (or equivalent); and
7. Pembrolizumab to be discontinued at signs of disease progression.

8.10. The Subcommittee recommended that if pembrolizumab in combination with chemotherapy were funded, that the Special Authority criteria for pemetrexed for NSCLC be amended to allow concomitant use with pembrolizumab as follows (additions in bold):

Initial application - (NSCLC) only from relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
Both:
1. Patient has locally advanced or metastatic non-squamous NSCLC; and
2. Either:
   2.1. Both:
      2.1.1. Patient has chemotherapy naïve disease; and
      2.1.2. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days in combination with cisplatin or carboplatin for a maximum of 6 cycles; or
   2.2. All of the following:
      2.2.1. Patient has had first-line treatment with platinum based chemotherapy **or immune checkpoint inhibitor**; and
      2.2.2. Patient has not received prior funded treatment with pemetrexed; and
      2.2.3. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days for a maximum of 6 cycles**.**

Renewal – (NSCLC) only from relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
All of the following:
1. No evidence of disease progression; and
2. Treatment remains clinically appropriate and patient is benefitting from treatment; and
3. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days for a maximum of 6 cycles.

9.6. The Subcommittee recommended that alectinib be funded with high priority for the treatment of anaplastic-lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC), subject to the following Special Authority criteria:

Initial application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has locally advanced, or metastatic, unresectable, non-small cell lung cancer; and
2. There is documentation confirming that the patient has an ALK tyrosine kinase gene rearrangement using an appropriate ALK test; and
3. Patient has an ECOG performance score of 0-2.

Renewal application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. No evidence of progressive disease according to RECIST criteria; and
2. The patient is benefitting from and tolerating treatment.

9.7. The Subcommittee recommended that crizotinib be funded with a medium priority for the treatment of ALK-positive advanced NSCLC subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced, or metastatic, unresectable, non-small cell lung cancer; and
> 2. There is documentation confirming that the patient has an ALK tyrosine kinase gene rearrangement using an appropriate ALK test; and
> 3. Patient has an ECOG performance score of 0-2.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of progressive disease according to RECIST criteria; and
> 2. The patient is benefitting from and tolerating treatment

10.10. The Subcommittee recommended pembrolizumab for the first-line treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing therapy be declined based on the poor strength and quality of currently available evidence.

10.11. The Subcommittee recommended pembrolizumab be funded with medium priority for the second-line treatment of locally advanced or metastatic UC after failure of a platinum-containing chemotherapy regimen.

10.12. The Subcommittee recommended that atezolizumab be listed with low priority for the second-line treatment of locally advanced or metastatic UC following progression on platinum-containing chemotherapy

10.13. The Subcommittee recommended that immune checkpoint inhibitors for the second-line treatment of locally advanced or metastatic UC be funded subject to the following Special Authority criteria:

> Special Authority for Subsidy – PCT only
> Initial - only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has inoperable locally advanced (T4) or metastatic urothelial carcinoma; and
> 2. Patient has an ECOG performance status of 0-2; and
> 3. Patient has documented disease progression following treatment with platinum-containing chemotherapy; and
> 4. [Treatment] to be used as monotherapy at a maximum dose of [dose regimen] for a maximum of 12 weeks; and
> 5. Baseline measurement of overall tumour burden is documented according to RECIST version 1.1.
>
> Renewal - only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> 1. Any of the following:
>   1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
>   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
>   1.3. Patient has stable disease according to RECIST criteria; and
> 2. Response to treatment has been determined by radiologic assessment following the most recent treatment period; and
> 3. No evidence of disease progression according to RECIST criteria: and
> 4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
> 5. [Treatment] is to be used as monotherapy at a [dose regimen] for a maximum of 12 weeks.

11.5. The Subcommittee recommended that two years duration of venetoclax in combination with six cycles of rituximab for the treatment of patients with relapsed/refractory CLL be funded for with a high priority subject to the following Special Authority criteria:

> Venetoclax – Retail Pharmacy – Specialist
> Initial application (relapsed/refractory chronic lymphocytic leukaemia) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has chronic lymphocytic leukaemia requiring treatment; and
> 2. Patient has received at least one prior therapy for chronic lymphocytic leukaemia; and
> 3. Patient has not previously received venetoclax; and
> 4. The patient's disease has relapsed within 36 months of previous treatment; and
> 5. Venetoclax to be used in combination with six 28-day cycles of rituximab commencing after the 5-week dose titration schedule with venetoclax; and
> 6. Patient has an ECOG performance status of 0-2.
>
> Renewal application (relapsed/refractory chronic lymphocytic leukaemia) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> 1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.
> 2. Venetoclax is to be discontinued after a maximum of 24 months of treatment unless earlier discontinuation is required due to disease progression or unacceptable toxicity.
>
> Note: 'Chronic lymphocytic leukaemia (CLL)' includes small lymphocytic lymphoma (SLL).

12.4. The Subcommittee recommended that raltitrexed be funded with low priority for the treatment of locally advanced or metastatic colorectal cancer for patients who are intolerant to fluoropyrimidines due to cardiotoxicity, subject to the following Special Authority criteria:

> Initial application – (colorectal cancer) only from a medical oncologist or relevant specialist on the recommendation of medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced or metastatic colorectal cancer; and
> 2. Patients is intolerant to fluoropyrimidines due to cardiotoxicity; and
> 3. Appropriate investigations have been undertaken to confirm the absence of anatomic cardiac disease; and
> 4. Raltitrexed to be administered at a maximum of 3 mg/kg^2 once every 3 weeks; and
> 5. Raltitrexed to be discontinued at disease progression.
>
> Renewal – (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. Raltitrexed remains appropriate and the patient is benefitting from treatment.

12.5. The Subcommittee recommended that raltitrexed be declined for the adjuvant treatment of early colorectal cancer for patients who are intolerant or contraindicated to fluoropyrimidines due to cardiac toxicity.

1. Correspondence and Matters Arising

Nivolumab for renal cell carcinoma Special Authority criteria

1.1. The Subcommittee noted that at its meeting in August 2017, CaTSoP recommended that nivolumab for the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy be funded with a medium priority, but also considered that its priority rating would decrease if the cost-effectiveness of nivolumab in this setting was poor.

1.2. The Subcommittee noted that at its meeting in November 2018, PTAC reviewed the application for nivolumab for the second-line treatment of relapsed clear cell RCC following prior angiogenic therapy and recommended funding with a low priority subject to Special Authority criteria aligned with published evidence and to be determined based on further advice from CaTSoP.

1.3. The Subcommittee noted that the key clinical evidence for the use of nivolumab in the second-line treatment of advanced RCC comes from CHECKMATE-025, a randomised, open-label, phase 3 study of nivolumab (3mg/kg IV Q2W) in comparison with everolimus (10mg orally OD) in 821 patients with metastatic clear-cell RCC who had received previous antiangiogenic therapy (Motzer et al. N Engl J Med. 2015;373:1803–13). Members noted that the trial population had a variety of prior treatment regimens.

1.4. The Subcommittee considered that it would be appropriate to align the Special Authority criteria with those for first-line agents, sunitinib and pazopanib; and that access criteria should target patients with predominant clear cell histology as this would be the main population seeking a second-line treatment.

1.5. The Subcommittee considered that eligibility for second-line treatment should be targeted to those patients who have progressed on previous treatment rather than commencing patients who are stable on current treatment.

1.6. The Subcommittee **recommended** that nivolumab for the second-line treatment of relapsed clear cell RCC be funded subject to the following Special Authority criteria:

Initial Application — only from a medical oncologist or from a relevant specialist on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:

1. Patient has metastatic renal-cell carcinoma; and
2. The disease is of predominant clear-cell histology; and
3. Patient has a Karnofsky performance status of 70 or greater; and
4. Patient has documented measurable disease according to RECIST; and
5. Patient has had received one or two previous regimens of antiangiogenic therapy; and
6. Patient has had no more than three total previous regimens of systemic therapy, including cytokines and cytotoxic chemotherapy drugs; and
7. Disease progression has occurred following previous treatment; and
8. Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks and discontinued at disease progression.

Renewal application — only from a medical oncologist or from a relevant specialist on the recommendation of 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; or
   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or

1.3. Patient has stable disease according to RECIST criteria; and
2. No evidence of disease progression according to RECIST criteria; and
3. Response to treatment in target lesions has been determined by radiologic assessment following the most recent treatment period; and
4. The treatment remains clinically appropriate and the patient is benefitting from treatment and tolerating treatment; and
5. Nivolumab is to be used as monotherapy at a maximum dose of 3 mg/kg every 2 weeks and discontinued at disease progression.

1.7. The Subcommittee noted that the current Medsafe registered dose regimen was 3mg/kg every 3 weeks however, there would likely be alternative dose regimens approved in future which could improve suitability for patients and reduce service delivery costs such as fixed doses or lower frequency administration schedules. The Subcommittee considered that should alternative dose regimens be registered that the Special Authority be reviewed and amended to allow for this.

Olaparib for the maintenance treatment of platinum-sensitive BRCA mutated relapsed ovarian cancer

1.8. The Subcommittee noted that at its meeting in November 2018, PTAC recommended that olaparib be funded with a medium priority for the treatment of BRCA-mutated platinum-sensitive relapsed ovarian, fallopian tube, or primary peritoneal cancer with high grade serous features or a high-grade serous component subject to the Special Authority criteria proposed by CaTSoP at its April 2018 meeting but requested clarification from CaTSoP as to the appropriate definition of germline BRCA mutation to be used.

1.9. The Subcommittee noted that PTAC had queried whether restriction to definitively defined pathological mutation types would be appropriate in a New Zealand setting and that that consideration should be given to whether this could disenfranchise minorities who may be less likely to have mutations classified as pathological in databases, primarily due to limited data points.

1.10. The Subcommittee considered that further genetic testing may result in reporting of further pathologic mutations and that currently non-Caucasian populations were likely under-represented in the current databases; and therefore inequity could be exacerbated for these populations with further specificity in the definition.

1.11. The Subcommittee **recommended** that the appropriate clarification to the definition in the olaparib Special Authority criteria was ‘pathogenic germline BRCA1 or BRCA2 gene mutation’ as this was the intent of the population to be treated.

Abiraterone 500 mg tablet presentation

1.12. The Subcommittee noted that a 500mg tablet presentation of abiraterone acetate (Zytiga) had been Medsafe registered and the supplier was seeking to supply this strength in place of the current 250 mg tablet presentation.

1.13. The Subcommittee noted that recommended dosage of abiraterone acetate is 1000 mg (either two 500 mg tablets or four 250 mg tablets) as a single daily dose. The Subcommittee considered that while there could be some suitability advantages with the 500 mg presentation, in terms of reducing the number of pills patients needed to take, there was no clinical need for the proposed alternative presentation.

Hexylaminolevulinate hydrochloride for detection of bladder cancer correspondence

1.14. The Subcommittee noted that at its meeting in April 2018, CaTSoP deferred making a recommendation regarding the funding of hexylaminolevulinate hydrochloride for the detection of bladder cancer and that correspondence had since been received from the supplier regarding its consideration of the product. The Subcommittee noted and thanked the supplier for its comments.

BCAC letter regarding September 2018 CaTSoP record

1.15. The Subcommittee noted correspondence from Breast Cancer Aotearoa Coalition (BCAC) in response to the record of the September 2018 CaTSoP meeting at which a number of applications for breast cancer treatments, (including fulvestrant, pertuzumab, palbociclib and trastuzumab emtansine) had been considered as well as broader consideration of the breast cancer treatment landscape; and also raised issues regarding access to medicines for people with breast cancer in New Zealand.

1.16. The Subcommittee noted that CaTSoP was further considering the funding of palbociclib as a second-line treatment for advanced breast cancer at this meeting, PTAC would be further considering funding for palbociclib at its next meeting in May 2019; and that BCAC's applications for everolimus and nab-paclitaxel for the treatment of breast cancer would also be considered by PTAC at its next meeting.

1.17. The Subcommittee noted the significant amount of information provided by BCAC regarding the various breast cancer treatments under consideration by PHARMAC.

1.18. The Subcommittee considered a comprehensive review of the currently available evidence for breast cancer treatments was undertaken at its September 2018 meeting, however welcomes the provision of new published evidence to support further consideration of these treatments.

1.19. The Subcommittee considered there would be value in and encouraged the development of a New Zealand treatment paradigm for breast cancer treatments to help provide guidance on the sequence and relative priorities for funding for breast cancer treatments.

2. Palbociclib in combination with fulvestrant for the second-line treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer

Application

2.1. The Subcommittee reviewed a funding application from the Breast Cancer Aotearoa Coalition (BCAC) for palbociclib to be used in combination with fulvestrant for the second-line treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

2.2. The Subcommittee also reviewed information regarding other CDK4/6 inhibitors and considered whether there was a class effect with these agents for the treatment of HR-positive, HER2-negative advanced breast cancer.

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

Recommendation

2.4. The Subcommittee **recommended** that palbociclib for use in combination with fulvestrant for the second-line treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer be funded with a **medium** priority subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has unresectable locally advanced or metastatic breast cancer; and
> 2. There is documentation confirming disease is hormone-receptor positive and HER2-negative; and
> 3. Patient has relapsed or progressed during prior endocrine therapy; and
> 4. Patient has an ECOG performance score of 0-2; and
> 5. Palbociclib must be used in combination with an endocrine partner.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Palbociclib must be used in combination with an endocrine partner; and
> 2. No evidence of progressive disease; and
> 3. The treatment remains appropriate and the patient is benefitting from treatment.

