Cancer Treatments Subcommittee of PTAC
Meeting held 9 September 2016

(minutes for web publishing)

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

The Cancer Treatments Subcommittee may:

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

These Subcommittee minutes were reviewed by PTAC at its meeting 3 & 4 November 2016.

1 Pemetrexed criteria for mesothelioma and non-small cell lung cancer

1.1 The Subcommittee considered a request from PHARMAC staff to provide feedback regarding the potential funding of pemetrexed for patients with mesothelioma and non-small cell lung cancer (NSCLC) and proposed Special Authority criteria.

Recommendation

1.2 The Subcommittee **recommended** that pemetrexed be funded for patients with mesothelioma subject to the following Special Authority criteria:

> Initial application - (mesothelioma) only from a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has been diagnosed with mesothelioma; and
> 2. Pemetrexed to be administered at a dose of 500mg/m^2 every 21 days in combination with cisplatin for a maximum of 6 cycles.
>
> Renewal application - (mesothelioma) only from 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. The treatment remains appropriate and the patient is benefitting from treatment; and
> 3. Pemetrexed to be administered at a dose of 500mg/m^2 every 21 days for a maximum of 6 cycles.

1.3 The Subcommittee **recommended** that pemetrexed be funded for the first line treatment of NSCLC subject to the following Special Authority criteria:

> Initial application - (non-small cell lung carcinoma – first-line) only from a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
> All of the following
> 1. Patient has locally advanced or metastatic non-squamous non-small cell lung carcinoma; and
> 2. Patient has treatment naïve disease; and
> 3. Pemetrexed is to be administered at a dose of 500mg/m^2 every 21 days in combination with cisplatin for a maximum of 6 cycles.

1.4 The Subcommittee **recommended** that pemetrexed be funded for the second line treatment of NSCLC subject to the following Special Authority criteria:

> Initial application - (non-small cell lung carcinoma – second-line) only from a relevant specialist. Approvals valid for 8 months for applications meeting the following criteria:
> All of the following
> 1. Patient has locally advanced or metastatic non-squamous non-small cell lung carcinoma; and
> 2. Patient has had first line treatment with platinum based chemotherapy; and
> 3. Patient has not received prior funded treatment with pemetrexed; and
> 4. Pemetrexed is to be administered at a dose of 500mg/m^2 every 21 days for a maximum of 6 cycles.

1.5 The Subcommittee **recommended** that pemetrexed be funded for maintenance treatment of NSCLC subject to the following Special Authority criteria:

Renewal application - (non-small cell lung carcinoma - maintenance) only from 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. The treatment remains appropriate and the patient is benefitting from treatment; and
3. Pemetrexed is to be administered at a dose of 500mg/m^2 every 21 days.

1.6 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

1.7 The Subcommittee noted that pemetrexed is not currently funded on the Pharmaceutical Schedule. The Subcommittee noted that NPPA applications for pemetrexed had been approved for patients with mesothelioma and that the Accident Compensation Corporation (ACC) approves funding of pemetrexed for patients with work-related malignant pleural mesothelioma because of its causal relationship with asbestos.

1.8 The Subcommittee noted that pemetrexed is indicated for the treatment of:

- malignant pleural mesothelioma in combination with cisplatin, and single agent as maintenance,
- for initial treatment of patients with locally advanced or metastatic NSCLC other than predominantly squamous cell histology in combination with cisplatin,
- locally advanced or metastatic NSCLC other than predominantly squamous cell histology after prior platinum-based chemotherapy as second-line monotherapy and maintenance.

1.9 The Subcommittee noted that the funding of pemetrexed had been previously considered by both PTAC and CaTSoP on a number of occasions and most recently by PTAC at its meeting in August 2015. The Subcommittee noted that in August 2015 PTAC made the following recommendations with regards to pemetrexed:

- pemetrexed be funded only if cost-neutral to gemcitabine taking into account the cost of treating gemcitabine related haematological adverse events for the first-line treatment of patients with advanced non-squamous NSCLC
- pemetrexed be funded only if cost-neutral, including the costs of treating adverse events in particular neutropenia/FN, as second-line treatment of patients with advanced non-squamous NSCLC in patients who had not received prior treatment with pemetrexed.
- pemetrexed maintenance treatment for patients with advanced non-squamous NSCLC be funded with low priority.

1.10 The Subcommittee noted evidence for the use of pemetrexed had been previously considered and documented in the relevant PTAC and CaTSoP meeting minutes.

1.11 The Subcommittee noted final overall survival results from the PARAMOUNT trial – a phase III randomised double-blind, international placebo-controlled study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin in 939 patients with advanced non-squamous NSCLC (Paz-Ares et al. JCO 2013;31:2895-902). The Subcommittee noted the mean number of maintenance cycles was 7.9 (range 1 to 44) for pemetrexed and 5.0 (range, 1 to 38) for placebo. The Subcommittee noted that after a median follow-up of 24.3 months (95% CI, 23.2 to 25.1 months), median overall survival was reported as 13.9 months with pemetrexed compared to 11.0 months with placebo which is a 22% reduction in the risk of death with pemetrexed (HR, 0.78; 95% CI, 0.64 to 0.96; P = .0195). The Committee considered that this was a good quality trial but that results may be confounded by patients receiving post-study treatments.

1.12 The Subcommittee considered that evidence for the use of pemetrexed for the treatment of mesothelioma and NSCLC indicated benefit in terms of progression-free survival and overall survival and appeared to be well tolerated with lower toxicity than current treatment options.

1.13 The Subcommittee considered that in the maintenance setting the advantage of pemetrexed appeared modest with an overall survival gain of 2.9 months. The Subcommittee considered that the PTAC low priority recommendation reflected the current poor survival for this patient population, lack of alternative treatments, and lower toxicity when compared with current treatments.

1.14 The Subcommittee considered that if pemetrexed were funded in both the first and second line settings that all existing patients would likely receive second-line treatment within 12 to 18 months and new patients would access funded pemetrexed in the first line.

2 PD-1 inhibitors for advanced melanoma access criteria review

Application

2.1 The Subcommittee reviewed a supplementary paper from PHARMAC staff on the Special Authority criteria for programmed cell death-1 (PD-1) inhibitors nivolumab (Opdivo, Bristol-Myers Squibb) and pembrolizumab (Keytruda, Merck Sharpe and Dohme) for patients with advanced melanoma and issues raised both by the Subcommittee at its last meeting and during consultation on the proposals to fund these agents.

Recommendation

2.2 The Subcommittee **recommended** that the Special Authority criteria for PD-1 inhibitors for the treatment of advanced melanoma be amended with high priority

to include a new criteria for patients who have had a period of time off treatment and no disease progression to recommence treatment as follows:

> **Renewal – (unresectable or metastatic melanoma PERIOD OFF TREATMENT)** only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria
> All of the following:
> 1. Patient has previously discontinued treatment with [nivolumab/pembrolizumab] for reasons other than severe toxicity or progression; and
> 2. Patient has signs of disease progression; and
> 3. [nivolumab/pembrolizumab] will be used at a maximum dose of [dose regimen].
>
> **Renewal—** (same as current)

2.3 The Subcommittee **recommended** that the Special Authority criteria for PD-1 inhibitors for the treatment of advanced melanoma be amended with high priority to include a new renewal criteria for patients who are stable on long term treatment as follows:

> **Renewal— (unresectable or metastatic melanoma LONG TERM RESPONDERS)** only from a medical oncologist**.** Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1 Any of the following:
> 1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or
> 1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
> 1.3 Patient has stable disease according to RECIST criteria (see Note); and
> 2 Patient has received treatment with [nivolumab/pembrolizumab] for a continuous duration of 24 months or more; and
> 3 Patient has ongoing clinical benefit and is undergoing regular clinical and radiological review, with response documented in patient notes; and
> 4 No evidence of progressive disease according to RECIST criteria (see Note); and
> 5 The treatment remains clinically appropriate and the patient is benefitting from the treatment; and
> 6 [nivolumab/pembrolizumab] will be used at a maximum dose of [dose regimen].

