Record of the Cancer Treatment Subcommittee of PTAC Meeting held on 03 July 2020

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

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

The Cancer Treatment Subcommittee may:

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

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

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

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

The record of this Subcommittee meeting will be reviewed by PTAC at its August 2020 meeting.

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

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

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

Apologies:
None noted

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1. The role of PTAC Subcommittees and records of meetings

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

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

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

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

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

2. Record of Subcommittee meeting held Friday, October 18, 2019

2.1. The Committee reviewed the record of the PTAC meeting held on October 18, 2019 and agreed that the record be accepted.

3. Correspondence and Matters Arising

Potential erlotinib brand change

3.1. The Subcommittee noted that erlotinib hydrochloride (tab 100 mg, and 150 mg) were included in the 2019/20 Invitation to Tender (ITT) with the aim of realising savings in this market that could be used to invest in other medicines.

3.2. The Subcommittee noted that advice was sought regarding management of a potential change in the funded brand of erlotinib as a result of the ITT process.

3.3. The Subcommittee noted that erlotinib is currently funded for the first-line treatment of patients with locally advanced or metastatic, unresectable, non-squamous non-small cell lung cancer (NSCLC).

3.4. The Subcommittee considered that there was no significant clinical reason why a brand change in the erlotinib market could not be implemented.

3.5. The Subcommittee considered that, while erlotinib is a small molecule treatment, it would be essential that information regarding the clinical equivalence of any generic brand be available to support any brand change.

3.6. The Subcommittee considered that a transition period of 3-6 months would be appropriate to provide time for patients and clinicians to manage a brand change. Members noted that patients are usually reviewed at regular clinic visits of not more than 3 month intervals.

Azacitidine access widening

Recommendations

3.7. The Subcommittee **recommended** that access to azacitidine be widened to include patients with therapy related myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) with a high priority within the context of treatment of malignancy, when used as primary therapy

3.8. The Subcommittee **recommended** that access to azacitidine be widened to include patients with AML whose blast counts exceed 30% with a medium priority within the context of treatment of malignancy, when used as primary therapy

3.9. The Subcommittee recommended that the Special Authority criteria for azacitidine be amended as follows to affect the above recommendations (deletions in strikethrough, additions in bold):

> Initial application - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 months for applications meeting the following criteria:
> All of the following:
> 1. Any of the following:
> 1.1. The patient has International Prognostic Scoring System (IPSS) intermediate-2 or high risk myelodysplastic syndrome; or
> 1.2. The patient has chronic myelomonocytic leukaemia (10%-29% marrow blasts without myeloproliferative disorder); or
> ~~1.3.~~ The patient has acute myeloid leukaemia ~~with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO)~~; and
> 2. The patient has performance status (WHO/ECOG) grade 0-2; and
> ~~3. The patient does not have secondary myelodysplastic syndrome resulting from chemical injury or prior treatment with chemotherapy and/or radiation for other diseases and~~
> 3. The patient has an estimated life expectancy of at least 3 months**; and**
> **4. Azacitidine is to be used as primary therapy for AML/MDS**
>
> Renewal application - only from a haematologist or medical practitioner on the recommendation of a haematologist. Approvals valid for 12 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.

Discussion

3.10. The Subcommittee noted that advice was sought in relation to a request received from a clinician to widen access to azacitidine for patients with myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML), specifically:

- remove for AML patients the pre-requisite for low blast count and associated dysplasia; and

- remove the restriction precluding its use in therapy-related MDS (t-MDS)

3.11. The Subcommittee noted that patients with therapy-related MDS/AML are not able to access funded azacitidine under the current Special Authority criteria. The Subcommittee considered that there is evidence that these patients do respond to treatment, but that there is limited evidence from trials as these patients have not been included in the trial population. The Subcommittee considered that the exclusion of this patient group from such trials is likely due to their propensity to dilute the effect of treatment on the primary population investigated.

3.12. The Subcommittee noted with respect to the request for widened access to include patients with a blast count above 30%, the primary evidence was from a randomised controlled trial that included 488 patients and considered it reported modest overall survival benefit. The Subcommittee noted that in this study the median overall survival (OS) was increased with azacitidine vs conventional care regimens: 10.4 months (95% confidence interval [CI], 8.0-12.7 months) vs 6.5 months (95% CI, 5.0-8.6 months) and there was a reduction in transfusion requirements (Dombret et al. Blood;2015;126:291–299). The Subcommittee considered that given the population, this benefit was substantial.

3.13. The Subcommittee considered that azacitidine is usually administered until disease progression and can take up to 6 cycles before a response is seen and that some patients that respond can have a durable response. The Subcommittee considered that the number and efficacy of alternative funded treatment options for this population are insufficient.

3.14. The Subcommittee considered that depending on cytogenetics, patients may be able to receive subcutaneous cytarabine. The Subcommittee considered that patients with adverse cytogenetics have the greatest unmet need as the current standard of care for these patients is best supportive care. The Subcommittee considered that the treatment paradigm for AML patients with normal cytogenetics has moved from low-dose AraC to azacitidine. The Subcommittee considered that internationally azacitidine is the standard of care for both patient groups and that generally other agents are added on to azacitidine.

3.15. The Subcommittee considered that it would be appropriate to retain the current duration of 12 months with renewal criteria for both patient groups. The Subcommittee considered that azacitidine treatment would be likely to be discontinued within this timeframe if disease had progressed. The Subcommittee considered that the current renewal criteria remained appropriate if access were to be widened as requested.