2.5. The Subcommittee considered there is a class effect with cyclin dependent kinase 4/6 (CDK4/6) inhibitors, and that there is likely to be no significant difference in which endocrine partner the CDK4/6 inhibitors are combined with. The Subcommittee therefore provided the following recommendations:

2.6. The Subcommittee **recommended** that a CDK4/6 inhibitor for use in combination with an endocrine partner for the first-line treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer be funded with a high priority.

2.7. The Subcommittee **recommended** that a CDK4/6 inhibitor for use in combination with an endocrine partner for the second-line treatment of HR-positive, HER2-negative locally advanced or metastatic breast cancer in patients with hormone-sensitive disease be funded with a **high** priority.

2.8. The Subcommittee **recommended** that a CDK4/6 inhibitor for use in combination with an endocrine partner for the second-line treatment of all HR-positive, HER2-negative locally advanced or metastatic breast cancer be funded with a **medium** priority.

Discussion

2.9. The Subcommittee noted that 3,300 new cases of breast cancer are diagnosed each year in New Zealand and that approximately 20% of patients will develop metastatic disease at some point. The Subcommittee noted that up to two-thirds of patients with advanced breast cancer have HR-positive, HER2-negative disease.

2.10. The Subcommittee considered that it was difficult to estimate the number of patients with HR-positive, HER2-negative disease who would be eligible for second-line treatment each year in New Zealand, but that it was likely around 200 to 400 patients.

2.11. The Subcommittee considered that, while chemotherapy may be used in cases of progressive visceral disease, the standard first-line endocrine therapy for HR-positive HER2-negative advanced breast cancer in New Zealand is usually with either an aromatase inhibitor or tamoxifen. The Subcommittee considered that these are also the agents most commonly used for second-line treatment, along with some use of megestrol acetate. The Subcommittee considered that chemotherapy is used in cases of progressive visceral disease.

2.12. The Subcommittee considered that the choice of endocrine therapy is dependent on menopausal status in addition to other risk factors. The Subcommittee considered that aromatase inhibitors are generally used in women who are postmenopausal, and that tamoxifen is used in both pre- and post-menopausal women. The Subcommittee considered that tamoxifen would be more likely to be used if osteopenia was a concern, and it would be more likely to use an aromatase inhibitor in women with a history or risk of cardiovascular (thromboembolic) complications.

2.13. The Subcommittee considered that there is a significant health need for patients who have progressed after first-line therapy, as response rates to second-line endocrine therapies are lower (~20%) and often not durable. Members considered the response to chemotherapy is also poor due to the high rate of chemoresistant disease among this subtype.

2.14. The Subcommittee noted that palbociclib is a CDK4/6 inhibitor which reduces cellular proliferation by blocking cell-cycle progression.

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

2.16. The Subcommittee noted that an application for the registration of ribociclib, another CDK4/6 inhibitor, is currently being evaluated by Medsafe; and a third CDK4/6 inhibitor, abemaciclib, is also in late-stage clinical development.

2.17. The Subcommittee noted that in September 2018, CaTSoP considered an application for the use of palbociclib in combination with an aromatase inhibitor as initial (first-line) endocrine-based therapy for HR-positive HER2-negative locally advanced or metastatic breast cancer (CaTSoP minutes – Sep 2018). At this time, the Subcommittee considered that palbociclib should be funded with a medium priority in a first-line setting, concluding that there was reasonable evidence of a modest benefit in this setting.

Palbociclib

2.18. The Subcommittee noted the double-blind, randomised, placebo-controlled, phase 3 PALOMA-3 trial, which investigated the efficacy of palbociclib plus fulvestrant compared with placebo plus fulvestrant in 521 women with HR-positive, HER2-negative advanced breast cancer who had relapsed or

progressed during prior endocrine therapy. The Subcommittee considered evidence from PALOMA-3 from five publications:

- PALOMA-3 interim analysis, median follow-up 5.6 months (Turner et al. N Engl J Med. 2015;373:209-19).
- PALOMA-3 final analysis, median follow-up 8.9 months (Cristofanilli et al. Lancet Oncol. 2016;17:425-39).
- PALOMA-3 detailed safety analysis, median follow-up 8.9 months (Verma et al. Oncologist. 2016;21:1165-75).
- PALOMA-3 overall survival analysis, median follow-up 44.8 months (Turner et al. N Engl J Med. 2018;379:1926-36).
- PALOMA-3 patient reported outcomes (Harbeck et al. Ann Oncol. 2016;27:1047-54).

2.19. The Subcommittee noted that 52% of individuals in PALOMA-3 had received two or more lines of prior endocrine therapy (Cristofanilli et al. 2016). The Subcommittee considered that the population included in PALOMA-3 therefore represented patients receiving late therapy, not just second-line therapy.

2.20. The Subcommittee noted that at the time of the final analysis of PALOMA-3, Cristofanilli et al. 2016 reported a median progression-free survival (PFS) of 9.5 months in the palbociclib arm compared with 4.6 months in the placebo arm (HR 0.46; 95% CI 0.36 to 0.59; *P*<0.0001). The Subcommittee considered that the response to treatment was relatively slow to manifest, with a median time to response of 112 days in the palbociclib arm.

2.21. The Subcommittee noted that endocrine therapy resistance was assessed by a number of parameters in PALOMA-3, including by tumour PIK3CA mutational status. The Subcommittee considered that at the time of the final analysis (median follow-up 8.9 months) PIK3CA status did not significantly affect treatment response (median PFS PIK3CA positive: 9.5 months palbociclib vs 3.6 months placebo; median PFS PIK3CA negative: 9.9 months palbociclib vs 4.6 months placebo; two-sided Pinteraction=0.83) (Cristofanilli et al.2016).

2.22. The Subcommittee noted that at the time of the prespecified overall survival (OS) analysis of PALOMA-3, Turner et al. 2018 reported a median OS of 34.9 months in the palbociclib arm compared with 28.0 months in the placebo arm (stratified HR 0.81; 95% CI 0.64 to 1.03; *P*=0.09). The Subcommittee noted that PALOMA-3 was not powered to detect an OS benefit.

2.23. The Subcommittee noted the results of the subgroup analysis conducted at the time of the prespecified OS analysis as reported by Turner et al. 2018. The Subcommittee considered that the subgroups who appeared to benefit most from treatment with palbociclib included patients with sensitivity to previous hormonal therapy, patients who were postmenopausal at study entry, patients aged 65 years or over, and patients with a disease-free interval of more than 24 months.

2.24. The Subcommittee noted that assessing OS is difficult in diseases such as HR-positive, HER2-negative breast cancer, particularly in early-line settings, due to the long survival time and because patients often receive multiple lines of subsequent therapy. The Subcommittee noted that in PALOMA-3, 4% of patients

in the palbociclib arm and 16% of patients in the placebo arm received a CDK4/6 inhibitor in a subsequent line of therapy. The Subcommittee considered that this makes the interpretation of benefit difficult, and that, if anything, may underestimate the magnitude of benefit.

2.25. The Subcommittee considered that palbociclib in combination with fulvestrant was well tolerated in PALOMA-3 (Verma et al. 2016).

2.26. The Subcommittee noted that patients with advanced disease inevitably have a shorter progression-free periods in response to each additional line of treatment; and considered that the PFS benefit observed in later line patients in PALOMA-3 reflected this. The Subcommittee noted that in PALOMA-2, which investigated the efficacy of palbociclib plus letrozole as a first-line treatment in HR-positive, HER2-negative advanced breast cancer the median PFS was 24.8 months palbociclib vs 14.5 months placebo (HR 0.58; 95% CI 0.46 to 0.72; *P*<0.001) (Finn et al. N Engl J Med. 2016;375:1925-1936).

2.27. The Subcommittee noted that palbociclib in combination with fulvestrant for the second-line treatment of HR-positive, HER2-negative advanced breast cancer has received a score of 4 on the European Society for Medical Oncology – Magnitude of Benefit Scale (ESMO-MCBS; graded from 1 [worst] to 5 [best]).

2.28. The Subcommittee considered that there is a significant health need for an additional treatment option for women with previously-treated HR-positive, HER2-negative advanced breast cancer, and that PALOMA-3 provides good evidence that palbociclib in combination with fulvestrant provides a clinically meaningful PFS benefit in this setting and that further data would likely show an OS benefit.

Other CDK4/6 inhibitors

2.29. The Subcommittee noted that there is a growing body of data regarding the use of CDK4/6 inhibitors for the first- and second-line treatment of HR-positive, HER2-negative breast cancer.

Ribociclib

2.30. The Subcommittee noted the results of the second interim analysis of the phase 3 MONALEESA-2 trial, which investigated the efficacy and safety of first-line ribociclib plus letrozole compared with placebo plus letrozole in 668 postmenopausal women with HR-positive, HER2-negative advanced breast cancer (Hortobagyi et al. Ann Oncol. 2018;29:1541-7). The Subcommittee noted that at a median follow-up of 26.4 months, the median PFS was 25.3 months in the palbociclib arm compared with 16.0 month in the placebo/letrozole arm (HR 0.568; 95% CI 0.457 to 0.704; log-rank $P = 9.63 \times 10^{-8}$). The Subcommittee considered that this result was comparable to that observed in PALOMA-2.

2.31. The Subcommittee noted the results of the phase 3 MONALEESA-7 trial, which investigated the efficacy and safety of ribociclib plus endocrine therapy compared with placebo and endocrine therapy in 672 premenopausal women with HR-positive, HER2-negative advanced breast cancer who had not previously received a CDK4/6 inhibitor (Tripathy et al. Lancet Oncol. 2018;19:904-15). The Subcommittee noted that patients could receive either tamoxifen or a nonsteroidal aromatase inhibitor as endocrine therapy. The Subcommittee noted that at a median follow-up of 19.2 months, that the median

PFS was 23.8 months in the ribociclib arm compared with 13.0 months in the placebo/endocrine therapy arm (HR 0.55; 95% CI 0.44 to 0.69; *P*<0.0001).

2.32. The Subcommittee noted the initial results of the phase 3 MONALEESA-3 trial, which investigated the efficacy of ribociclib plus fulvestrant compared with placebo plus fulvestrant in 484 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who were treatment naïve or had received up to one line of prior endocrine therapy (Slamon et al. J Clin Oncol. 2018;36:2465-72). The Subcommittee noted that at a median follow-up of 20.4 months, that the median PFS was 20.5 months in the ribociclib arm compared with 12.8 months in the placebo/fulvestrant arm (HR 0.593; 95% CI 0.480 to 0.732; *P*<0.001). The Subcommittee noted that the median PFS in patients who were treatment-naïve in this trial was not reached in the ribociclib arm compared with 18.3 months in the placebo/fulvestrant arm.

Abemaciclib

2.33. The Subcommittee noted the results of a planned interim analysis of the phase 3 MONARCH-3 trial, which investigated the efficacy of abemaciclib plus an aromatase inhibitor compared with placebo plus an aromatase inhibitor in 493 postmenopausal women with HR-positive, HER2-negative advanced breast cancer who had not received prior systemic therapy in the advanced setting (Goetz et al. J Clin Oncol. 2017;35:3638-3646). The Subcommittee noted that after a median follow up of 17.8 months, the median PFS was not reached in the abemaciclib arm compared with 14.7 months in the placebo/aromatase inhibitor arm (HR 0.54; 95% CI 0.41 to 0.72; *P*=0.000021).

2.34. The Subcommittee noted the results of the phase 3 MONARCH 2 trial, which investigated the efficacy and safety of abemaciclib plus fulvestrant compared with fulvestrant alone in 669 women with HR-positive, HER2-negative advanced breast cancer who had progressed while receiving endocrine therapy (Sledge et al. J Clin Oncol. 2017;35:2875-2884). The Subcommittee noted that the median PFS was 16.4 months in the abemaciclib plus fulvestrant arm compared with 9.3 months in the fulvestrant monotherapy arm (HR 0.553; 95% CI 0.449 to 0.681; *P*<0.001).

2.35. The Subcommittee noted the results of the single-arm, phase 2 MONARCH-1 trial, which investigated the activity and safety of abemaciclib monotherapy in 132 women with HR-positive, HER2-negative metastatic breast cancer who had progressed on or after prior endocrine therapy and had one or two chemotherapy regimens in the metastatic setting (Dickler et al. Clin Cancer Res. 2017;23:5218-5224). The Subcommittee noted that at the 12-month final analysis, the objective response rate was 19.7% (95% CI 13.3 to 27.5), the clinical benefit rate was 42.4%, the median PFS was 6.0 months, and the median OS was 17.7 months.

General Comments

2.36. The Subcommittee considered that, although there are no head to head trials, the body of data available to date regarding the efficacy and safety of CDK4/6 inhibitors for the first-line and second-line treatment of HR-positive, HER2-negative advanced breast cancer suggests that there is likely to be a class effect with these agents, and that they can be considered to provide the same or similar therapeutic benefit in these settings.

2.37. The Subcommittee considered that additional data would be helpful to further clarify the role of the endocrine partner in combination with a CDK4/6 inhibitor. However, from currently available data the choice of endocrine partner appears not to have a significant impact on the efficacy of combination treatment with CDK4/6 inhibitors; and that tamoxifen, non-steroidal aromatase inhibitors, and fulvestrant could potentially be used interchangeably in this setting.

2.38. The Subcommittee considered that there is currently no evidence available regarding whether it is better to use a CDK4/6 inhibitor in the first- or second-line for the treatment of HR-positive, HER2-negative advance breast cancer. The Subcommittee considered that the evidence for use in the first-line is more mature at this time, but that the health need for patients who have received prior endocrine therapy for advance disease is higher than for treatment-naïve patients.

2.39. The Subcommittee considered that the group of patients who responded well to first-line endocrine therapy (hormone sensitive patients) were the group most likely to respond well to second-line CDK4/6 inhibitors in combination with endocrine therapy.