2.4 The Subcommittee **recommended** that the initial Special Authority criteria for nivolumab and pembrolizumab for advanced melanoma be amended as follows (deletions in strikethrough, additions in bold):

> Initial Application — (unresectable or metastatic melanoma) only from a medical oncologist**.** Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1 Patient has metastatic or unresectable melanoma stage III or IV; and
> 2 Patient has measurable disease as defined by the presence of at least one CT or MRI measurable lesion; and

3 The patient has ECOG performance score of 0-2; and

~~3.~~**4.** Either:

~~3.1~~**4.1** Patient has not received funded [nivolumab/pembrolizumab]; or

3.2**4.2** Both:

~~3.2.1~~**4.2.1 Patient** has received an initial Special Authority approval for [nivolumab/pembrolizumab] and has discontinued [nivolumab/pembrolizumab] within 12 weeks of starting treatment due to intolerance; and

~~3.2.2~~**4.2.2** The cancer did not progress while the patient was on [nivolumab/pembrolizumab]; and

~~4.~~**5.** [nivolumab/pembrolizumab] is to be used at a maximum dose of [dose regimen]; and

~~5.~~**6.** Baseline measurement of overall tumour burden is documented (see Note); and

~~6.~~**7.** Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of [nivolumab/pembrolizumab] will not be continued beyond 12 weeks (# cycles) if their disease progresses during this time.

2.5 The Subcommittee **recommended** that access be widened to PD-1 inhibitors with high priority to advanced melanoma patients with evaluable but not radiologically measurable disease, subject to amendments to the current Special Authority criteria as follows (deletions in strikethrough, additions in bold):

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

All of the following:

1 Patient has metastatic or unresectable melanoma stage III or IV; and

2 Patient has measurable disease as defined by **RECIST version 1.1** ~~the presence of at least one CT or MRI measurable lesion~~; and

3 Either:

3.1 Patient has not received funded [nivolumab/pembrolizumab]; or

3.2 Both:

3.2.1 Patient has received an initial Special Authority approval for [nivolumab/pembrolizumab] and has discontinued nivolumab within 12 weeks of starting treatment due to intolerance; and

3.2.2 The cancer did not progress while the patient was on [nivolumab/pembrolizumab]; and

4 [nivolumab/pembrolizumab] is to be used at a maximum dose of [dose regimen]; and

5 Baseline measurement of overall tumour burden is documented (see Note); and

6 Documentation confirming that the patient has been informed and acknowledges that the initial funded treatment period of [nivolumab/pembrolizumab] will not be continued beyond 12 weeks (# cycles) if their disease progresses during this time.

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

All of the following:

1 Any of the following:

1.1 Patient's disease has had a complete response to treatment according to RECIST criteria (see Note); or

1.2 Patient's disease has had a partial response to treatment according to RECIST criteria (see Note); or
1.3 Patient has stable disease according to RECIST criteria (see Note); and

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

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

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

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

2.6 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

2.7 The Subcommittee noted that that PHARMAC Board recently made decisions to fund the PD-1 inhibitors nivolumab and pembrolizumab for patients with unresectable or metastatic (stage III or IV) melanoma (advanced melanoma) from 1 July 2016 and 1 September 2016 respectively.

2.8 The Subcommittee noted that during the consultation period on the proposals to list nivolumab and pembrolizumab a number of issues related to the proposed access criteria were identified both by CaTSoP at its April 2016 meeting and raised in consultation feedback.

2.9 The Subcommittee noted that as a result of this feedback, some minor changes to the wording of the Special Authority criteria were made but for some issues raised PHARMAC considered that further advice would be required in order to appropriately address them. The Subcommittee noted that the three main issues relate to pseudoprogression, treatment duration for long-term responders, and patients with rapidly progressive disease.

Pseudoprogression

2.10 The Subcommittee noted that pseudoprogression is the term used to describe tumour response in patients treated with immune stimulating agents who have an initial increase in tumour lesion size before demonstrating clinical objective responses and/or stable disease.

2.11 The Subcommittee noted that currently the standard guideline for measuring tumour response is by World Health Organisation (WHO) or Response Evaluation Criteria in Solid Tumours (RECIST) criteria and that tumour growth on therapy or disease progression as per WHO or RECIST criteria signals treatment failure and discontinuation.

2.12 The Subcommittee noted that patients with pseudoprogression would be categorised as having disease progression as measured by conventional WHO or RECIST criteria and do not meet the current Special Authority renewal criteria for ongoing funded PD-1 inhibitor treatment that require no evidence for disease progression according to RECIST criteria version 1.1.

2.13 The Subcommittee considered that although pseudoprogression was a clinically well described phenomenon a formal definition in terms of RECIST is not available in currently published literature. The Subcommittee noted that currently published literature in melanoma generally defines pseudoprogression in terms of immune-related response criteria (irRC).

2.14 The Subcommittee noted that in a re-analysis of the relationship between atypical response patterns and overall survival (OS) and best overall response measured by irRC and RECIST, version 1.1 in patients with advanced melanoma treated with pembrolizumab in the open-label, phase 1b KEYNOTE001 study (Hodi et al. JCO 2016;34:1510-20) describes the differences between irRC and RECIST criteria and defines pseudoprogression as a ≥25% increase in tumour burden at

week 12 (early) or any assessment after week 12 (late) that was not confirmed as progressive disease (PD) at next assessment.

2.15 The Subcommittee noted that Hodi et al. reports 24 (7%) of the 327 patients with ≥ 28 weeks of imaging had an atypical response (15 (5%) patients early pseudoprogression and 9 (3%) patients with late pseudoprogression) and 84 (14%) of all 592 patients in the study had progression as per RECIST but non-progression as per irRC. The Subcommittee noted that two-year OS were 77.6% in patients with non-PD as per both criteria (n=331), 37.5% in patients with PD as per RECIST but non-PD as per irRC (n=84), and 17% of patients were reported to have PD as per both criteria (n=177). The Subcommittee considered that this indicated accurate determination of clinical efficacy with immunotherapy agents was challenging and that patients with discordance appear to have worse survival than those with concordanct response or stable disease by irRC and RECIST measures.

2.16 The Subcommittee noted that in phase III trial comparing nivolumab and dacarbazine in 418 previously untreated patients with advanced melanoma (Robert et al. NEJM 2015;372:320-30) the treatment protocol specified that treatment after disease progression was permitted for patients who had clinical benefit and did not have substantial adverse effects with the study drug. The Subcommittee noted that 54 patients in the nivolumab arm had disease progression and continued on treatment with 17 patients (8%) reported to have subsequent partial response or better.

2.17 The Subcommittee considered that based on currently available evidence it was difficult to clearly define patients with pseudoprogression (early and late) either by RECIST or irRC such that patients with pseudoprogression could be distinguished from those with progressive disease.

2.18 The Subcommittee considered it was not appropriate to define patients with pseudoprogression in terms of other clinical indicators including performance status as there was a lack of data to support this approach, however, the evidence was developing in this area.

2.19 The Subcommittee considered that irRC is not routinely used in clinical practice in New Zealand and that if the current Special Authority criteria were to be amended to include tumour response measurement by irRC this would require significant implementation support.

2.20 The Subcommittee considered that without a clear definition of pseudoprogression, the potential result of amending the current Special Authority criteria to allow re-evaluation of the 8%-14% patients with pseudoprogression could be to provide all patients with PD, up to 40% of all treated patients, an additional period of treatment. The Subcommittee considered that this would represent a large additional cost for minimal additional clinical benefit.

2.21 The Subcommittee considered that the evidence for pseudoprogression was still developing and that the Special Authority criteria for PD-1 inhibitors for advanced melanoma be reviewed once further information was available regarding

evidence for the management of patients with pseudoprogression and its clinical definition.

Treatment for long term responders

Finite treatment duration

2.22 The Subcommittee noted that available evidence suggests that there will be a proportion of advanced melanoma patients who respond to treatment with PD-1 inhibitors and would likely remain on treatment for an indefinite period of time, as long as they could still tolerate treatment. The Subcommittee considered the duration of treatment for these patients was uncertain based on currently available evidence, as the maximum duration of treatment reported to date in published trials is up to 96 weeks.

2.23 The Subcommittee noted that at its meeting in April 2016, CaTSoP considered that it may be appropriate to limit the duration of treatment to 96 weeks or 2 years as this was the maximum treatment duration currently reported in the literature however, members noted that and studies were ongoing and therefore further data would become available.

2.24 The Subcommittee noted that clinical trial protocols for PD-1 inhibitors for advanced melanoma were for treatment until disease progression.

2.25 The Subcommittee considered that while it may be appropriate for treatment to be limited to a defined period there is currently a lack of data to support this. The Subcommittee considered that a defined treatment period for PD-1 inhibitor treatment should be reviewed once 3 year follow-up data has been published.

Restarting after a period off treatment

2.26 The Subcommittee noted that patients who were stable on long term treatment may wish to cease treatment for reasons other than toxicity or disease progression, such as overseas travel or due to good response to treatment.

2.27 The Subcommittee noted that the current Special Authority criteria for PD-1 inhibitors allow patients who had a period of time off treatment and no disease progression to recommence treatment but that patients with signs of relapse would not meet the current criteria.

2.28 The Subcommittee considered that, while there is currently no data to support patients with signs of relapsed disease having the same level of response to retreatment, it is reasonable for patients who planned stopping treatment for reasons other than disease progression or toxicity to recommence treatment upon signs of relapse.

2.29 The Subcommittee considered that evidence for the long-term use of PD-1 inhibitors was evolving and amending the Special Authority criteria to allow restarting treatment would facilitate clinical management of patients on long-term treatment.

Monitoring requirements for long term responders

2.30 The Subcommittee noted that at its meeting in April 2016, CaTSoP considered it may not be appropriate for patients who are responding to treatment long-term to require three-monthly scans as specified by the current access criteria.

2.31 The Subcommittee noted that a consensus statement from 13 New Zealand Medical Oncologists received as consultation feedback notes that CT or MRI scanning performed every 3 months is pertinent in early course treatment but may be less relevant if a patient is on long term treatment.

2.32 The Subcommittee considered there based on survival curves from currently published evidence for the use of nivolumab (Robert et al. NEJM 2015;372:320-30) and pembrolizumab (Ribas et al JAMA 2016;315:1600-9) in advanced melanoma it appears that the majority disease progression while on treatment occurs within the first 12 months of treatment and that following 18 months of PD-1 inhibitor treatment it appeared patients could be determined as clinically stable and that it would likely be clinically appropriate to relax the ongoing monitoring requirements for these patients.

2.33 The Subcommittee considered that removal of the requirement for 3 monthly CT or MRI scanning was associated with a risk that patients would receive treatment beyond disease progression but considered the reduced ongoing cost of monitoring patients would mitigate the fiscal impact of this.

Exclusion of patients with rapidly progressive disease

2.34 The Subcommittee noted that at its April 2016 meeting, CaTSoP considered that, due to the delayed response to treatment, generally 8-16 weeks, patients with advanced melanoma and rapidly progressive disease were unlikely to benefit from treatment with PD-1 inhibitors and that funding should be restricted to patients with Eastern Cooperative Oncology Group (ECOG) performance scores of 0-2.

2.35 The Subcommittee considered that while defining patients by ECOG status alone did not provide all the relevant clinical details as to whether they had rapidly progressive disease this was the most available measure by which to target access to advanced melanoma patients most likely to benefit from treatment with PD-1 inhibitors.

Evaluable but not radiologically-measurable disease

2.36 The Subcommittee noted that a consensus statement from 13 New Zealand Medical Oncologists received as consultation feedback notes that some advanced melanoma patients have disease that is not measurable by RECIST criteria yet would be considered clinically appropriate for PD-1 inhibitor treatment and examples include patients with extensive cutaneous disease, bone metastases, or peritoneal disease.

[redacted]

2.38 The Subcommittee considered that RECIST version 1.1 offers an appropriate objective measure of tumour burden and does include clinically measurable disease – the definition of measurable is 10mm caliper measurement.

2.39 The Subcommittee considered treatment of patients with clinically measurable lesions represents standard clinical practice but this is not reflected in the current Special Authority that requires at least one CT or MRI measurable lesion. The Subcommittee considered there was uncertainty regarding the number of patients with these clinical circumstances but it was likely to be only a small percentage of patients.

2.40 The Subcommittee considered that the wording of the current Special Authority has likely resulted in further clinical investigation to identify a radiologically measurable lesion and removal of this requirement would be unlikely to result in more patients accessing treatment.

Oligometastatic CNS disease

2.41 The Subcommittee noted that a consensus statement from 13 New Zealand Medical Oncologists received as consultation feedback notes that patients may develop oligometastatic CNS disease, that is appropriate for radical treatment, without systemic progression and for these patients it would be clinically appropriate to continue PD-1 inhibitor treatment.

2.42 The Subcommittee considered that the majority of patients developing clinically symptomatic brain metastases early in the course of immune checkpoint inhibitor treatment were possibly related to pseudoprogression. The Subcommittee considered there is variable practice in staging the brain in patients with metastatic melanoma and no clinical symptoms of CNS disease.

2.43 The Subcommittee considered there is limited data to support PD-1 inhibitor treatment for patients with metastatic CNS disease compared to systemic metastatic disease, however, considered that continued PD-1 inhibitor treatment concurrent with treatment of brain metastases appeared to be a clinically reasonable approach within the first 3 months of starting treatment.

2.44 The Subcommittee considered that these patients would likely meet the intent of the Special Authority criteria and that application via the waiver process would be the most appropriate mechanism.

Non-cutaneous melanoma

2.45 The Subcommittee noted that the Special Authority criteria were not restricted to cutaneous melanoma and that patients with ocular or mucosal melanomas would be eligible for treatment.

2.46 The Subcommittee noted that these populations were excluded from the currently published PD-1 inhibitor clinical trial populations. The Subcommittee noted that data for uveal and mucosal melanoma indicated a low response rates to PD-1 inhibitor treatment at 3.6% and 32% respectively (Algazi et al. Cancer 2016 doi:10.1002/cncr.30258 [Epub ahead of print], Shoustari et al. Cancer 2016 doi:10.1002/cncr.30259 [Epub ahead of print]).