3. Lung Cancer Review

Discussion

3.1. The Subcommittee noted advice was sought by PHARMAC staff regarding the current lung cancer treatment landscape, the lung cancer treatments currently being considered for funding by PHARMAC, and the pipeline of immunotherapeutic agents in late-stage clinical development for the treatment of lung cancer.

3.2. The Subcommittee considered a consensus statement regarding the funding of lung cancer treatments in New Zealand from the New Zealand Lung Oncology Special Interest Group (comprising medical oncologists who specialise in the treatment of lung cancer).

3.3. The Subcommittee considered information provided by Lung Foundation New Zealand on behalf of 2189 patients and their families who are currently dealing with a lung cancer diagnosis; this information outlined the health need and treatment priorities for patients with lung cancer in New Zealand and included a number of personal stories from people with lung cancer and their families.

3.4. The Subcommittee noted that lung cancer is the fifth most commonly diagnosed cancer in New Zealand and is the leading cause of cancer-related death. The Subcommittee noted that more than 2000 cases of lung cancer are diagnosed each year, and more than 1600 people die from the disease annually.

3.5. The Subcommittee noted that the incidence of lung cancer is 77.8 per 100,000 population in Māori compared with 24.2 per 100,000 for non-Māori, and that the mortality rate is more than three-fold higher in Māori than non-Māori.

3.6. The Subcommittee noted the survival rates for Māori patients with lung cancer are worse than survival rates for the total New Zealand population (7% compared with 10%, respectively).

3.7. The Subcommittee noted that there are two main types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). The Subcommittee noted that NSCLC accounts for approximately 80% of all lung cancers and can be further categorized as having squamous or non-squamous histology.

3.8. The Subcommittee noted that molecular diagnostics are used to further categorise patients with lung cancer by targetable oncogenic genetic alterations (eg EGFR, ALK, ROS1, BRAF) or by molecular biomarker (eg PD-L1).

3.9. The Subcommittee considered that the treatment paradigm for lung cancer is evolving rapidly due to the number and rate of new lung cancer treatments being developed, and that this will result in guidelines becoming quickly outdated.

3.10. The Subcommittee noted that a large number of targetable oncogenic alterations have been identified in lung cancer. The Subcommittee noted that there are currently targeted agents available for only some of these alterations (eg EGFR, ALK, ROS1, BRAF) and that there are a number of agents under development for others (eg RET, NTRK, HER2, MET, KRAS).

3.11. The Subcommittee noted that the majority of patients with targetable alterations have EGFR mutations and that the remaining identified alterations represent relatively small groups of patients.

3.12. The Subcommittee considered that there is variability in access to molecular and genetic diagnostic testing in New Zealand, which has the potential to result in inequalities of access to treatments and outcomes if medicines are targeted to patient populations and eligibility for funding is defined by mutational status.

3.13. The Subcommittee considered that, unlike other alterations, EGFR mutation testing for patients with NSCLC is routinely performed in New Zealand and there are targeted therapies funded for EGFR-positive disease. The Subcommittee noted that there is a higher incidence of EGFR mutation in south-east Asian patients (40%) and Pacific patients (24%) than in New Zealand European (18%) or Māori patients (10%) (McKeage et al. 2015. Technical report for the Heath Innovation Partnership of the Health Research Council of New Zealand and National Health Committee). The Subcommittee noted that 10% to 15% of patients with EGFR-positive NSCLC will develop resistance to EGFR targeted therapy.

3.14. The Subcommittee noted that two first-generation EGFR inhibitors, erlotinib and gefitinib, were funded as first-line treatments for EGFR mutant NSCLC but that second and third generation agents were currently unfunded. The Subcommittee noted that only one, third generation agent, osimertinib, is currently indicated for use in a second-line setting, and that this is the only unfunded EGFR-targeted agent for which a funding application has been received to date.

3.15. The Subcommittee noted that there was a rapid increase in the rate of EGFR mutation testing following the funding of the EGFR-inhibitor gefitinib in late 2012, but that the rate of testing plateaued in 2014 to 2015 at approximately 60% (Tin Tin et al. Cancer Epidemiol. 2018;57:24-32). The Subcommittee considered that these data indicate that clinicians appear to be using clinical characteristics to refine the populations being tested, and there may therefore not be complete uptake of any agent funded for a group defined by a mutational marker.

3.16. The Subcommittee considered that ALK genetic alteration testing for patients with NSCLC is not routinely performed in New Zealand and that there is currently no funded targeted therapy for ALK-positive disease. Members considered that ALK testing was available in some parts of the country and this testing was self-funded.

3.17. The Subcommittee noted that, while two ALK inhibitors (alectinib and crizotinib) were under consideration for funding and would be considered specifically at this meeting, there were a number of other ALK targeted agents with published data available (e.g. ceritinib, brigatinib and lorlatinib); however, the Subcommittee noted that no applications for these agents had been made to PHARMAC to date.

3.18. The Subcommittee noted that no applications for funding of agents for the treatment of advanced NSCLC for patients specifically with ROS1, BRAF or other genetic alterations had been received to date. Members noted that they would welcome submissions for the funding of agents in these settings.

3.19. The Subcommittee considered that the development of a number of new-generation targeted agents has increased the complexity of the treatment paradigm for lung cancer. The Subcommittee considered there remains significant uncertainty regarding the optimal use of these agents including whether they should be used as sequential therapies following earlier-generation agents or in first-line settings (Recondo et al. Nat Rev Clin Oncol. 2018;15:694-708).

3.20. The Subcommittee considered that the majority of research regarding the use of immunotherapies for lung cancer to date has been conducted in patients who do not express targetable mutations (eg EGFR-negative, ALK-negative). The Subcommittee considered that this group constitutes approximately 80% of individuals with NSCLC.

3.21. The Subcommittee considered that immunotherapies first demonstrated improved outcomes in second- or later-line therapy and have now been shown to provide benefit as first-line therapy either as monotherapy (where PD-L1 ≥50%) or in combination with chemotherapy. The Subcommittee considered that to date published evidence for the use of immune checkpoint inhibitors does not indicate there is a 'tail' of long-term survivors with advanced NSCLC.

3.22. The Subcommittee noted the results of a retrospective real-world analysis which reported that there was no difference in overall survival when immunotherapies were used as different lines of treatment (Khozin et al. Oncologist. 2019;24:648-56). The Subcommittee considered that this suggests a benefit may be observed regardless of where an immunotherapeutic agent is used within the treatment paradigm; and that current evidence shows a median overall survival gain of approximately three months regardless of the line of treatment (Doroshow et al. Clin Cancer Res. 2019;doi: 10.1158/1078-0432.CCR-18-1538).

3.23. The Subcommittee considered that the trial populations for studies investigating immunotherapy agents for NSCLC have often been defined or stratified by PD-L1 status, but that the definitions and thresholds used between trials vary.

3.24. The Subcommittee considered there is also significant variability in PD-L1 testing used in the different trials and in practice, including the specificity and sensitivity of different platforms, threshold definition and interpretation, and accessibility

throughout the country, as had been discussed and documented in records of previous CaTSoP meetings.

3.25. The Subcommittee considered that PD-L1 expression is not a straight forward biomarker. The Subcommittee considered that the commonly used thresholds for identifying PD-L1 positive patients are PD-L1 ≥50% and PD-L1 ≥1%. The Subcommittee considered that PD-L1 expression may indicate which patients could have a higher response rate to a certain agent or regimen, but that it is not a definitive marker of response.

3.26. The Subcommittee considered that, although subgroup analysis of this population has only been published in one trial to date, there appears to be an emerging signal that patients who are PD-L1 negative (around 30% to 40% of the NSCLC population) may not derive benefit from immune checkpoint inhibitor treatment.

3.27. The Subcommittee considered that the evidence base for the use of immune checkpoint inhibitors in an ALK/EGFR mutated population is very limited, as most of the trials investigating immune checkpoint inhibitors excluded these patients. The Subcommittee noted that where they were included, a benefit did not appear to be demonstrated in these patients.

3.28. The Subcommittee considered that based on currently available evidence, and in the absence of further data, it would be appropriate to exclude EGFR/ALK mutated populations from any funding for these agents. Members considered that it may also be appropriate to exclude PD-L1 negative (less than 1%) patients.

3.29. The Subcommittee noted that while the majority of currently available evidence for targeted and immunotherapeutic agents has been in non-squamous NSCLC populations, that there is also rapidly evolving data for patients with squamous NSCLC and SCLC.

3.30. The Subcommittee noted that ongoing research is investigating whether tumour mutational burden can be used to predict sensitivity to immunotherapy.

3.31. The Subcommittee considered that the subgroup of patients with lung cancer who have the highest health need are those with ALK-positive disease. The Subcommittee considered that this was a small patient population which could be reliably defined based on ALK rearrangement, have poor survival rates, a poor response to current funded treatments, and evidence suggests these patients would likely gain a good clinical effect from ALK-targeted agents.

3.32. The Subcommittee considered that, based on the totality of currently available data, PD-1/PD-L1 inhibitors (ie pembrolizumab, nivolumab, and atezolizumab) appear to provide the same or similar effect in the treatment of advanced NSCLC, and that additional clinical trial data due to be published in the near future would likely be helpful to inform further discussions regarding specific populations or combination regimens.

3.33. The Subcommittee considered that if one or more PD-1/PD-L1 inhibitors were to be funded in only a second line setting, that it would be reasonably likely that patients would seek to progress quickly from chemotherapy to an immune checkpoint inhibitor given the toxicities associated with chemotherapy. The Subcommittee considered that an adequate trial of chemotherapy was

considered to be two cycles; however, this would be difficult to include in any access criteria given the high level of interpretation and variation between clinicians and different centres as to which patients are contraindicated to chemotherapy. The Subcommittee considered that any funding in a second-line setting only could in practice amount to use in a first-line population.

3.34. The Subcommittee considered that, if a PD-1/PD-L1 inhibitor were to be funded as a first-line treatment for advanced NSCLC, pemetrexed would likely move to a solely second-line treatment for NSCLC and that changes to the Special Authority criteria for pemetrexed may be required to enable this.

3.35. The Subcommittee considered it would be appropriate to limit patients to a single line of treatment with PD-1/PD-L1 inhibitors which could be administered at any point in the treatment sequence for patients with EGFR wild-type or ALK-negative advanced NSCLC. The Subcommittee considered that, to date, there is a lack of evidence to support a positive recommendation for PD-1/PD-L1 inhibitors to for use in advanced NSCLC patients with EGFR-positive or ALK-positive disease.

3.36. The Subcommittee further considered that it would be appropriate to limit the total duration for a course of PD-1/PD-L1 inhibitor treatment for advanced NSCLC patients to a maximum of two years of continuous treatment. The Subcommittee considered that while it was expected there may be gaps in treatment due to adverse events, as with many oncology treatments, there was a lack of data to support retreatment following disease progression in immune checkpoint inhibitor pre-treated NSCLC patients, and that treatment should cease at signs of disease progression. Members considered that the appropriate duration of treatment for NSCLC patients should be re-evaluated when further data is available.

4. Atezolizumab with paclitaxel and carboplatin with or without bevacizumab for metastatic non-squamous non-small cell lung cancer (NSCLC)

Application

4.1. The Subcommittee reviewed an application from Roche Products (New Zealand) Ltd for atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, for the first-line treatment of adult patients with metastatic non-squamous non-small cell lung cancer (NSCLC).

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

Recommendation

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

4.4. The Subcommittee considered that, based on the totality of currently available data, PD-1/PD-L1 inhibitors appear to provide the same (or similar) effect in the treatment of advanced NSCLC, and that additional clinical trial data which is due

to be published in the near future would likely be helpful to inform further discussions regarding potential benefits of their use in specific populations or combination regimens.

Discussion

4.5. The Subcommittee noted the health need for patients with non-squamous NSCLC has been well documented in previous minutes for atezolizumab monotherapy as second-line treatment of advanced NSCLC (PTAC minutes August 2017; CaTSoP minutes August 2017) and was discussed during review of the lung cancer treatment landscape at this meeting.

4.6. The Subcommittee noted the supplier estimates 310 patients per year with metastatic non-squamous NSCLC may be suitable for the proposed treatment regimen. The Subcommittee considered it would be reasonable to assume there would likely be a similar number of patients as those who currently receive pemetrexed first-line therapy for NSCLC, however, there was potential for this to underestimate patient numbers as the advanced age of many patients would mean they are likely considered unsuitable for pemetrexed treatment.

4.7. The Subcommittee noted that atezolizumab has been investigated in a number of clinical trials including OAK (a randomised phase III trial of atezolizumab compared to docetaxel in locally-advanced or metastatic non-squamous NSCLC) and POPLAR (a randomised phase II trial of atezolizumab compared to docetaxel in advanced or metastatic NSCLC), which provide efficacy data for its use as a single agent in the second-line treatment of NSCLC.