2.47 The Subcommittee considered non-cutaneous melanoma to be rare subtypes for which treatment may be clinically appropriate. The Subcommittee considered amendment of the current Special Authority criteria to specifically exclude these patients was not appropriate.

3 Targeted treatments for advanced melanoma review

Application

3.1 The Subcommittee considered a supplementary paper from PHARMAC staff regarding funding of BRAF inhibitors (vemurafenib (Zelboraf, Roche) and dabrafenib (Tafinlar, Novartis)) and BRAF/MEK inhibitors (dabrafenib/trametinib (Taflinar/Mekinist, Novartis)) in light of the recent decisions to fund PD1 inhibitors for the treatment of advanced melanoma.

Recommendation

3.2 The Subcommittee **recommended** that a BRAF inhibitor (vemurafenib or dabrafenib) as monotherapy be funded with a low priority for patients with BRAF V600 mutation positive unresectable stage IIIc or IV melanoma subject to the following Special Authority criteria:

> CHEMICAL – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma confirmed by a validated molecular pathology laboratory; and
> 2. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor (either alone or when used in combination); and
> 3. Patient's disease has not progressed following previous treatment with a PD-1 inhibitor; and
> 4. {CHEMICAL} to be administered at a maximum dose of {DOSE}.
>
> Renewal (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> Both:
> 1. No evidence of disease progression; and
> 2. The treatment remains appropriate and patient is benefitting from treatment.

3.3 The Subcommittee **recommended** that a BRAF inhibitor (vemurafenib or dabrafenib) as monotherapy be funded with a low priority for patients BRAF V600 mutation positive unresectable stage IIIc or IV melanoma and rapidly progressive disease be funded as a bridge to PD1 inhibitor therapy subject to the following Special Authority criteria:

CHEMICAL – Retail Pharmacy - Specialist
Special Authority for Subsidy
Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma confirmed by a validated molecular pathology laboratory; and
2. Patient has rapidly progressive disease; and
3. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor (either alone or when used in combination); and
4. Patient's disease has not progressed following previous treatment with a PD-1 inhibitor; and
5. {CHEMICAL} to be administered at a maximum dose of {DOSE} for a maximum of 12 weeks' treatment.

3.4 The Subcommittee **recommended** that dabrafenib in combination with trametinib for patients with patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation be funded with low priority subject to the following Special Authority criteria:

CHEMICAL – Retail Pharmacy - Specialist
Special Authority for Subsidy
Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:

1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma confirmed by a validated molecular pathology laboratory; and
2. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor (either alone or when used in combination); and
3. Patient's disease has not progressed following previous treatment with a PD-1 inhibitor; and
4. {CHEMICAL} to be administered at a maximum dose of {DOSE} in combination with {chemical} at a maximum dose of {dose}.

Renewal (advanced melanoma) - only from a medical oncologist. Approvals valid for 6 months for applications meeting the following criteria:
Both:

1. No evidence of disease progression; and
2. The treatment remains appropriate and patient is benefitting from treatment.

3.5 The Subcommittee **recommended** that dabrafenib in combination with trametinib for patients with patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation and rapidly progressive disease be funded as a bridge to PD1 inhibitor therapy be funded with low priority subject to the following Special Authority criteria:

> CHEMICAL – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (advanced melanoma) - only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has BRAF V600 mutation positive unresectable (Stage III) or metastatic (Stage IV) melanoma confirmed by a validated molecular pathology laboratory; and
> 2. Patient has rapidly progressive disease; and
> 3. Patient's disease has not progressed following previous treatment with a BRAF or MEK inhibitor (either alone or when used in combination); and
> 4. Patient's disease has not progressed following previous treatment with a PD-1 inhibitor; and
> 5. {CHEMICAL} to be administered at a maximum dose of {DOSE} in combination with {chemical} at a maximum dose of {dose} for a maximum of 12 weeks' treatment.

Discussion

3.6 The Subcommittee noted that the funding of BRAF and MEK targeted treatments – vemurafenib monotherapy, dabrafenib monotherapy and dabrafenib in combination with trametinib – for the treatment of advanced melanoma had previously been considered by PTAC and CaTSoP, with the most recent review being by CaTSoP in April 2016, however, subsequently decisions had been made to fund PD-1 inhibitors (nivolumab and pembrolizumab) for the treatment of advanced melanoma and that updated advice was sought in the context of the changed melanoma treatment landscape.

Vemurafenib monotherapy

3.7 The Subcommittee noted that PTAC and CaTSoP had considered the funding of vemurafenib monotherapy for patients with unresectable stage IIIC or stage IV melanoma positive for BRAF V600 mutation on several occasions and each time had been recommended for decline by PTAC due to its very high cost and small, short-term (limited) clinical benefit.

3.8 The Subcommittee noted that CaTSoP had recommended vemurafenib monotherapy be funded with a low priority noting that if the price were to significantly decrease its priority rating may improve.

Dabrafenib monotherapy

3.9 The Subcommittee noted that the application for dabrafenib as monotherapy for the treatment of BRAF V600 mutation-positive unresectable (Stage III) or metastatic (Stage IV) malignant melanoma had been considered by CaTSoP at its meeting in October 2014 and that it had been recommended that dabrafenib monotherapy be funded with a low priority noting the priority would increase if the cost was reduced.

3.10 The Subcommittee noted that PTAC reviewed the application for dabrafenib as monotherapy at its November 2014 meeting and had recommended that it be declined primarily due to the poor cost effectiveness at the proposed price.

Dabrafenib and trametinib combination therapy

3.11 The Subcommittee noted PTAC had considered an application for dabrafenib in combination with trametinib at its November 2015 meeting and recommended the application be declined noting the associated toxicity, uncertainty regarding the magnitude and duration of benefit, and high price sought.

3.12 The Subcommittee noted that CaTSoP had considered the application at its April 2016 meeting and recommended that dabrafenib in combination with trametinib be funded with high priority in the absence of other funded treatments for melanoma. The Subcommittee noted, when making this recommendation, that the priority was based on the high health need and lack of effective funded options for the treatment of advanced melanoma, and that if another class of treatments were to be funded the priority would be lower.

3.13 The Subcommittee noted that it was unclear from the April 2016 CaTSoP meeting minute what priority the Subcommittee would assign for this combination treatment now that PD1 inhibitors were funded for advanced melanoma.

General Comments

3.14 The Subcommittee noted that BRAF inhibitors were only effective for advanced melanoma patients who were BRAF mutation positive and therefore their use would be limited to this subset of advanced melanoma patients.

3.15 The Subcommittee considered that the mechanism and funding of BRAF mutation testing was currently inconsistent between centres but that test results could be returned quickly. The Subcommittee considered that if a BRAF targeted treatment were to be funded that BRAF mutation testing would likely become a standardised DHB service test with associated additional costs for DHBs.

3.16 The Subcommittee noted that PD1 inhibitors were funded for all patients with advanced melanoma regardless of BRAF mutation status.

3.17 The Subcommittee considered that PD1 inhibitors were unlikely to provide benefit for patients with rapidly progressive advanced melanoma, as defined by poor performance status, due to the delay in achieving a response from PD1 inhibitor treatment following the commencement of these treatments. The Subcommittee noted that PD1 inhibitors were currently funded regardless of performance status but that the Subcommittee had reviewed the Special Authority criteria for PD1 inhibitors at this meeting and recommended that the Special Authority be amended to include only those patients with good or moderate performance status as defined by Eastern Cooperative Oncology Group (ECOG) score 0-2.