4.8. The Subcommittee noted that the primary evidence for the use of atezolizumab in combination with the requested agents in a first-line NSCLC setting is from the IMpower150 trial; a phase III, randomised, double-blind clinical trial of atezolizumab in 1,202 patients with stage IV non-squamous NSCLC. The Subcommittee noted that IMpower150 has three treatment arms: atezolizumab with carboplatin and paclitaxel (ACP); atezolizumab with carboplatin, paclitaxel and bevacizumab (ABCP); and carboplatin, paclitaxel and bevacizumab (BCP). The Subcommittee considered the following evidence from the IMpower150 trial:

4.9. Primary and secondary analysis of progression-free survival (PFS) and interim analysis of overall survival (OS). Data cut-off September 2017 after a median follow-up of 15 months. Socinski et al. N Engl J Med. 2018: 24:2288-2301

4.10. Analysis of PFS in subgroups with data cut-off September 2017. Kowanetz et al. Cancer Res 2018;78(13 Suppl). Abstract nr CT076

4.11. Analysis of patient-reported outcomes Reck et al. J Clin Oncol. 2018.36(15 Suppl). Abstract nr 9047.

4.12. Analysis of OS in the intention-to-treat (ITT) population (incl. patients with EGFR or ALK mutations). Data cut-off of January 2018 after median follow-up of 19.6 months. Reck et al. Lancet Respir Med. 2019. DOI: 10.1016/S2213-2600(19)30084-0)

4.13. The Subcommittee noted median PFS was reported to be 8.3 months for patients in the ABCP arm compared to 6.8 months for the BCP arm (HR 0.62, 95% CI 0.52 to 0.74, *P*<0.0001) in the wild-type (WT) population which excluded patients with EGFR or ALK mutations (Socinski et al.). The Subcommittee noted

subgroup analyses reported a PFS benefit of ABCP compared to BCP in all patient subgroups including those with low PD-L1 expression, with EGFR or ALK mutations, and regardless of the presence or absence of liver metastases (Kowanetz et al.).

4.14. The Subcommittee noted the reported median OS in the ITT population of 19.8 months in the ABCP arm compared to 14.9 months in the BCP arm (HR 0.76, 95% CI 0.63 to 0.93), and a median OS in the WT population of 19.2 months in the ABCP arm compared to 14.7 months in the BCP arm (HR 0.78, 95% CI: 0.64 to 0.96, *P*=0.0164) (Reck et al.).

4.15. The Subcommittee noted that the IMpower150 trial analyses of OS in key subgroups showed a similar benefit of ABCP compared to BCP across all subgroups including those with low or negative PD-L1 expression, those with EGFR or ALK mutations and regardless of the presence or absence of liver metastases (Reck et al.). However, the Subcommittee noted that some long confidence intervals were reported. The Subcommittee considered that the OS analysis of ITT-WT appeared to indicate there could be a larger effect in the subgroup with high PD-L1 expression as had been seen in other immune checkpoint inhibitor NSCLC trials, although this was based on small patient numbers.

4.16. The Subcommittee noted that Reck et al. reported OS data for all three treatment arms in the ITT population with a median OS of 19.5 months for ACP compared to 14.9 months for BCP (HR 0.85, 95% CI 0.71 to 1.03), and median OS of 19.8 months for ABCP compared to 14.9 months for BCP (HR 0.76, 95% CI 0.63 to 0.93). The Subcommittee considered the IMpower150 trial data showed an advantage of ABCP compared to ACP and BCP but no clear advantage of ACP compared to BCP. Members considered that data from all three arms presented together rather than in pairs would have been beneficial.

4.17. The Subcommittee noted that Reck et al. reported that the median OS for the EGFR-positive patient subgroup was not evaluable for ABCP compared to 18.7 months for BCP (HR 0.61, 95% CI 0.29 to 1.28) and 21.4 months for ACP compared to 18.7 months for BCP (HR 0.93, 95% CI 0.51 to 1.68).

4.18. The Subcommittee noted subgroup analyses by age group (supplementary appendix Reck et al.) which reported a median OS of 16.6 months for ABCP compared to 14.1 months for BCP in patients aged 75 to 84 years (HR 0.94, 95% CI 0.50 to 1.76). The Subcommittee considered there appeared to be a lower level of benefit from the addition of atezolizumab or bevacizumab in this age group.

4.19. The Subcommittee noted Reck et al. reported treatment-related adverse events (AEs) in around 95% of patients in each of the three treatment arms; and that a larger proportion of patients had at least one serious AE in the ABCP arm (44%) than in the BCP arm (34%) or ACP arm (39%). The Subcommittee noted that a larger proportion of patients had AEs leading to treatment withdrawal in the ABCP arm (34%) than in the BCP arm (25%) or ACP arm (13%).

4.20. The Subcommittee noted that the supplementary appendix by Socinski et al. reported more treatment-related AEs with the ABCP regimen than with BCP, including febrile neutropenia (9.7% ABCP vs 5.8% BCP), haemoptysis (4.6% ABCP vs 2.0% BCP) and immune-related AEs, of which rash (28.8% ABCP vs

13.2% BCP), hepatitis (12.0% ABCP vs 7.4% BCP) and hypothyroidism (12.7% ABCP vs 7.4% BCP) were most common.

4.21. The Subcommittee considered that assessment of AEs required careful comparison against the AEs associated with currently used NSCLC treatment regimens due to the variation in toxicities from different agents. Members considered the AEs reported in the IMpower150 trial were substantial for palliative treatment regimens and would likely require additional resources in their management and monitoring.

4.22. The Subcommittee noted patient-reported outcomes data from IMpower150 (Kowanetz et al. Cancer Res 2018;78(13 Suppl). Abstract nr CT076) and that there appeared to fairly stable health-related quality of life (HRQOL) of patients in all three treatment arms. The Subcommittee considered there may be a small improvement in HRQOL during the maintenance cycles (after treatment cycle 6) except for neuropathy which had less improvement over time, and that lung cancer symptoms such as cough and dyspnoea improved across the course of treatment.

4.23. The Subcommittee noted that administration of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, requires sequential infusion of agents taking up to 5 or 6 hours (for ABCP) for each six induction treatment cycles, with subsequent maintenance infusions of one hour. The Subcommittee considered the increase in infusion time, as compared to current treatments which are 70 minutes for induction and 10 minutes for maintenance doses, was modest given the number and type of agents to be administered in these regimens but that this would represent an increase in infusion requirements.

4.24. The Subcommittee considered that treatment with atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab, may require more frequent imaging of patients than with current treatments, but considered that less frequent imaging may be appropriate for patients who are stable on treatment and that current practice is to monitor stable NSCLC patients with chest x-rays rather than CT scans.

4.25. Subcommittee noted that bevacizumab is not funded in New Zealand for use in the treatment of any type of cancer. The Subcommittee noted the evidence provided for bevacizumab is from two randomised clinical trials: a phase II/III trial of paclitaxel and carboplatin with or without bevacizumab in 842 patients with advanced, metastatic or recurrent NSCLC (Sandler et al. N Engl J Med 2006;355:2542-50) and a phase III clinical trial of cisplatin and gemcitabine with or without bevacizumab in 1,044 patients with non-squamous NSCLC (Reck et al.). The Subcommittee noted Sandler et al. reported a higher rate of grade 3 bleeding events with bevacizumab (4.4% bevacizumab arm compared to 0.7% paclitaxel-carboplatin alone) and a higher rate of death due to pulmonary haemorrhage in patients receiving bevacizumab (5 deaths with bevacizumab vs 0 paclitaxel-carboplatin alone). The Subcommittee considered that the evidence was unclear regarding what benefit the addition of bevacizumab provided this patient population.

4.26. The Subcommittee noted that other clinical trials investigating atezolizumab in NSCLC are currently in progress or completed, and that unpublished results have been presented for the IMpower132 trial which investigated atezolizumab with carboplatin or cisplatin and pemetrexed compared to carboplatin or cisplatin

and pemetrexed in patients with non-squamous NSCLC without EGFR or ALK genetic alterations. The Subcommittee considered the IMpower132 trial control arm of carboplatin or cisplatin and pemetrexed was the current standard first-line treatment for patients with non-squamous NSCLC in New Zealand. Members also noted that the results of the IMpower110 clinical trial (atezolizumab monotherapy compared with carboplatin or cisplatin, combined with pemetrexed or gemcitabine) would also be of interest particularly when considering squamous and non-squamous NSCLC populations.

4.27. The Subcommittee noted the IMpower132 trial analysis of PFS, safety and interim OS (data cut-off date May 2018) demonstrated a PFS benefit with addition of atezolizumab, reporting median PFS of 7.6 months in the atezolizumab arm compared to 5.2 months in the chemotherapy arm (HR 0.60, 95% CI: 0.49 to 0.72, *P*<0.0001) (Papadimitrakopoulou et al. 19th World Conference on Lung Cancer. 2018. Abstract nr OA05.07).

4.28. The Subcommittee noted that the interim OS analysis did not show a statistically significant benefit with median OS of 18.1 months for the atezolizumab arm compared to 13.6 months for the chemotherapy arm (HR 0.81, 95% CI: 0.64 to 1.03, *P*=0.0797) (Papadimitrakopoulou et al.). The Subcommittee considered the OS data is likely to have been influenced by cross-over of patients on the control arm who subsequently received immunotherapy treatment (37%). The Subcommittee noted the IMpower132 exploratory analysis results of PFS by PD-L1 expression status and considered that the effectiveness of atezolizumab potentially diminished from high to low PD-L1 expression. The Subcommittee noted that the final outcomes of the IMpower132 trial are not yet published but the analysis is anticipated in 2019. The Subcommittee considered that the final efficacy outcomes of the IMpower132 trial, once published, would provide a useful comparison with currently funded treatment of non-squamous NSCLC in New Zealand.

4.29. The Subcommittee noted data from the Keynote-189 trial, which investigated pemetrexed and platinum chemotherapy with or without pembrolizumab (a PD-1 checkpoint inhibitor) in first-line treatment of metastatic non-squamous NSCLC, was used in a cross-trial comparison which reported median OS of not reached in the pembrolizumab arm compared to 11.3 months in the chemotherapy arm in Keynote-189 (HR 0.49, 95% CI: 0.38 to 0.64, *P*<0.00001) (Ghandi et al. N Engl J Med. 2018:378;2078-92) compared to median OS of 18.1 months for the atezolizumab arm compared to 13.6 months for the chemotherapy arm in IMpower132 (HR 0.81, 95% CI: 0.64 to 1.03, *P*=0.0797) (Papadimitrakopoulou et al.). The Subcommittee considered that treatment crossover effect had likely influenced these OS results as patients had subsequently received immunotherapy after trial treatment.

4.30. The Subcommittee noted the efficacy and safety results of the IMpower130 trial, which investigates atezolizumab with carboplatin and nab-paclitaxel compared to carboplatin and nab-paclitaxel in chemotherapy-naïve patients with stage IV non-squamous NSCLC, were presented in 2018 (Cappuzzo et al. European Society for Medical Oncology Congress 2018. Abstract nr LBA53). The Subcommittee noted that nab-paclitaxel was not a currently funded treatment for patients in New Zealand.

4.31. The Subcommittee noted the IMpower130 trial results (data cut-off date March 2018) reported median PFS of 7.0 months in the atezolizumab arm compared to 5.5 months in the chemotherapy arm (HR 0.64, 95% CI:0.54 to 0.77, *P*<0.0001)

and median OS of 18.6 months in the atezolizumab arm compared to 13.9 months in the chemotherapy arm (HR 0.79, 95% CI: 0.64 to 0.98, *P*=0.033). The Subcommittee noted that 59% of the control arm patients crossed over to receive subsequent immunotherapy and considered that this would have diminished the reported OS benefit of atezolizumab. The Subcommittee noted the IMpower130 trial reported a benefit of atezolizumab in PD-L1 subgroups including the PD-L1 negative group. However, the Subcommittee noted that, for patient subgroups with EGFR or ALK genetic alterations, there was a lack of a clear PFS benefit (median PFS 7.0 months atezolizumab arm compared to 6.0 months chemotherapy arm, HR 0.75, 95% CI: 0.36 to 1.54) or OS benefit (median OS 14.4 months atezolizumab arm compared to 10.0 months chemotherapy arm, HR 0.98, 95% CI: 0.41 to 2.31).

4.32. The Subcommittee noted currently available data indicated there was a benefit of treatment with atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab across all subgroups in IMpower150 which was associated with a modest increase in toxicities. However, the Subcommittee considered that at this time the role of bevacizumab in this combination regimens remained unclear, and the potential benefit of an atezolizumab combination regimen compared to standard chemotherapy remained unclear (given the lack of published, comparable chemotherapy control arm data from the IMpower150 and IMpower132 trials).

4.33. The Subcommittee considered that while the benefit of atezolizumab in the specific combination treatment regimen was uncertain, based on the totality of currently available data for the use of PD-1/PD-L1 inhibitors in the treatment of advanced NSCLC, both first-line and second-line settings, immune checkpoint inhibitors appear to provide the same (or similar) effect in the treatment of advanced NSCLC.

4.34. The Subcommittee considered that, based on the evidence available and reviewed to date for the use of PD-1/PD-L1 inhibitors in the treatment of advanced NSCLC, there was an absence of strong evidence to suggest that there was a difference in the mechanism of action of these agents or that there would be any difference in the potential benefit from use of these agents as first-line treatments for advanced NSCLC.

4.35. The Subcommittee considered that additional data which is due to be published in the near future would further inform discussions regarding the potential benefits of the various agents, the appropriate combinations of chemotherapy regimens to use and their placement in the paradigm for specific histologically or biomarker defined populations.

5. Pembrolizumab for the first-line treatment of advanced NSCLC

Application

5.1. The Subcommittee noted that further advice was sought regarding the funding of pembrolizumab as a first-line treatment for advanced NSCLC both as monotherapy and in combination with chemotherapy.

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

Recommendation

5.3. The Subcommittee **recommended** that pembrolizumab be funded in a first-line setting for advanced NSCLC patients subject to the following access criteria:

Special Authority for Subsidy – PCT only
Initial application - (NSCLC first-line) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1. Patient has not received prior treatment with an immune checkpoint inhibitor for NSCLC; and
2. Either:
   - 2.1. All of the following:
     - 2.1.1. Patient has locally advanced or metastatic, unresectable, non-small cell lung cancer; and
     - 2.1.2. The patient has not had prior chemotherapy treatment for their disease; and
     - 2.1.3. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase; and
     - 2.1.4. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 50% as determined by a validated Dako-based diagnostic test; and
     - 2.1.5. Patient has an ECOG 0-1; and
     - 2.1.6. Pembrolizumab to be used as monotherapy at a maximum dose of 200 mg every 3 weeks (or equivalent) for a maximum of 12 weeks; and
     - 2.1.7. Baseline measurement of overall tumour burden is documented; or
   - 2.2. All of the following:
     - 2.2.1. Patient has metastatic, unresectable, non-small cell lung cancer; and
     - 2.2.2. The patient has not had prior treatment for their metastatic disease; and
     - 2.2.3. There is documentation confirming that the disease does not express activating mutations of EGFR or ALK tyrosine kinase; and
     - 2.2.4. Patient has an ECOG 0-1; and
     - 2.2.5. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks (or equivalent); and
     - 2.2.6. Pembrolizumab to be used in combination with platinum-pemetrexed or carboplatin-paclitaxel; and
     - 2.2.7. Baseline measurement of overall tumour burden is documented.

Renewal – (NSCLC first line) only from a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following:
1. Patient has received prior funded pembrolizumab treatment for NSCLC; and
2. Any of the following:
   - 2.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
   - 2.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
   - 2.3. Patient has stable disease according to RECIST criteria; and
3. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
4. No evidence of disease progression according to RECIST criteria; and
5. The treatment remains clinically appropriate and patient is benefitting from treatment; and
6. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks (or equivalent); and
7. Pembrolizumab to be discontinued at signs of disease progression.

5.4. The Subcommittee considered that depending on the sequence of funding decisions around NSCLC treatments, any access criteria for pembrolizumab may need to be amended to consider the wider treatment paradigm and lines of treatment available to NSCLC patients. The Subcommittee noted consideration of the wider lung cancer treatment paradigm had been reviewed as a separate agenda item at this meeting.

5.5. The Subcommittee **recommended** that if pembrolizumab in combination with chemotherapy were funded, that the Special Authority criteria for pemetrexed for NSCLC be amended to allow concomitant use with pembrolizumab as follows (additions in bold):

Initial application - (NSCLC) only from relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:

Both:
1. Patient has locally advanced or metastatic non-squamous NSCLC; and
2. Either:
   2.1. Both:
      2.1.1. Patient has chemotherapy naïve disease; and
      2.1.2. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days in combination with cisplatin or carboplatin for a maximum of 6 cycles; or
   2.2. All of the following:
      2.2.1. Patient has had first-line treatment with platinum based chemotherapy **or immune checkpoint inhibitor**; and
      2.2.2. Patient has not received prior funded treatment with pemetrexed; and
      2.2.3. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days for a maximum of 6 cycles**.**

Renewal – (NSCLC) only from relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
All of the following:
1. No evidence of disease progression; and
2. Treatment remains clinically appropriate and patient is benefitting from treatment; and
3. Pemetrexed is to be administered at a dose of 500mg/m2 every 21 days for a maximum of 6 cycles.

Discussion

5.6. The Subcommittee noted that the funding of pembrolizumab as a first-line treatment for advanced NSCLC has been considered by CaTSoP and by PTAC on a number of occasions.

5.7. The Subcommittee noted that at its meeting in November 2018, PTAC considered the funding of pembrolizumab in combination with chemotherapy as a first-line treatment for metastatic NSCLC and recommended listing with a medium priority. The Subcommittee noted that PTAC had also recommended that advice be sought from CaTSoP regarding the lung cancer treatment landscape, potential placement of pembrolizumab combination regimens in the treatment paradigm, appropriate Special Authority criteria, and further consideration of use of PD-L1 expression as a biomarker.

5.8. The Subcommittee noted that, at its February 2019 meeting, PTAC further considered the funding of pembrolizumab as monotherapy as a first-line treatment for advanced NSCLC tumours with PD-L1 expression ≥ 50% in a first-line setting for EGFR wildtype patients. The Subcommittee noted that PTAC had recommended pembrolizumab be funded with medium priority in this setting but that advice be sought from CaTSoP regarding the New Zealand lung cancer treatment landscape and various aspects related to interpretation of the data

5.9. The Subcommittee noted that the specific advice PTAC had requested included the role of pemetrexed use on the reported survival results in the relevant clinical trials; further information regarding interpretation of the clinical significance of HRQoL and OS data in the context of lung cancer patients; consideration of the relative benefit of monotherapy vs chemotherapy particularly in different patient populations (PD-L1 status, histology or other); and appropriate access criteria for pembrolizumab in the treatment of advanced NSCLC.

Pembrolizumab as monotherapy

5.10. The Subcommittee noted that the pivotal evidence for the use of pembrolizumab monotherapy as a first-line treatment for advanced NSCLC comes from KEYNOTE-024 (Reck et al. N Engl J Med. 2016;375:1823-33) and additional

evidence had been provided including updated longer-term survival analysis for KEYNOTE-024 published online in the Journal of Clinical Oncology (JCO) in January 2019 (Reck et al. J Clin Oncol. 2019;37:537-46), the clinical study report (CSR) for overall survival (OS) (CSR code P024V02MK3475, database locked 18 August 2017), and published HRQoL results from KEYNOTE-024 (Brahmer et al. Lancet Oncol. 2017;18:1600-09).

5.11. The Subcommittee noted the update to survival from KEYNOTE-024 published by Reck et al. 2019; after a median follow-up of 25.2 months, the median OS was 30.0 months (95% CI, 18.3 months to not reached) with pembrolizumab and 14.2 months (95% CI, 9.8 to 19.0 months) with chemotherapy (hazard ratio, 0.63; 95% CI, 0.47 to 0.86). The Subcommittee noted that when adjusted for crossover using the two-stage method, the hazard ratio for OS for pembrolizumab versus chemotherapy was 0.49 (95% CI, 0.34 to 0.69).

5.12. The Subcommittee noted that 65% of patients who progressed on the chemotherapy arm crossed over to receive pembrolizumab. The Subcommittee considered this most likely means that, while there is an element of uncertainty regarding the exact magnitude of survival benefit with pembrolizumab, the reported hazard ratio for OS are likely underestimated. However, members considered that trial data often provides improved outcomes compared with that observed in a real world setting where patients with poorer performance status and comorbidities are treated. The Subcommittee considered that current data is highly censored but does not appear to indicate a 'tail' of long-term responders.

5.13. The Subcommittee noted that overall treatment related-toxicity remained in keeping with previously published adverse event profiles for pembrolizumab.

Role of pemetrexed

5.14. The Subcommittee noted that PTAC had requested advice regarding the role of pemetrexed use on the reported survival results in the relevant clinical trials; and noted that pemetrexed is the standard treatment for non-squamous histologies.

5.15. The Subcommittee considered that the chemotherapy arm in KEYNOTE-024 outperformed historical norms for survival of patients treated with platinum/pemetrexed chemotherapy where median OS in a PDL1 agnostic population is approximately 12 months (AVAPERL) compared with 14 months in KEYNOTE-024.

5.16. The Subcommittee considered that while some studies of pemetrexed (PARAMOUNT, POINTBREAK) report a median OS of approximately 16 months, these studies excluded the around one third of patients who had progressed on induction chemotherapy and so analyse only those who moved to maintenance treatment.

5.17. The Subcommittee noted that in the control arm of KEYNOTE-024 the 27 squamous patients received platinum/gemcitabine (22) or platinum/taxol (5), and the 123 non-squamous received platinum/pemetrexed (122) or platinum/gemcitabine (9) or platinum/taxol (12). The Subcommittee considered that platinum/taxol and platinum/pemetrexed chemotherapy are therapeutically equivalent in outcome, with maintenance pemetrexed providing approximately two months of OS gain. The Subcommittee considered that the chemotherapy regimens would not have influenced any differences in trial outcomes.

5.18. The Subcommittee considered that the control arm from KEYNOTE-189 appeared to be the most appropriate comparator for control arm performance, where a similar 12-month survival not adjusted for cross-over was reported.

5.19. The Subcommittee considered that while the data were difficult to interpret, there was no evidence that pemetrexed changed the response in one arm and not the other. The Subcommittee considered that it was also unlikely that the results were influenced by any difference in chemotherapy regimen received by different histologies or additional best supportive care received by patients on trial.

Clinical significance of HRQoL and OS

5.20. The Subcommittee noted a QLQ-C30 baseline mean (SD) for pembrolizumab of 62.2 (22.3) and for chemotherapy of 59.9 (22.3) improved to 71.0 (21.1) and 63.7 (20.6) respectively, with an estimated difference of 7.8 (95% CI 2.9 to 12.8) between treatments after 15 weeks; and that the mean QLQ-C30 was the same in the two groups after 33 weeks. The Subcommittee noted that QLQ-C30 measured time to deterioration in composite endpoint of cough, chest pain, dyspnoea and favoured pembrolizumab at 15 weeks but that this does not appear to be sustained.

5.21. The Subcommittee considered that in the context of median PFS in the pembrolizumab arm of 10.3 months (41 weeks) the quality of life results reported at the 33-week timepoint are likely influenced by disease progression in some patients in the pembrolizumab arm. Members considered there may also be an effect from improvements for patients in the chemotherapy arm who crossed over at week 24.

Pembrolizumab as combination therapy

5.22. The Subcommittee noted that the pivotal evidence for the use of pembrolizumab in combination with chemotherapy as a first-line treatment for advanced NSCLC comes from KEYNOTE-189 in non-squamous histology and KEYNOTE-407 in squamous histology.

5.23. The Subcommittee noted KEYNOTE-189 is a randomised double-blind phase 3 trial of pembrolizumab (200 mg Q3W up to a total of 35 cycles) or saline placebo plus platinum (Q3W for 4 cycles) and pemetrexed (Q3W) in 616 patients with metastatic non-squamous NSCLC without EGFR or ALK mutations who had received no previous treatment for metastatic disease (Gandhi et al. NEJM. 2018; 378:2078-2092).

5.24. The Subcommittee noted that after a median follow-up of 10.5 months, the median OS was not reached in the pembrolizumab arm and was 11.3 months (95% CI, 8.7 to 15.1) in the control arm (HR for death, 0.49; 95% CI, 0.38 to 0.64; P<0.001).

5.25. The Subcommittee noted that 41% of patients in the control arm who had verified disease progression crossed-over to pembrolizumab monotherapy.

5.26. The Subcommittee noted that KEYNOTE-407 is a randomized double-blind phase 3 trial of carboplatin-paclitaxel/nab paclitaxel with or without pembrolizumab (200mg up to 35 cycles) in 559 patients with untreated metastatic (stage IV) squamous NSCLC (Paz-Ares et al. N Engl J Med 2018;379:2040-51).

5.27. The Subcommittee noted that after a median follow-up of 7.8 months (range 0.1-19.1), the median OS was 15.9 months in the pembrolizumab arm and 11.3 months in the control arm (HR 0.64; 95% CI, 0.49 to 0.85; P<0.001); and the median PFS was 6.4 months in the pembrolizumab arm and 4.8 months in the control arm (HR 0.56; 95% CI, 0.45 to 0.70; P<0.001).

5.28. The Subcommittee noted that 31% of patients in the control arm who had centrally confirmed radiologic disease progression crossed-over to pembrolizumab monotherapy.

5.29. The Subcommittee noted that participants in both studies had good performance status (ECOG 0-1) and that responses were observed irrespective of PD-L1 status and no new safety signals are observed in both trials.

General comments

5.30. The Subcommittee considered that there appeared to be no published head-to-head clinical trials comparing pembrolizumab as monotherapy with the chemotherapy combination regimens. The Subcommittee noted that an indirect comparison had been provided (Dougherty et al.) however this was an unpublished abstract and so considered to be low quality evidence.

5.31. The Subcommittee considered that there was currently very limited and low quality comparative evidence on which to guide decisions about the relative benefits of pembrolizumab as monotherapy or use in combination with chemotherapy in the treatment of first-line advanced NSCLC. The Subcommittee considered that these treatment regimens appear to provide the same or similar clinical effect in the various advanced NSCLC populations; however, noted that current evidence for use of monotherapy is confined to patients whose tumours express PD-L1 at 50% or greater.

5.32. The Subcommittee considered that both health-related quality of life and overall survival results reported for pembrolizumab were clinically meaningful for patients with advanced NSCLC.

5.33. The Subcommittee disagreed with PTAC's February 2019 medium priority recommendation for funding of pembrolizumab as monotherapy in a first-line setting for locally advanced or metastatic NSCLC. The Subcommittee recommended that pembrolizumab as monotherapy in a first-line setting for locally advanced or metastatic NSCLC be funded with high priority based on the likely clinical benefit, quality of evidence, reduced toxicity and improved quality of life but noting the significant cost of pembrolizumab at pricing currently being sought by the supplier.

5.34. The Subcommittee considered that based on currently available evidence the population that would benefit most from treatment with pembrolizumab as monotherapy in a first-line setting was NSCLC patients whose tumours express PD-L1 at a level of 50% or greater, with ECOG 0-1, without EGFR or ALK mutations for non-squamous, without pneumonitis requiring the use of steroid, without autoimmune disease and no symptomatic brain metastases.

5.35. The Subcommittee considered that while current trial evidence was for use of pembrolizumab as monotherapy in the PD-L1 50% or greater population, there remained questions about the prognostic and predictive value of PD-L1 testing as discussed by CaTSoP when previously considering the funding of

pembrolizumab for advanced NSCLC. The Subcommittee considered that given the costs and issues associated with PD-L1 testing that there was likely only value in undertaking PD-L1 testing if treatment eligibility was dependant on the result.

5.36. The Subcommittee agreed with PTAC's November 2018 recommendation that pembrolizumab in combination with chemotherapy in a first-line setting for metastatic NSCLC be funded with medium priority given the duration of follow-up in currently published evidence was shorter than for use as a monotherapy.