3.18 The Subcommittee considered that for 70%-80% of patients whose disease responds to targeted treatments (BRAF inhibitors or BRAF/MEK inhibitors) in a first line setting the response may be very rapid but the durability of response

was limited, with a median response of around 9-12 months. The Subcommittee considered that it was unclear whether in clinical practice targeted treatments would be used until disease progression or patients transitioned to PD1 inhibitor treatment prior to disease relapse.

3.19 The Subcommittee considered that there was a place for the use of targeted treatments in current melanoma treatment paradigm in New Zealand, as there remained an unmet health need for those patients with rapidly progressive disease despite the recent funding of PD1 inhibitors.

3.20 The Subcommittee noted that there was a lack of evidence to support the use of targeted treatments specifically in patients with rapidly progressive disease, but considered it clinically reasonable that these patients would benefit from targeted treatments due to the short response time.

3.21 The Subcommittee considered that the major benefit of targeted treatments for patients with rapidly progressive disease would be in achieving disease control, such that patients could transition to maintenance with PD1 inhibitor treatment.

3.22 The Subcommittee considered that there was limited benefit for targeted treatments' use in the absence of second line PD1 inhibitor treatment, particularly due to the limited duration of response and associated toxicity profiles of these treatments.

3.23 The Subcommittee considered that the response rate and adverse events with combination treatment and monotherapy appeared similar with short term treatment, particularly as squamous cell carcinomas did not appear to emerge with early treatment, but that the BRAF/MEK combination treatment appears to have better efficacy and generally lower toxicity than BRAF monotherapy treatment over longer treatment durations.

3.24 The Subcommittee considered that at the current prices being sought for these treatments, funding could be targeted for rapidly progressing patients as a short term defined course of treatment as a bridge to maintenance therapy with a PD1 inhibitor.

3.25 The Subcommittee considered that there was currently a lack of evidence regarding the sequencing of targeted treatments and PD1 inhibitors for advanced melanoma. The Subcommittee noted that there was currently no evidence to support the use of targeted treatments in a second-line setting following prior PD1 inhibitor treatment, and considered that the benefit of targeted treatments in the second line was uncertain.

4 Chronic Lymphocytic Leukaemia Treatments Review

Application

4.1 The Subcommittee considered a supplementary paper from PHARMAC staff regarding the current treatment paradigm for patients with chronic lymphocytic leukaemia (CLL), possible future CLL treatment paradigms and proposed Special

Authority criteria for bendamustine (Ribomustin, Janssen), obinutuzumab (Gazyva, Roche), ibrutinib (Imbruvica, Janssen) and rituximab retreatment (Mabthera, Roche).

Recommendation

4.2 The Subcommittee **recommended** bendamustine be funded with medium priority for the first-line treatment of CLL subject to the following Special Authority criteria:

BENDAMUSTINE – PCT only
Special Authority for Subsidy
Initial application — (treatment naïve CLL) only from a relevant specialist 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. The patient has Binet stage B or C, or progressive stage A chronic lymphocytic leukaemia requiring treatment; and
2. The patient is chemotherapy treatment naive; and
3. The patient is unable to tolerate toxicity of highly effective FCR; and
4. Patient has ECOG performance status 0-2, and
5. Patient has GFR >50 and Cumulative Illness Rating Scale (CIRS) score of <6; and
6. Bendamustine is to be administered at a maximum dose of 100mg/m2 on days 1 and 2 every 4 weeks for a maximum of 6 cycles.

Note: 'Chronic lymphocytic leukaemia (CLL) includes small lymphocytic lymphoma (SLL). Chemotherapy treatment is considered to comprise a known standard therapeutic chemotherapy regimen and supportive treatments.

4.3 The Subcommittee **recommended** obinutuzumab be funded with medium priority for the first line treatment of CLL subject to the following Special Authority criteria:

OBINUTUZUMAB – PCT only
Special Authority for Subsidy
Initial application – (chronic lymphocytic leukaemia) only from a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
All of the following:

1. The patient has progressive Binet stage A, B or C CD20+ chronic lymphocytic leukaemia requiring treatment; and
2. The patient is obinutuzumab treatment naive; and
3. The patient is not eligible for full dose FCR due to comorbidities with a score >6 on the Cumulative Illness Rating Scale (CIRS) or reduced renal function (creatinine clearance <70mL/min); and
4. Patient has absolute neutrophil count ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L and no evidence of additional bone marrow dysfunction; and
5. Patient has good performance status; and
6. Obinutuzumab to be administered at a maximum cumulative dose of 8000 mg and in combination with chlorambucil for a maximum of 6 cycles.

Notes: Chronic lymphocytic leukaemia includes small lymphocytic lymphoma. Comorbidity refers only to illness/impairment other than CLL induced illness/impairment in the patient.

4.4 The Subcommittee **recommended** ibrutinib be funded with medium priority for the treatment of patients with 17p deletion of TP53 mutation CLL subject to the following Special Authority criteria:

IBRUTINIB – Retail Pharmacy - Specialist

Special Authority for Subsidy
Initial application (17p deletion or TP53 mutation CLL) - 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. Either:
   1.1. Patient has treatment naïve CLL; or
   1.2. Patient has previously treated CLL with relapsed disease; and
2. There is documentation confirming that patient has 17p deletion by FISH testing or TP53 mutation by sequencing; and
3. Patient has good performance performance status; and
4. The patient has adequate renal function (creatinine clearance ≥ 30ml/mm).

Renewal application (17p deletion or TP53 mutation CLL) - 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. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment.

4.5 The Subcommittee **recommended** that the initial Special Authority criteria for ibrutinib for relapsed CLL (within 24 months of prior therapy), refractory CLL (progressed within 12 months) and relapsed/refractory MCL (that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy) proposed by CaTSoP at its meeting in May 2016 be amended to remove criterion 6 'ibrutinib is to be given with curative intent'.

4.6 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations

Discussion

4.7 The Subcommittee noted that chronic lymphocytic leukaemia (CLL) is the most common haematological malignancy. The Subcommittee noted that most patients do not require treatment at diagnosis, but may be monitored and treatment initiated when clinical symptoms develop. The Subcommittee considered there to be around 200 patients with CLL per year requiring treatment in New Zealand.

4.8 The Subcommittee noted that the treatment paradigm for CLL in New Zealand has remained relatively unchanged for a number of years, with currently funded treatment options generally being fludarabine-cyclophosphamide (FC) with or without rituximab, chlorambucil or supportive therapy

4.9 The Subcommittee noted that funding applications for a number of treatments for CLL had been considered in the last five years including bendamustine, obinutuzumab, ibrutinib and rituximab retreatment.

4.10 The Subcommittee noted that there were also a number of newer treatments for CLL registered overseas or in advanced stages of clinical trials or registration, which members expected would be brought to the New Zealand market in the near future. The Subcommittee considered that venetoclax (Abbvie) and idelalisib

(Zydelig, Gilead) which were both registered overseas would likely be the next CLL treatments to be brought to market in New Zealand.

Rituximab Retreatment

4.11 The Subcommittee noted that rituximab is currently funded for patients with treatment naïve CLL (first line) as well as rituximab naïve patients whose CLL disease has relapsed following up to three prior lines of therapy.

4.12 The Subcommittee noted that funding for rituximab as a second line treatment in rituximab pre-treated patients was considered by PTAC in May 2010, August 2010 and August 2014 and was recommended for decline each time as it was considered there was insufficient evidence to support the use of rituximab retreatment in patients with relapsed or refractory disease.