5.37. The Subcommittee considered that based on currently available evidence the population that would benefit most from treatment with pembrolizumab in combination with chemotherapy in a first-line setting was advanced NSCLC patients, agnostic of PD-L1 status, with ECOG 0-1, without EGFR or ALK mutations, without pneumonitis requiring the use of steroid, without autoimmune disease and no symptomatic brain metastases.

5.38. The Subcommittee considered while data indicates patients may have higher response rates with higher PD-L1 expression thresholds, there is also data which shows that patients with lower levels of PD-L1 expression can respond to immune checkpoint inhibitors. The Subcommittee further considered that there is a fairly consistent signal that patients who are PD-L1 negative (around 30% to 40% of the NSCLC population) do not derive benefit from immune checkpoint inhibitor treatment, although subgroup analysis of this population has only been published in one trial to date. However, the Subcommittee considered that all NSCLC patients should be able to access immune checkpoint inhibitor treatment and, although not a consensus, funding should not exclude patients with PD-L1 expression of less than 1%.

5.39. The Subcommittee considered that if pembrolizumab, or another PD-1 or PD-L1 inhibitor, were to be funded in both a first- and second-line setting it would be appropriate to limit patients to a single line of treatment.

5.40. The Subcommittee further considered that it would be appropriate to limit the total duration for a course of pembrolizumab treatment for advanced NSCLC patients to a maximum of two years of continuous treatment. The Subcommittee considered that while it was expected there may be gaps in treatment due to adverse events as with many oncology treatments, there was a lack of data to support retreatment following disease progression in immune checkpoint inhibitor pre-treated patients and that treatment should cease at signs of disease progression.

5.41. The Subcommittee noted that alternative pembrolizumab dose regimens were currently under consideration by Medsafe, including a six-weekly administration regimen, and that this could provide flexibility for administration and infusion requirements. The Subcommittee considered that analysis should consider whether these alternative regimens would result in increased milligrams dispensed by comparison to the 200mg Q3W regimen.

5.42. The Subcommittee considered were pembrolizumab in combination with chemotherapy funded, pemetrexed would remain a first-line treatment and it would be inappropriate for patients to receive a second line of pemetrexed treatment.

6. Alectinib for the first-line treatment of anaplastic lymphoma kinase (ALK)-positive locally advanced or metastatic non-small cell lung cancer (NSCLC)

Application

6.1. The Subcommittee reviewed a funding application from Roche Products (New Zealand) Ltd for alectinib for the first-line treatment of anaplastic-lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC).

6.2. The Subcommittee also reviewed a clinician application and letter of support for alectinib for the first-line treatment of ALK-positive advanced NSCLC, and a submission from a member of the public for alectinib for the second- and later-line treatment of ALK-positive advanced NSCLC.

6.3. The Subcommittee also reconsidered a supplier application for crizotinib for the treatment of ALK-positive advanced NSCLC in light of the publication of overall survival data from the PROFILE 1014 trial.

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

Recommendation

6.5. The Subcommittee **recommended** that alectinib be funded with **high** priority for the treatment of anaplastic-lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC), subject to the following Special Authority criteria:

> Initial application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced, or metastatic, unresectable, non-small cell lung cancer; and
> 2. There is documentation confirming that the patient has an ALK tyrosine kinase gene rearrangement using an appropriate ALK test; and
> 3. Patient has an ECOG performance score of 0-2.
>
> Renewal application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. No evidence of progressive disease according to RECIST criteria; and
> 2. The patient is benefitting from and tolerating treatment.

6.6. The Subcommittee **recommended** that crizotinib be funded with a **medium** priority for the treatment of ALK-positive advanced NSCLC subject to the following Special Authority criteria:

> Initial application only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has locally advanced, or metastatic, unresectable, non-small cell lung cancer; and
> 2. There is documentation confirming that the patient has an ALK tyrosine kinase gene rearrangement using an appropriate ALK test; and
> 3. Patient has an ECOG performance score of 0-2.
>
> Renewal only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:

1. No evidence of progressive disease according to RECIST criteria; and
2. The patient is benefitting from and tolerating treatment

Discussion

6.7. The Subcommittee considered that NSCLC accounts for 75% of all lung cancers and that, while the exact frequency of ALK mutation in a New Zealand setting is uncertain, it is reasonable to assume that approximately 5% of individuals with NSCLC have a rearrangement of the ALK gene (reported range 2% to 8%).

6.8. The Subcommittee noted that the majority of ALK-positive NSCLCs have non-squamous histology and do not harbour an epidermal growth factor receptor (EGFR) mutation.

6.9. The Subcommittee noted that ALK-positive NSCLC is associated with a history of never or light smoking.

6.10. The Subcommittee noted that patients with ALK-positive NSCLC are more likely to present with advanced disease, more likely to develop central nervous system metastases, and have a poorer prognosis with conventional chemotherapy than patients with NSCLC associated with other oncogenic drivers.

6.11. The Subcommittee noted that approximately 50% of patients with lung cancer have locally advanced or metastatic disease at diagnosis that is currently not curable with surgery or radiotherapy.

6.12. The Subcommittee noted that the standard first-line treatment for advanced NSCLC for patients who do not have an EGFR mutation in NZ is platinum-based chemotherapy in combination with pemetrexed (non-squamous) or gemcitabine or paclitaxel (squamous). The Subcommittee considered that patients who progress on platinum-based chemotherapy and went on to a further treatment would likely receive docetaxel.

6.13. The Subcommittee considered that between 40 and 70 patients with ALK-positive advanced NSCLC would be eligible for ALK-targeted treatment each year in New Zealand.

6.14. The Subcommittee noted that crizotinib and alectinib are first- and second-generation ALK inhibitors, respectively. The Subcommittee noted that both agents are Medsafe registered for the treatment of ALK-positive advanced NSCLC, and that crizotinib is also Medsafe registered for ROS1-positive NSCLC.

Alectinib

6.15. The Subcommittee noted that PTAC had previously considered the funding of alectinib for the first-line treatment of ALK-positive NSCLC in August 2018, and recommended that alectinib be funded with medium priority.

6.16. The Subcommittee reviewed the results of the ALEX trial which investigated the efficacy and safety of first-line alectinib compared with crizotinib for the treatment of ALK-positive advanced NSCLC (Peters et al. N Engl J Med. 2017;377:829-838; Camidge et al. 2018 ASCO Annual meeting. Abstract no. 9043). The Subcommittee noted that at the time of the updated analysis presented at ASCO 2018, the median progression-free survival (PFS) was 34.8 months in the alectinib arm compared with 10.9 months in the crizotinib arm. The Subcommittee noted that the OS analysis was still immature at this data cut.

6.17. The Subcommittee noted that at the time of the updated analysis, the median PFS in patients with CNS metastases was 27.7 months in the alectinib arm compared with 7.4 months in the crizotinib arm.

6.18. The Subcommittee noted that while crossover was not permitted in the ALEX trial, that some patients received subsequent ALK inhibitors after exiting the trial.

6.19. The Subcommittee noted that there appear to be no trials directly comparing the efficacy of alectinib and chemotherapy for the first-line treatment for ALK-positive NSCLC and considered that a trial of this type would be unlikely to be undertaken given the widespread international use of ALK inhibitors in this population. The Subcommittee noted the indirect comparison provided by the supplier of alectinib.

6.20. The Subcommittee noted a retrospective real-world analysis of 110 patients with advanced ALK-positive NSCLC treated with ALK inhibitors at the University of Colorado Cancer Center from 2009 through 2017 (Pacheco et al. J Thorac Oncol. 2019;14:691-700). The Subcommittee noted that the median OS for patients with ALK-positive NSCLC in this analysis was 81 months; the authors compared this with a median OS of 9 months for molecularly unselected patients from a separate analysis (HR 0.19; 95% CI 0.14 to 0.26; *P*<0.0001). The Subcommittee noted that there was no difference in OS between patients who received crizotinib in the first-line and those who received a non-ALK inhibitor before crizotinib (median OS 86 months vs 79 months; *P*=0.653).

6.21. The Subcommittee considered that there was good evidence that alectinib provides a significant benefit over platinum chemotherapy for the treatment of advanced ALK-positive NSCLC and noted the high health need of this patient population.

Crizotinib

6.22. The Subcommittee noted that PTAC had previously considered crizotinib for the first- and second-line treatment of ALK-positive advanced NSCLC in November 2015, August 2016, and August 2018, and had recommended that crizotinib be declined at each of these meetings due to concerns about trial design and the poor cost-effectiveness at the proposed price.

6.23. The Subcommittee noted that CaTSoP had previously considered crizotinib for the treatment of ALK-positive advanced NSCLC in May 2016, and had recommended that crizotinib be funded as a first- and second-line treatment with a low priority subject to Special Authority criteria. The Subcommittee noted that CaTSoP had previously emphasized the high health need of the population.

6.24. The Subcommittee noted that, since its previous consideration of crizotinib, the final overall survival (OS) results from the PROFILE 1014 had been published (Soloman et al. J Clin Oncol. 2018;36:2251-8). The Subcommittee noted that at a median follow-up of 46 months, the median OS was not reached in the crizotinib arm compared with 47.5 months in the chemotherapy arm (HR 0.760; 95% CI 0.548 to 1.053; two-sided *P*=0.0978).

6.25. The Subcommittee noted that in PROFILE 1014, 53.5% of patients in the crizotinib arm and 86.5% of patients in the chemotherapy arm received at least one subsequent systemic treatment, which included use of ALK inhibitors. The Subcommittee noted that when OS was adjusted for crossover the median OS

was 59.8 months in the crizotinib arm compared with 19.2 months in the chemotherapy arm (HR 0.346; 95% bootstrap CI, 0.081 to 0.718).

6.26. The Subcommittee noted that in the analysis of the impact of post-study treatment in PROFILE 1014, the longest OS was observed in crizotinib-treated patients who received a subsequent ALK inhibitor (not reached), and that the shortest OS was observed in chemotherapy-treated patients who received non-ALK inhibitor follow-up therapy (12.1 months).

6.27. The Subcommittee considered that the final OS data and the crossover analysis from the PRIOFILE 1014 adequately addressed their previous concerns regarding the short follow-up and confounding effect of subsequent treatments. The Subcommittee disagreed with PTAC's August 2018 recommendation that this agent should be declined and considered that in light of the additional data for use of this agent and ALK inhibitors in this population that it would be appropriate to increase the previous priority rating for crizotinib to medium.

General Comments

6.28. The Committee considered that ALK testing in New Zealand appears to be variable around the country and largely self-funded by patients. The Subcommittee considered that further information regarding ALK testing and its regional availability would be useful and that both a robust test and appropriate equitable access to testing would be needed were an ALK inhibitor to be funded.

6.29. The Subcommittee considered that if an ALK-inhibitor was funded, testing for ALK-rearrangement would need to be conducted at the time of initial diagnosis and in conjunction with EGFR testing, as there is limited tissue available for biopsy in these patients, and repeat biopsy should be avoided if possible.

6.30. The Subcommittee considered that if an ALK-inhibitor was funded, then it should be funded for individuals with ALK positive NSCLC with both squamous and non-squamous histologies. However, members noted that as patients with squamous NSCLC are not routinely tested for ALK rearrangements at this time, that the funding of an ALK-inhibitor may result in a significant increase on the demand for genetic testing.

6.31. The Subcommittee considered that the currently available evidence indicates that there is a class effect with the ALK inhibitors, but that the second generation alectinib has improved CNS activity as compared with the first generation crizotinib. Members considered that the evidence suggested alectinib may have activity in ALK mutations that crizotinib does not target. The Subcommittee considered that for these reasons alectinib should be funded with a higher priority than crizotinib.

6.32. The Subcommittee considered that there is evidence demonstrating that ALK inhibitors provide benefit in a second-line population after receiving chemotherapy or alternative ALK inhibitors. The Subcommittee therefore considered that the funding of alectinib or crizotinib should not be restricted to first-line use.

6.33. The Subcommittee considered that, although it had not considered the evidence for its use in this setting to date, crizotinib may be more appropriately targeted to patients with ROS-1 rearrangements and would welcome a funding application for the use of crizotinib for the treatment of ROS-1–positive advanced NSCLC.

7. Immune Checkpoint Inhibitors for Locally Advanced or Metastatic Urothelial Carcinoma

Application

7.1. The Subcommittee reviewed applications from Merck Sharp & Dohme NZ Limited for pembrolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who are not eligible for cisplatin-containing therapy (first-line treatment) and for patients after failure of a platinum-containing chemotherapy regimen (second-line treatment).

7.2. The Subcommittee reviewed a funding application from Roche Products NZ for atezolizumab for the treatment of patients with locally advanced or metastatic UC following progression on platinum-containing chemotherapy (second-line treatment).

7.3. The Subcommittee also noted a letter, dated 11 February 2019, drafted by Merck Sharpe & Dohme NZ Limited (MSD) the supplier of pembrolizumab which outlines the discussion at a facilitated meeting attended by MSD staff, three medical oncologists and 3 urologists who were invited to discuss the record of the May 2018 PTAC regarding pembrolizumab as a second-line treatment for UC. The Subcommittee noted the letter had been reviewed and confirmed by the six clinicians.

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

Recommendation

7.5. The Subcommittee **recommended** pembrolizumab for the first-line treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing therapy be declined based on the low strength and quality of currently available evidence.

7.6. The Subcommittee **recommended** pembrolizumab be funded with medium priority for the second-line treatment of locally advanced or metastatic UC after failure of a platinum-containing chemotherapy regimen.

7.7. The Subcommittee **recommended** that atezolizumab be listed with low priority for the second-line treatment of locally advanced or metastatic UC following progression on platinum-containing chemotherapy.

7.8. The Subcommittee **recommended** that immune checkpoint inhibitors for the second-line treatment of locally advanced or metastatic UC be funded subject to the following Special Authority criteria:

> Special Authority for Subsidy – PCT only
> Initial - only from a medical oncologist or medical practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has inoperable locally advanced (T4) or metastatic urothelial carcinoma; and
> 2. Patient has an ECOG performance status of 0-2; and
> 3. Patient has documented disease progression following treatment with platinum-containing chemotherapy; and

4. [Treatment] to be used as monotherapy at a maximum dose of [dose regimen] for a maximum of 12 weeks; and
5. Baseline measurement of overall tumour burden is documented according to RECIST version 1.1.

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

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

Discussion

7.9. The Subcommittee noted that in May 2018 PTAC considered the applications for pembrolizumab as first and second-line and atezolizumab as a second-line treatment of locally-advanced or metastatic urothelial carcinoma (UC). The Subcommittee noted that PTAC had recommended that pembrolizumab in the first-line setting be declined based on the poor strength and quality of currently available evidence; and recommended funding with low priority for both pembrolizumab and atezolizumab in the second-line setting.

7.10. The Subcommittee noted that in May 2018 PTAC had also recommended the applications be referred to CaTSoP for advice on appropriate access criteria, population size, current UC patient management and further consideration of a class effect.

7.11. The Subcommittee noted that the health need of patients with locally-advanced or metastatic UC has been described in the PTAC minutes from the May 2018 meeting. The Subcommittee noted that 75% of UC is non-muscle invasive, and that 90% of patients diagnosed with UC are greater than 55 years of age and that the average age at presentation is about 70 years.

7.12. The Subcommittee noted that patients with UC generally present with comorbidities which, combined with older age, makes some treatments unsuitable due to potential toxicities. The Subcommittee considered that around half of UC patients with advanced disease would be unsuitable for chemotherapy due to toxicity concerns. The Subcommittee considered that patients unsuitable for platinum-based chemotherapy would be offered non-platinum combination therapy, or non-platinum monotherapy.

7.13. The Subcommittee considered that, in the first-line setting, approximately 70 patients per year with advanced disease would receive first-line platinum-based doublet chemotherapy and that perhaps 50 of these patients would be eligible for second-line treatment.

7.14. The Subcommittee noted that carboplatin was often preferred to cisplatin due to the better toxicity profile The Subcommittee considered that in some centres up to 80% of UC patients receive carboplatin (instead of cisplatin), but that this varies between centres due to differences in criteria for use of cisplatin between institutions (eg creatinine clearance thresholds).

7.15. The Subcommittee considered that if cisplatin was contraindicated, carboplatin was a valid treatment alternative recognising the trade-offs of survival benefit versus toxicity particularly in elderly patients (Lindardou et al. Urology. 2004;64:479-84). The Subcommittee noted that median overall survival (OS) with first-line cisplatin-based therapy for patients with metastatic UC is 12 to 15 months, or about 9 months with first-line carboplatin-based therapy. The Subcommittee considered that in the second-line setting median OS was around 7 months.

7.16. The Subcommittee noted response rates of about 50% with platinum treatment in patients with UC however, durable responses only occur in about 10% to 20% of these patients.

7.17. The Subcommittee noted that the immune checkpoint inhibitors atezolizumab (targeting programmed death ligand-1, PD-L1) and pembrolizumab (targeting programmed death-1, PD-1) have been described in the May 2018 PTAC minutes.

Pembrolizumab first-line treatment

7.18. The Committee noted that the key clinical evidence for pembrolizumab as first-line therapy for cisplatin-ineligible patients with UC comes from the single-arm, non-randomised, phase 2 KEYNOTE-052 trial of 370 patients with locally advanced and unresectable or metastatic UC (Balar et al. Lancet Oncol. 2017;18:1483-92). The Subcommittee noted as this was a single-arm trial it did not compare pembrolizumab to carboplatin-based therapy which is the currently funded treatment in New Zealand. The Subcommittee noted that patients were stratified according to PD-L1 expression.

7.19. The Subcommittee noted the overall response rates in the KEYNOTE-052 trial were as described in the May 2018 PTAC minutes. The Subcommittee noted that it did not appear that any new data from the KEYNOTE-052 trial had been published since PTAC's review.

7.20. The Subcommittee agreed with PTAC's May 2018 view that there was currently limited weak evidence of poor-to moderate quality, and considered that currently available evidence was insufficient to support a positive recommendation.

7.21. The Subcommittee noted that the open label phase 2 IMvigor 210 trial of atezolizumab included two cohorts – previously treated and cisplatin ineligible treatment naïve; and that of the 119 previously untreated patients the objective response rate was 23% (95% CI 16–31), median progression-free survival was 2·7 months, and median overall survival was 15·9 months, with responses occurring across all PD-L1 subgroups.

7.22. The Subcommittee considered that based on currently available evidence it was unclear what benefit immune checkpoint inhibitors provided over carboplatin based therapy in a first-line advanced UC setting. However, data from the ongoing phase 3 IMvigor130 (which includes three arms atezolizumab/platinum chemo versus atezolizumab alone versus chemotherapy alone) and open-label, phase 3 KEYNOTE-361 (NCT02853305)(which also includes three arms pembrolizumab vs pembrolizumab/cisplatin chemotherapy vs cisplatin chemotherapy alone) may help to inform the role of immune checkpoint inhibitors for the first-line treatment of advanced UC. Although, it was noted that changes

in protocol meant that results would likely only be for patients with high PD-L1 expression.

Pembrolizumab second-line treatment

7.23. The Subcommittee noted that the primary evidence for the use of pembrolizumab in the treatment of second-line advanced UC comes from the randomised, open-label, phase 3 KEYNOTE-045 trial which investigated pembrolizumab 200 mg or investigator's choice of chemotherapy in 542 patients with advanced UC that had recurred or progressed after platinum-based chemotherapy, and noted the following publications:

- Bellmunt et al. N Engl J Med. 2017;376:1015-26
- Vaughn DJ, et al. J Clin Oncol. 2017;5 (suppl) Abstract Nr. 851PD
- Bellmunt J, et al. J Clin Oncol. 2018;36 (suppl) Abstract Nr. 410
- Vaughn et al. J Clin Oncol. 2018;36;1579-87

7.24. The Subcommittee noted that the results of the KEYNOTE-045 trial were as described in the May 2018 PTAC minutes, and that at a median follow-up of 14.1 months, the median OS was 10.3 months in the pembrolizumab arm compared with 7.4 months in the chemotherapy arm (HR for death 0.73; 95% CI 0.59-0.91; P=0.002).

7.25. The Subcommittee noted that the trial measured PD-L1 expression for all patients (but did not specify a level of PD-L1 expression for eligibility) and that higher response rates appeared to be in patients with a PD-L1 expression of 1% or greater.

7.26. The Subcommittee noted that a large proportion of KEYNOTE-045 patients on pembrolizumab had ongoing treatment responses at the time of data cut-off for the primary analysis in 2016 (72% of patients with responses on pembrolizumab compared to 35% with chemotherapy). The Subcommittee considered that for some UC patients it appeared there could be long term durable responses.

7.27. The Subcommittee noted that the frequency of adverse events (AEs) was lower with pembrolizumab (61%) compared to chemotherapy (90%), and that there were no pembrolizumab-related treatment discontinuations due to immune-related AEs in the KEYNOTE-045 trial.

7.28. The Subcommittee noted the KEYNOTE-045 trial reported median time to deterioration in global health status of 3.5 months with pembrolizumab compared to 2.3 months with chemotherapy. The Subcommittee considered that there is a quality of life (QoL) benefit with pembrolizumab compared to chemotherapy.

Atezolizumab second-line treatment

7.29. The Committee noted that the primary evidence for the use of atezolizumab in the second-line treatment of advanced UC comes from the randomised, open-label, phase 3 IMvigor211 trial which investigated atezolizumab 1200 mg or

investigator's choice of chemotherapy in 931 patients with metastatic UC who had progressed after platinum-based chemotherapy (Powles T, et al. Lancet. 2018;391:748-57).

7.30. The Subcommittee noted that the results of the IMvigor211 trial were as described in the May 2018 PTAC minutes, and noted that a median follow-up of 17.3 months, median OS in the intention-to-treat (ITT) population was 8.6 months in the atezolizumab arm compared with 8.0 months in the chemotherapy arm (stratified HR 0.85; 95% CI 0.73-0.99).

7.31. The Subcommittee considered that the IMvigor211 trial population had similar characteristics to participants of the previously mentioned studies of immune checkpoint inhibitors for UC and that the number of patients who were assessed for survival was small. The Subcommittee noted that PD-L1 expression of at least 5% was required for the primary analysis of the IMvigor211 trial.

7.32. The Subcommittee considered that the AEs reported in the IMvigor211 trial were similar to those previously reported in similar trials of immune checkpoint inhibitors.

General

7.33. The Subcommittee considered that response to immune checkpoint inhibitor treatment was observed quickly, after approximately two months, in second-line advanced UC patients but there is a proportion of patients who do not respond to immune checkpoint inhibitors and have disease progression within a few months of starting treatment.

7.34. The Subcommittee considered pseudo-progression did not appear to be seen in patients with UC as has been observed in other indications treated with immune checkpoint inhibitors.

7.35. The Subcommittee considered that quality of life appeared to be improved in advanced UC patients who received immune checkpoint inhibitors as compared to chemotherapy as was observed in other studies for immune checkpoint inhibitors and in other indications.

7.36. The Subcommittee considered that there was currently less evidence to support a benefit from treatment with immune checkpoint inhibitors in the first-line setting than was currently available in the second-line setting.

7.37. The Subcommittee considered that previously-treated (second-line) UC patients have a greater health need, and based on currently available evidence were most likely to receive the most benefit from immune checkpoint inhibitors.

7.38. The Subcommittee considered that there were difficulties in comparing the KEYNOTE-045 and IMvigor211 clinical trials given the differences between the studies. The Subcommittee considered that there was a lack of evidence to determine whether these difference could be due to differences between PD-1 and PD-L1 agents and considered that, while PD-L1 expression suggests a survival difference, it is unclear whether PD-L1 status could be used as a predictive or prognostic marker.

7.39. The Subcommittee considered that at the current time the evidence for pembrolizumab as a second-line advanced UC treatment demonstrated a more

certain survival benefit as compared to chemotherapy than was shown by the atezolizumab data.

7.40. The Subcommittee considered that while there is limited evidence available to inform consideration of a class effect for immune checkpoint inhibitors in the treatment of advanced UC at the current time, given to the effect of these agents in the treatment of other indications it is likely a class effect will be shown with further data.

7.41. The Subcommittee considered that there are a number of other immune checkpoint inhibitors, nivolumab (targeting PD-1), avelumab and durvalumab (both targeting PD-L1) in development.

8. Venetoclax in combination with rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL)

Application

8.1. The Subcommittee reviewed a supplier application for the use of venetoclax in combination with rituximab for the treatment of relapsed/refractory chronic lymphocytic leukaemia (CLL).

Recommendation

8.2. The Subcommittee **recommended** that two years duration of venetoclax in combination with six cycles of rituximab for the treatment of patients with relapsed/refractory CLL be funded for with a **high** priority subject to the following Special Authority criteria:

Venetoclax – Retail Pharmacy – Specialist
Initial application (relapsed/refractory chronic lymphocytic leukaemia) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has chronic lymphocytic leukaemia requiring treatment; and
2. Patient has received at least one prior therapy for chronic lymphocytic leukaemia; and
3. Patient has not previously received venetoclax; and
4. The patient's disease has relapsed within 36 months of previous treatment; and
5. Venetoclax to be used in combination with six 28-day cycles of rituximab commencing after the 5-week dose titration schedule with venetoclax; and
6. Patient has an ECOG performance status of 0-2.

Renewal application (relapsed/refractory chronic lymphocytic leukaemia) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment; and
2. Venetoclax is to be discontinued after a maximum of 24 months of treatment unless earlier discontinuation is required due to disease progression or unacceptable toxicity.

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

Discussion

8.3. The Subcommittee noted PHARMAC had received a letter in support of the application for venetoclax in combination with rituximab from a group of New

Zealand clinical haematologists. The Subcommittee noted that this letter particularly emphasized the high health need of patients with high-risk CLL, defined as those that bear a genetic mutation affecting the TP53 gene (17p deletion or TP53 mutation CLL) and patients who have relapsed within 36 months of prior chemoimmunotherapy.

8.4. The Subcommittee noted that PHARMAC has previously considered a number of treatments for CLL, including venetoclax monotherapy for both relapsed/refractory CLL with 17p deletion and venetoclax monotherapy for relapsed/refractory CLL with no other treatment options.

8.5. The Subcommittee noted their previous recommendation for venetoclax monotherapy in 17p deletion extended to treatment naïve patients based on expert opinion rather than clinical trial evidence based upon the available data for venetoclax and ibrutinib, and the few effective funded treatment options.

8.6. The Subcommittee noted the primary evidence for the efficacy and safety of venetoclax in combination with rituximab for the treatment of relapsed/refractory CLL is provided by the phase 3 MURANO trial (Seymour et al. N Engl J Med. 2018;378:1107-20; Kater et al. J Clin Oncol. 2019;37:269-77). The Subcommittee considered the median age of study participants at 65 years was young compared to what would be expected the New Zealand population of patients with relapsed/refractory CLL.

8.7. The Subcommittee noted that the comparator arm in the MURANO trial was bendamustine plus rituximab, which is restricted to only the first-line treatment of CLL in New Zealand. The Subcommittee considered the most likely comparator in New Zealand in the second-line setting is obinutuzumab, FC or chlorambucil or waiting until a 36-month interval has passed to allow additional FCR chemotherapy.