4.13 The Subcommittee noted that CaTSoP had considered the funding of rituximab retreatment in October 2014 and recommended that access be widened to rituximab with a medium priority for the treatment of relapsed CLL following no more than one prior line of treatment with rituximab, after a rituximab treatment free interval of 36 months or more and in combination with planned full dose FC and rituximab (FCR). The Subcommittee considered that even though there was no direct evidence to support its use, it seemed logical to expect similar outcomes for CLL patients with rituximab retreatment as for those observed in lymphoma patients whose disease had had a durable response to prior rituximab treatment.

4.14 The Subcommittee noted that there appeared to be no further published evidence to support the use of rituximab as a second-line treatment option for CLL since its previous consideration by PTAC and CaTSoP. The Subcommittee considered it was unlikely further evidence would be published as rituximab retreatment for CLL is a widely accepted practice outside of New Zealand.

4.15 The Subcommittee considered funding rituximab retreatment for CLL patients would bring the use of rituximab in CLL in-line with international practice and its use in New Zealand in other indications such as lymphoma for which rituximab retreatment was currently funded.

4.16 The Subcommittee noted the Special Authority criteria for rituximab retreatment for patients with relapsed CLL previously proposed at its meeting in October 2014 and considered these remained appropriate.

Bendamustine

4.17 The Subcommittee noted that the funding application for bendamustine as monotherapy for first line treatment of CLL patients who are unable to tolerate FCR was reviewed by PTAC at its meeting in August 2015. The Subcommittee noted that PTAC recommended bendamustine be funded with a medium priority.

4.18 The Subcommittee noted that CaTSoP had reviewed the application at its meeting in March 2015 and recommended that bendamustine in combination with rituximab be funded with medium priority for the first-line treatment of CLL.

The Subcommittee noted that bendamustine in combination with rituximab (BR) for the treatment of CLL was not included in the application but considered the combination was likely superior to bendamustine monotherapy.

4.19 The Subcommittee noted that evidence for the use of bendamustine as monotherapy was from Knauf et al. (JCO 2009;27:4378-84) and an update of this study (Knauf et al. Br J Haematol. 2012;159:67-77). The Subcommittee noted evidence for the use of BR in this population was presented at American Society of Haematology 2014 and published as Eichhorst et al Lancet Oncol, 2016;17:928-42.

4.20 The Subcommittee noted that the evidence for the use of bendamustine was in fit patients in a wide range of ages, with few co-morbidities (CIRS scores of less than six), good performance status and good renal function.

4.21 The Subcommittee considered bendamustine with rituximab (BR) to be inferior to FCR for younger, fitter patients; however, in older patients (aged over 65 years) BR was better tolerated than FCR leading to fewer adverse events from treatment. The Subcommittee noted that a higher number of treatment cycles of BR than FCR were generally completed in older patients for this reason. The Committee considered a number of older patients may currently be receiving reduced dose FCR and BR was considered superior to reduced dose FCR.

Obinutuzumab

4.22 The Subcommittee noted that the funding application for obinutuzumab in combination with chlorambucil as first-line treatment in patients with CLL who have co-morbidities preventing treatment with FCR was reviewed by PTAC at its meeting in February 2015 and CaTSoP at its meeting in March 2015. The Subcommittee noted that both PTAC and CaTSoP had recommended obinutuzumab be funded in this setting with a medium priority.

4.23 The Subcommittee noted that obinutuzumab is not currently funded on the Pharmaceutical Schedule.

4.24 The Subcommittee noted that the evidence for the use of obinutuzumab in combination with chlorambucil (Goede et al. 2014) was for a patient population that included frailer patients, though not necessarily older patients, with high comorbidities (CIRS score >6) and a good performance status or poor renal function.

4.25 The Subcommittee considered that a large proportion of older patients in New Zealand were currently being treated with chlorambucil monotherapy. The Subcommittee considered that the addition of obinutuzumab would result in improved treatment outcomes for these patients when compared to currently funded treatment options.

4.26 The Subcommittee noted that there were a number of ongoing studies of obinutuzumab in combination with FCR and, if these showed benefit over FCR alone, this would likely result in an increase in use of obinutuzumab as it would

be used both in combination with FCR and chlorambucil for a wider patient population.

4.27 The Subcommittee considered that obinutuzumab was associated with infusion reaction issues including tumour lysis syndrome which meant that administration of this agent, particularly for elderly patients, would need to be managed carefully.

Ibrutinib

4.28 The Subcommittee noted that a funding application for ibrutinib monotherapy for patients with high risk CLL (chromosome deletion 17p or TP53 mutation at diagnosis) or relapse; patients whose CLL has relapsed within 24 months of prior therapy and patients whose CLL is refractory to prior therapy (progressed within 12 months); and relapsed refractory mantle cell lymphoma had been reviewed by PTAC at its November 2015 meeting.

4.29 The Subcommittee noted that PTAC had recommended that applications for all CLL indications be declined, PTAC noting considerable uncertainty about the benefits of ibrutinib in the New Zealand setting, that long-term survival data could not be determined based on currently available evidence and, given the high price being sought, its poor cost-effectiveness.

4.30 The Subcommittee noted that the application was reviewed by CaTSoP at its teleconference in May 2016 and the following recommendations were made with regards to CLL indications:

- medium priority for the treatment of CLL with chromosome del (17p) or TP53 mutation at diagnosis subject to Special Authority criteria;
- low priority for the treatment of relapsed CLL (within 24 months of prior therapy) subject to Special Authority criteria;
- medium priority for the treatment of refractory CLL (progressed within 12 months) subject to Special Authority criteria.

4.31 The Subcommittee noted that when making these recommendations it had been noted that the currently available data are promising but immature and confounded by cross-over and that surrogate endpoints such as progression free survival (PFS) do not always correlate with overall survival (OS).

4.32 The Subcommittee noted that since previous consideration of the application for ibrutinib the Helios study had been published; this was an international, double-blind, placebo-controlled, phase 3 study comparing bendamustine plus rituximab (BR) in combination with ibrutinib or placebo in 578 patients with previously treated CLL or small lymphocytic lymphoma. The Subcommittee noted that this study reported outcomes for patients treated with BR plus ibrutinib were improved when compared with BR alone.

4.33 The Subcommittee noted that the RESONATE 17 study remained unpublished. The Subcommittee noted that RESONATE 17 was an open-label, single arm

study of ibrutinib in 144 patients with chromosome 17p deletion CLL who had failed at least one line of previous therapy. The Subcommittee considered that unpublished evidence from this study indicated ibrutinib in this population appeared promising.

4.34 The Subcommittee considered that at the pricing being sought for ibrutinib this treatment was poorly cost-effective. The Subcommittee considered that, despite immaturity of the data, the patient group that could be targeted for funding and would benefit most from access to this treatment were those with 17p deletion CLL due to the lack of funded treatment options. The Subcommittee considered this would represent 5%-10% of CLL patients or 10-20 patients per year in New Zealand.

4.35 The Subcommittee noted the Special Authority criteria for ibrutinib previously proposed at its meeting in May 2016 and considered these remained appropriate, with the exception of requiring treatment to be given with curative intent. The Subcommittee **recommended** that this criterion be removed from the proposed Special Authority criteria for ibrutinib for all indications.

General Comments

4.36 The Subcommittee considered that the currently funded treatment options for CLL in New Zealand to be limited when compared with international standard of care.