8.8. The Subcommittee noted the high rates of minimal residual disease (MRD) negativity in MURANO, the substantial differences in PFS at 36 months (71.4 vs.15.2%) and the improved overall survival at 36 months (87.9% vs. 79.5%) for venetoclax with rituximab compared to bendamustine with rituximab. The Subcommittee considered the applicants estimated gain in life expectancy of 8.15 years is likely over-optimistic given the current evidence base.

8.9. The Subcommittee noted early PFS results with venetoclax in combination with rituximab for a fixed duration of 24 months appear at least equivalent, if not slightly superior to open-ended treatment with single agent ibrutinib or venetoclax, although patients in the MURANO trial had received less prior treatment than the trials of single-agent venetoclax and ibrutinib.

8.10. The Subcommittee noted the high rates of undetectable MRD (uMRD; less than one CLL cell per 10^4 leukocytes) with venetoclax plus rituximab versus bendamustine plus rituximab (62% vs 13% respectively) in the MURANO trial, with superiority sustained through 24 months. The Subcommittee noted uMRD status at the end of combined treatment predicted longer PFS. The Subcommittee considered that MRD was increasingly being recognised as a meaningful surrogate maker in CLL to predict PFS, although its use currently remains more limited to clinical trials.

8.11. The Subcommittee noted that in patients who completed 2 years of venetoclax without progressive disease in MURANO, at a median follow-up of 9.9 months

(range, 1.4 to 22.5 months) of follow-up off venetoclax, only 12% (16 of 130) of patients developed disease progression (11 high-level MRD, three low-level MRD). At the end of therapy in MURANO, 70% of patients with uMRD remained in uMRD and 98% of patients with uMRD had no disease progression. The Subcommittee considered that these results support the approach for combination therapy of a limited 2-year duration. The Subcommittee noted it remained uncertain if the response will be sustained, and that additional follow-up of the MURANO population will be useful in addressing this.

8.12. The Subcommittee noted there was an increased risk of neutropenia associated with venetoclax; however, the infection risk appeared low. The Subcommittee considered this may result in the increased use of short-course G-CSF support. The Subcommittee considered that the potential for tumour lysis syndrome was effectively minimised by the dose ramp-up, but noted a possible requirement for hospital admission for two days in approximately one third of treated patients.

8.13. The Subcommittee considered that approximately 100 patients per annum would likely be eligible if funded, noting that there is likely to be some current patients who have received prior therapy and would be eligible for treatment with venetoclax plus rituximab. The Subcommittee considered the likely uptake of this regimen would be high in eligible patients.

8.14. The Subcommittee noted that venetoclax with rituximab would likely be preferred over FCR retreatment if unrestricted, although the Subcommittee considered it was reasonable to limit its use to those who relapsed within 36 months, who represent a higher risk CLL patient population.

8.15. The Subcommittee considered the MURANO trial data provided good quality evidence that showed substantial progression-free survival (PFS) and some overall survival (OS) improvement in the venetoclax with rituximab group versus bendamustine with rituximab. The Subcommittee considered that the 17p deletion population remained the highest priority for funding due to their high unmet health need.

8.16. The Subcommittee noted changes to the rituximab Special Authority criteria would be also required as most patients would have received rituximab in a first line setting.

8.17. The Subcommittee considered that, if funded, the combination of venetoclax and rituximab should be limited to patients with relapsed/refractory CLL. Patients with previously untreated CLL with 17p deletion would instead ideally receive venetoclax or ibrutinib monotherapy until progression. The Subcommittee considered that currently there was a lack of evidence to support the combination of venetoclax and rituximab for a limited 24 months duration in treatment naive CLL with 17p deletion.

8.18. The Subcommittee noted that the ongoing CLL 14 trial is comparing combinations of venetoclax and obinutuzumab (12 and 6 months duration respectively) with chlorambucil and obinutuzumab (12 and 6 months duration respectively) and that the results of this study this will add to the evidence base

9. Raltitrexed for the treatment of colorectal cancer for patients who are intolerant or contraindicated to fluoropyrimidines due to cardiac toxicity

Application

9.1. The Subcommittee reviewed a funding application from the Gastrointestinal Cancer Special Interest Group for the use of raltitrexed for the treatment of early and metastatic colorectal cancer for patients who are intolerant to fluoropyrimidines due to cardiotoxicity or where fluoropyrimidine chemotherapy is contraindicated in patients with pre-existing cardiac disease.

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

Recommendation

9.3. The Subcommittee **recommended** that raltitrexed be funded with **low** priority for the treatment of locally advanced or metastatic colorectal cancer for patients who are intolerant to fluoropyrimidines due to cardiotoxicity, subject to the following Special Authority criteria:

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

1. Patient has locally advanced or metastatic colorectal cancer; and
2. Patients is intolerant to fluoropyrimidines due to cardiotoxicity; and
3. Appropriate investigations have been undertaken to confirm the absence of anatomic cardiac disease; and
4. Raltitrexed to be administered at a maximum of 3 mg/kg2 once every 3 weeks; and
5. Raltitrexed to be discontinued at disease progression.

Renewal – (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:

6. Patient has no evidence of disease progression; and
7. Raltitrexed remains appropriate and the patient is benefitting from treatment.

9.4. The Subcommittee **recommended** that raltitrexed be **declined** for the adjuvant treatment of early colorectal cancer for patients who are intolerant or contraindicated to fluoropyrimidines due to cardiac toxicity.

Discussion

9.5. The Subcommittee noted that in New Zealand the standard treatment option for patients with early-stage colorectal cancer (CRC) is resection followed by adjuvant chemotherapy.

9.6. The Subcommittee noted that chemotherapy for patients with CRC involves a fluoropyrimidine (e.g. capecitabine, 5-fluorouacil [5-FU]) with or without additional agents such as leucovorin, oxaliplatin, and irinotecan.

9.7. The Subcommittee considered that cardiotoxicity associated with fluoropyrimidine treatment is an uncommon, but potentially life-threatening side effect. The Subcommittee considered that the majority of patients experiencing fluoropyrimidine-associated cardiotoxicity present with chest pain with electrocardiogram (ECG) changes concordant with cardiac ischemia but with no angiographic evidence of cardiovascular disease. The Subcommittee noted that less common manifestations can include myocardial infarction, arrythmias/dysrhythmias, acute pulmonary oedema, and cardiac arrest.

9.8. The Subcommittee noted that the mechanism underlying fluoropyrimidine-associated cardiotoxicity has not been fully elucidated, but that it is likely to be associated with extended exposure to cardiotoxic fluorouracil metabolites.

9.9. The Subcommittee noted that the incidence of fluoropyrimidine-associated cardiotoxicity is reported to be approximately 4% (Ransom et al. Ann Oncol. 2014;25:117-21) but considered there appears to be some variation in reported figures. The Subcommittee considered that approximately 30 patients per year with advanced CRC in New Zealand may experience fluoropyrimidine-associated cardiotoxicity, and an additional 20 CRC patients may be contraindicated due to underlying cardiac disease.

9.10. The Subcommittee noted that the risk of dying among patients who experience fluoropyrimidine-associated cardiotoxicity is reported to be 8% on first administration, and the rate of death upon re-exposure is 13% (Ransom et al. Ann Oncol. 2014;25:117-21).

9.11. The Subcommittee noted that the treatment of patients who experience fluoropyrimidine-associated cardiotoxicity differs between centres within New Zealand. The Subcommittee noted that in some centres, patients who experience cardiotoxicity with fluoropyrimidines discontinue treatment and are offered no further fluoropyrimidine-based chemotherapy. In contrast, patients in other centres undergo cardiac evaluation (e.g. ECG, cardiac catheterization, exercise testing), and if anatomical causes of cardiac dysfunction are excluded, receive 5-FU via bolus dosing. Members considered that the bolus administration protocol avoids the extended exposure to cardiotoxic fluorouracil metabolites.

9.12. The Subcommittee noted that raltitrexed is an antimetabolite that was originally developed as an alternative to 5-FU plus leucovorin.

9.13. The Subcommittee noted that there is no raltitrexed product currently registered by Medsafe.

9.14. The Subcommittee noted evidence for the use of raltitrexed as a single agent for the adjuvant treatment of resected CRC provided by the following publications:

- A retrospective analysis of the safety and efficacy of adjuvant raltitrexed in 44 patients intolerant to 5-FU (Wilson et al. Cancer Invest. 2007;25:711-4). The Subcommittee noted that the 3-year relapse-free survival was 70.8% and the 3-year OS was 83.6%.

- A phase 3 randomised controlled trial which investigated whether raltitrexed was non-inferior to 5-FU plus leucovorin in 993 patients with resected stage III colon cancer (PETACC-1 trial; Popov et al. Eur J Cancer. 2008;44:2204-11). The Subcommittee noted that the 5-year OS was 62.6% in the raltitrexed arm and 60.9% in the 5-FU plus leucovorin arm.

9.15. The Subcommittee noted that the PETACC-1 trial was closed prematurely after 17 (1.9%) raltitrexed-related deaths were reported (Popov et al. 2008). The Subcommittee noted that subsequent review identified that 11 of these deaths were linked with serious protocol deviations where dose reductions had not been applied. The Subcommittee noted that at final analysis, there was no significant survival deficit for patients who received raltitrexed.

9.16. The Subcommittee noted evidence for the use of raltitrexed as a single agent for the treatment of advanced CRC provided by the following publications:

- A phase 3 randomised controlled trial which compared raltitrexed with 5-FU plus leucovorin in 439 patients with previously untreated advanced CRC (Cunningham et al. Eur J Cancer. 1995;31A:1945-54). The Subcommittee noted that there was no significant difference in OS (HR 0.84; 95% CI 0.57 to 1.24; P=0.374).

- A randomised clinical trial which compared raltitrexed with 5-FU plus leucovorin in 495 patients with previously untreated advanced CRC Cocconi et al. J Clin Oncol. 1998;16:2943-52). The Subcommittee noted that the median OS was 10.9 months in the raltitrexed arm and 12.3 months in the 5-FU plus leucovorin (HR 1.15; 95% CI 0.93-1.42; P=0.197).

- A review of three phase 3 clinical trials investigating the efficacy and tolerability of raltitrexed in patients with advanced CRC (Cunningham D. Br J Cancer. 1998;77:15-21). The authors concluded that the ORR and palliative benefits with raltitrexed were equivalent to 5-FU plus leucovorin, and that raltitrexed had an acceptable and predictable toxicity profile.

9.17. The Subcommittee noted that the only evidence for the use of raltitrexed in combination with another agent is provided by a phase 2 trial which investigated the safety and efficacy of raltitrexed plus oxaliplatin in 58 patients with previously untreated metastatic CRC (Cascinu et al. Ann Oncol. 2002;13:716-20). The Subcommittee noted that the ORR was 50% and the median OS was >9 months; the authors concluded that the combination of raltitrexed and oxaliplatin was an effective and well-tolerated treatment for advanced CRC.

9.18. The Subcommittee noted the results of the ARCTIC study, which was a retrospective analysis that investigated the incidence of cardiac events in 42 patients who had switched to raltitrexed following the development of cardiac toxicity with fluoropyrimidines (Ransom et al. Ann of Oncol. 2014;25:117-21). The Subcommittee noted that the majority of patients included had CRC (CRC, n = 39; oesophageal cancer n = 2; ampullary carcinoma, n = 1). The Subcommittee noted that no patients experienced further cardiac toxicity after changing to raltitrexed.

9.19. The Subcommittee noted the results of a recent retrospective study which investigated the efficacy and cardiotoxic safety profile of raltitrexed in consecutively treated patients at the Royal Marsden Hospital with gastrointestinal malignancies (Khan et al. Clin Colorectal Cancer. 2019;8:64-71). The Subcommittee noted that this study included 247 patients with gastrointestinal malignancies with previous cardiovascular toxicity to fluoropyrimidines or pre-existing cardiovascular risk factors who were treated with raltitrexed. The Subcommittee noted the conclusion of the study was that raltitrexed-based treatment was well-tolerated with comparable efficacy to fluoropyrimidines in patients with gastrointestinal malignancies with significant CV toxicities or risk factors.

9.20. The Subcommittee considered that it is unlikely that there will be any further trials conducted investigating raltitrexed for the treatment of CRC.

9.21. The Subcommittee considered that while there is a mechanistic precedent for patients with non-CRC malignancies to experience fluoropyrimidine-associated cardiotoxicity, that there is limited evidence for the use of raltitrexed in these populations.

9.22. The Subcommittee considered that, if it were funded, patients would receive raltitrexed for an average of approximately 6 months.

9.23. The Subcommittee considered that there is moderate quality evidence demonstrating that raltitrexed has similar safety and efficacy to 5-FU monotherapy in patients with locally advanced or metastatic CRC; but noted that there is insufficient evidence to demonstrate that raltitrexed is equivalent to fluoropyrimidine combination therapy (e.g. FOLFOX, FOLFIRI, CAPOX).

9.24. The Subcommittee noted bolus 5-FU administration is already funded and is a viable alternative to long-term fluoropyrimidine treatment for low-risk patients but considered that there may be a need for patients who have experienced more severe cardiotoxicity or for patients being treated at centres where fluoropyrimidine rechallenge is not undertaken. Members considered that the costs associated with administration of bolus 5-FU may be higher than raltitrexed.

9.25. The Subcommittee considered that overall the evidence for raltitrexed is poor but that it would be a reasonable alternative in patients with advanced CRC who are intolerant to fluoropyrimidines due to cardiac toxicity, provided that appropriate investigation has been conducted to exclude anatomic cardiac disease.

9.26. The Subcommittee considered that there is insufficient evidence to recommend raltitrexed be funded for the treatment of early CRC.