4.37 The Subcommittee considered that of the currently unfunded CLL treatments ibrutinib and rituximab retreatment would, on a purely clinical basis, be the top two preferred agents despite limited or early data for their use. However, when taking into account the Factors for Consideration, the Subcommittee considered that the current pricing for ibrutinib was very high which reduced its preferred ranking when compared to other unfunded CLL treatments.

4.38 The Subcommittee considered that taking into account the Factors for Consideration the order of preference for the current options for investment for CLL treatments would be bendamustine, rituximab retreatment, ibrutinib for 17p deletion patients only and then obinutuzumab (in that order recognising that this order of preference is subjective and ideally the Subcommittee would recommend as many of these options be funded).

4.39 The Subcommittee considered that the currently unfunded CLL treatments would each provide benefit for patients in different CLL subpopulations.

4.40 The Subcommittee noted that for younger, fit patients the standard of care would remain full dose FCR, even if ibrutinib or bendamustine were to be funded. The Subcommittee considered retreatment with FCR for this population would provide benefit. The Subcommittee considered that rituximab retreatment should be funded only when given in combination with FC.

4.41 The Subcommittee considered that in older patient groups the relative benefit of bendamustine compared to obinutuzumab was uncertain but that the clinical use of bendamustine and obinutuzumab would be in different CLL sub-populations.

4.42 The Subcommittee noted that for older, fit patients who cannot or may not tolerate full dose FCR, there would be benefit from bendamustine in terms of improved outcomes, avoiding severe complications with FCR and the associated management costs.

4.43 The Subcommittee noted that for older, frail patients for whom FCR and BR are not appropriate, obinutuzumab in combination with chlorambucil would be the most appropriate treatment.

4.44 The Subcommittee noted that for patients with 17p deletion CLL that ibrutinib appeared to be the most effective treatment option.

5 Rituximab for Hairy Cell Leukaemia

Application

5.1 The Subcommittee considered an application from a clinician for the funding of rituximab (Mabthera, Roche) for patients with CD20+ hairy cell leukaemia (HCL) requiring treatment including patients with: residual disease or relapsed disease after purine analogue therapy, those ineligible for purine analogue therapy, or with hairy cell leukaemia variant (HCLv).

Recommendation

5.2 The Subcommittee **recommended** that access to rituximab be widened for patients with CD20+ HCL including untreated HCL, relapsed HCL following purine analogue therapy, those ineligible for purine analogue therapy and patients with HCLv with a medium priority subject to the following Special Authority criteria:

> Initial application - (Indolent, Low-grade lymphomas **or hairy cell leukaemia***) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
> Either:
> 1. Both:
> 1.1. The patient has indolent low grade NHL **or hairy cell leukaemia*** with relapsed disease following prior chemotherapy; and
> 1.2. To be used for a maximum of 6 treatment cycles; or
> 2. Both:
> 2.1. The patient has indolent, low grade lymphoma **or hairy cell leukaemia*** requiring first-line systemic chemotherapy; and
> 2.2. To be used for a maximum of 6 treatment cycles.
>
> Renewal - (Indolent, Low-grade lymphomas) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
>
> All of the following:
> 1. The patient has had a rituximab treatment-free interval of 12 months or more; and
> 2. The patient has indolent, low-grade NHL **or hairy cell leukaemia*** with relapsed disease following prior chemotherapy; and
> 3. To be used for no more than 6 treatment cycles.
>
> Note: 'Indolent, low-grade lymphomas' includes follicular, mantle, marginal zone and lymphoplasmacytic/Waldenstrom macroglobulinaemia. Rituximab is not funded for Chronic

lymphocytic leukaemia/small lymphocytic lymphoma**. *Hairy cell leukaemia includes hairy cell leukaemia variant *Unapproved indication.**

5.3 The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework for these recommendations.

Discussion

5.4 The Subcommittee noted that HCL is an uncommon CD20+ indolent B cell malignancy that presents in either classic or variant form with approximately 14 patients diagnosed per year in New Zealand. The Subcommittee noted that HCLv is a more aggressive and less treatment responsive disease than HCL.

5.5 The Subcommittee considered that not all patients would require treatment upon diagnosis as many HCL patients are asymptomatic for months or years after diagnosis and that treatment is initiated only when symptoms or blood cytopenias develop. The Subcommittee noted that almost all patients would require treatment at this point in time.

5.6 The Subcommittee considered that current treatment options for patients with HCL include standard first-line treatment with cladrabine daily for 5 days and retreatment with either cladribine or pentostatin. The Subcommittee considered that use of interferon or other chemotherapy for HCL patients was very limited.

5.7 The Subcommittee noted that rituximab is used to treat most CD20 positive lymphoproliferative disorders and is funded for the treatment of B-cell lymphoproliferative disorders after transplant, indolent low grade Non-Hodgkin's Lymphoma, aggressive CD20 positive NHL, and Chronic Lymphocytic Leukaemia subject to Special Authority criteria.

5.8 The Subcommittee noted that the clinician application had been considered by PTAC at its November 2015 meeting. The Subcommittee noted that PTAC recommended rituximab be funded for patients with CD20+ HCL with medium priority noting that from the available evidence the position of rituximab within the treatment paradigm and duration of treatment was uncertain. The Subcommittee noted PTAC had also recommended that the application be referred to CaTSoP.

5.9 The Subcommittee considered evidence for the use of rituximab is primarily in combination with purine analogues in the treatment of HCL and HCLv in first-line and relapsed or refractory settings. A number of studies and summaries of these studies are noted in the November 2015 PTAC meeting minute. The Subcommittee particularly noted the following:

- Ravandi et al. Blood 2011;118:3818-23 – a phase 2 study of cladribine (5.6 mg/m2 daily for 5 days) one month later followed by rituximab (375 mg/m2 per dose weekly for eight weeks) in 36 patients with newly diagnosed classic HCL and untreated HCLv. The Subcommittee noted that 44% had persistent disease following cladribine and when treated with second line rituximab 100% had a complete response (n=36), and no relapses occurred in patients with HCL at a median follow up of 25 months.

- Else et al. Leuk & Lymph 2011;52(Suppl 2);75-8 – a retrospective review of rituximab treatment (375 mg/m2 per dose) in combination with PA (cladribine or pentostatin) in patients with relapsed HCL (n=18) who had previously been treated with one or more lines of single agent cladribine or pentostatin. The Subcommittee noted that 89% of patients obtained a complete response (CR) and after 36 months of follow up (5-83 months) the estimated recurrence rate was 7% with no relapses occurring in patients achieving a CR. The Subcommittee considered this compared favourably to historical relapse rates with single agent PA therapy.

- Krietman et al. Clin Canc Res 2013;19:6873-80 – non-randomised study of the use of rituximab (375 mg/m2 per dose weekly for eight weeks) in combination with cladribine (0.15mg/kg per day for 5 days) in the treatment of patients with HCLv in both first line and relapsed or refractory settings. The Subcommittee noted that 90% of patients achieved complete response when treated with rituximab in combination with cladribine compared with 8% of patients treated with cladribine alone and at median follow-up of 27 months (12 to 48) eight of the nine patients remain in complete response.

5.10 The Subcommittee considered overall the evidence for the use of rituximab in the treatment of HCL or HCLv was of low quality from small cohort studies and case series, however, given the small number of patients with these indications it was unlikely that larger randomised studies would be undertaken.

5.11 The Subcommittee considered that HCL and HCLv were clinically similar to other indolent lymphomas and that based on the limited available evidence it was likely that treatment with rituximab would provide benefit for the requested patient populations.

5.12 The Subcommittee noted that the application included patients with persisting HCL after first-line treatment. However, the Subcommittee considered that all patients with HCL are likely to benefit from the addition of rituximab to first-line chemotherapy and that this is consistent with the current use of rituximab in other indolent lymphomas.

6 Bendamustine for relapsed/refractory indolent Non-Hodgkin's Lymphoma

Application

6.1 The Subcommittee reviewed the application for funding of bendamustine (Ribomustine, Janssen) with or without rituximab for the treatment of relapsed/refractory indolent non-Hodgkin's lymphoma.

Recommendation

6.2 The Subcommittee **recommended** that bendamustine be funded for relapsed/refractory indolent non-Hodgkin's lymphoma with a medium priority subject to the following Special Authority criteria:

INITIAL APPLICATION (Indolent, Low-grade lymphomas) – only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. The patient has indolent low grade CD20+ NHL requiring treatment; and
2. Patient has relapsed refractory disease following prior chemotherapy; and
3. Patient has a WHO performance status of 0-2; and
4. The patient has not received prior bendamustine therapy; and
5. Either:
    - 5.1. Both:
        - 5.1.1. Bendamustine is to be administered in combination with rituximab for a maximum of 6 cycles in relapsed patients, and
        - 5.1.2. Patient has had a rituximab treatment-free interval of 12 months or more; or
    - 5.2. Bendamustine is to be administered as a monotherapy for a maximum of 6 cycles in rituximab refractory patients.

RENEWAL (Indolent, Low-grade lymphomas) – Applications only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 9 months for applications meeting the following criteria:
All of the following:

1. Patients have not received a bendamustine regimen within the last 12 months; and
2. Either:
    - 1.1. Both:
        - 1.1.1. Bendamustine is to be administered in combination with rituximab for a maximum of 6 cycles in relapsed patients; and
        - 1.1.2. Patient has had a rituximab treatment-free interval of 12 months or more; or
    - 1.2. Bendamustine is to be administered as a monotherapy for a maximum of 6 cycles in rituximab refractory patients.

Note: 'indolent, low-grade lymphomas' includes follicular, mantle cell, marginal zone and lymphoplasmacytic/ Waldenström's macroglobulinaemia.

Discussion

6.3 The Subcommittee noted that indolent lymphomas are characterised by a chronic relapsing remitting disease course, with patients usually exposed to several successive treatment courses. The Subcommittee noted that the grade and stage of non-Hodgkin's lymphoma (NHL) informs treatment choice and that chemotherapy treatments routinely used for symptomatic low grade NHL in New Zealand were 6-8 cycles of R-CHOP (rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone) or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone). The Subcommittee noted that there was no current standard therapy for patients with relapsed or refractory iNHL.

6.4 The Subcommittee noted that the application for the funding of bendamustine for the first-line treatment of chronic lymphocytic leukaemia (CLL), first-line treatment of indolent NHL (iNHL) and relapsed refractory iNHL was considered by PTAC at its August 2015 meeting and CaTSoP at its September 2015 meeting. The Subcommittee noted that in relation to relapsed refractory iNHL both PTAC and CaTSoP had deferred making a recommendation pending the publication of NHL 2-2003 study.

6.5 The Subcommittee noted that the NHL 2-2003 study had recently been published (Rummel et al. Lancet Oncol 2016;17:57-66).

6.6 The Subcommittee noted the NHL 2-2003 study was a multicentre, randomised open label, non-inferiority phase III trial in 230 patients with relapsed iNHL or mantle cell lymphoma comparing rituximab (375 mg/m2, day 1) plus either bendamustine (90 mg/m2, days 1 and 2, n=116) or fludarabine (25 mg/m2), days 1-3, n=114) every 28 days for a maximum of six 28-day cycles.

6.7 The Subcommittee noted that eligibility criteria included WHO performance status 0-2, Stage II, III or IV disease, and relapsed or refractory CD20-positive lymphoma (follicular lymphoma, lymphoplastic lymphoma (Waldenstroms macroglobulinaermia), small lymphocytic lymphoma (SLL), nodular and generalised marginal cell lymphoma, or mantle cell lymphoma). The Subcommittee noted that the median number of prior treatments was one (IQR 1–2), and most patients were previously treated with CHOP-based chemotherapy.

6.8 The Subcommittee noted that exclusion criteria included patients with comorbidities such as severe disorders of the heart, lung, liver, or kidneys, severe hypertension, or diabetes, active autoimmune diseases, and active infections (eg, hepatitis) in need of antibiotics and that potentially curable patients were also excluded.

6.9 The Subcommittee noted that during the study, rituximab maintenance treatment was approved for patients with relapsed follicular lymphoma leading to an amendment to the protocol in 2006 (3 years into the study) to allow administration of rituximab maintenance therapy (375 mg/m² rituximab alone once every 3 months for up to 2 years) for patients who responded to rituximab in combination with either bendamustine or fludarabine.

6.10 The Subcommittee noted that after a median follow-up was 96 months (IQR 73·2–112·9) median progression-free survival (PFS), the primary endpoint, for patients treated with bendamustine and rituximab (BR) was 34·2 months (95% CI 23·5–52·7) versus 11·7 months (8·0–16·1) for patients treated with fludarabine plus rituximab (FR) (HR 0·54 [95% CI 0·38–0·72], log-rank test p<0·0001).

6.11 The Subcommittee noted that median overall survival (OS) for patients receiving BR was 109·7 months [95% CI 50·2–not reached] vs 49·1 months for patients receiving F-R [36·2–59·0]; HR 0·64, 95% CI 0·45–0·91, p=0·012.

6.12 The Subcommittee noted a subanalysis was completed to assess the effect of rituximab maintenance therapy for the 152 patients who had responded to either study treatment which reported median OS was not reached in the rituximab maintenance subgroup vs a median of 69.7 months for patients who did not have maintenance treatment (HR 0·52, 95% CI 0·34–0·92, p=0·03).

6.13 The Subcommittee noted that no substantial differences were noted between the two study arms in terms of the occurrence of adverse events such as alopecia, stomatitis, erythema, allergic reactions, or infectious episodes.

6.14 The Subcommittee considered evidence for a benefit in terms of PFS and OS with the use of bendamustine for the treatment of relapsed refractory iNHL from

the NHL 2-2003 study to be of good quality and strength, however noted that the study was open-label and designed to demonstrate non-inferiority.

6.15 The Subcommittee considered the NHL 2-2003 study to be relevant to a New Zealand setting despite study patients having received rituximab maintenance treatment which is not currently funded in New Zealand.

6.16 The Subcommittee noted and agreed with PTAC's comments in its August 2015 minute that the supplier's estimates of patient uptake were conservative, and considered that approximately 60 relapsed refractory iNHL patients annually would be treated if bendamustine were to be funded in this setting.

6.17 The Subcommittee noted that the subgroup of patients with SLL clinically the same as patients with CLL and considered that if bendamustine were to be funded for patients with SLL then for this reason it should be funding for patients with CLL at the same time.

6.18 The Subcommittee noted that a subset of relapsed refractory iNHL patients, particularly those with mantle cell lymphoma, relapse within 12 months of their previous rituximab therapy (and are not currently eligible to receive further funded rituximab treatment). The Subcommittee considered that these patients may seek funded access to bendamustine.