3.16. The Subcommittee considered that there would be approximately 80 additional patients who would be eligible for treatment if access were widened to both subgroups, however it was difficult to quantify the number of patients contributing to each change in criteria.

3.17. The Subcommittee considered that it was not intended that this widened access would include patients receiving azacitidine as consolidation post induction chemotherapy, and considered that the current criteria should be amended to include the addition of the requirement that azacitidine be used as primary therapy.

3.18. The Subcommittee considered that there would be significant savings associated with patients receiving azacitidine instead of other chemotherapeutic regimens and that patients who respond may have reduced transfusion requirements. The

Subcommittee considered that analysis of the likely magnitude of savings could be informed by previous NPPA applications for treatment.

4. Gemtuzumab ozogamicin and midostaurin for AML

Applications

4.1. The Subcommittee considered the following applications for gemtuzumab ozogamicin:

4.1.1. Clinician applications for gemtuzumab ozogamicin for the treatment of patients with AML, submitted on behalf of the New Zealand Branch of the Haematology Society of Australia and New Zealand and the National New Zealand Haematology Trials Group; and

4.1.2. A supporting supplier application from Pfizer for gemtuzumab ozogamicin (Mylotarg) was received in May 2020, for combination therapy with standard anthracycline and cytarabine for patients aged 15 years and above with previously untreated, de novo acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).

4.2. The Subcommittee considered the following applications for midostaurin:

4.2.1. Clinician applications for midostaurin for the treatment of patients with AML, submitted on behalf of the New Zealand Branch of the Haematology Society of Australia and New Zealand and the National New Zealand Haematology Trials Group; and

4.2.2. A supporting supplier application from Novartis for midostaurin (Rydapt), received in February 2020, for the treatment of newly diagnosed FLT3-mutation positive AML, considered eligible for standard intensive remission induction and consolidation therapy, and as monotherapy maintenance for eligible patients.

4.3. The Subcommittee also noted that in April 2020, PHARMAC received multiple letters of support from clinicians at District Health Boards (DHBs) across New Zealand regarding the funding applications for gemtuzumab ozogamicin and midostaurin.

4.4. The Subcommittee noted that, the clinician applications for gemtuzumab ozogamicin and midostaurin refer to patients with acute myeloid leukaemia (AML) and in addition, those who may participate in the UK Medical Research Council (MRC) AML-19 clinical trial. The Subcommittee considered the above applications for gemtuzumab ozogamicin and midostaurin for listing on the Pharmaceutical Schedule for the treatment of AML, irrespective of clinical trial participation.

Recommendation

4.5. The Subcommittee **recommended** that gemtuzumab ozogamicin (one dose only, with intensive chemotherapy) be funded for the treatment of *de novo* acute myeloid leukaemia with a high priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application — only from a haematologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1 Patient has not received prior chemotherapy for this condition; and

2 Patient has de novo CD33-positive acute myeloid leukaemia; and
3 Patient does not have acute promyelocytic leukaemia; and
4 Gemtuzumab ozogamicin will be used in combination with standard anthracycline and cytarabine (AraC); and
5 Patient is being treated with curative intent; and
6 Patient's disease risk has been assessed by cytogenetic testing to be good or intermediate; and
7 Patient must be considered eligible for standard intensive remission induction chemotherapy with daunorubicin and cytarabine; and
8 Gemtuzumab ozogamicin to be funded for one dose only.

Notes: Acute myeloid leukaemia excludes acute promyelocytic leukaemia and acute myeloid leukaemia that is secondary to another haematological disorder (e.g. myelodysplasia or myeloproliferative disorder).

4.5.1. In making this recommendation, the Subcommittee noted that the supplier of gemtuzumab ozogamicin had requested funding for five doses. However, the Subcommittee considered that the incremental benefit of five doses, compared with a single dose, was not sufficient to warrant the additional four doses. The Subcommittee considered that there was likely a small additional benefit in relapse rate and survival from five doses compared with that provided by one dose of gemtuzumab ozogamicin, and that the potential for treatment-related toxicity may also preclude subsequent transplant.

4.6. The Subcommittee **recommended** that midostaurin (up to four cycles with intensive chemotherapy, without maintenance therapy) be funded for the treatment of *de novo* acute myeloid leukaemia that is FLT3 mutation positive with a high priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application — only from a haematologist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:
1 Patient has a diagnosis of acute myeloid leukaemia; and
2 Condition must be FMS tyrosine kinase 3 (FLT3) mutation positive; and
3 Patient must not have received a prior line of intensive chemotherapy for acute myeloid leukaemia; and
4 Patient must be considered eligible for standard intensive chemotherapy; and
5 Midostaurin to be funded for a maximum of 4 cycles.

4.6.1. In making this recommendation, the Subcommittee noted that the supplier of midostaurin had requested funding for up to six cycles with intensive chemotherapy and funding for up to 12 cycles of maintenance therapy. However, the Subcommittee considered that the incremental benefit of six cycles of midostaurin over four cycles in combination with intensive chemotherapy was not sufficient to warrant the additional two cycles, and that the available evidence did not support a benefit of midostaurin maintenance in this patient population.

4.7. The Subcommittee also considered that, if PHARMAC was only able to fund one of these medicines (i.e gemtuzumab ozogamicin or midostaurin) for the treatment of patients with favourable, intermediate or undetermined risk AML, the greater clinical benefit could be obtained through first funding gemtuzumab ozogamicin, as this would result in benefits for a wider population rather than a defined subset of the population.

Discussion

4.8. The Subcommittee noted that acute myeloid leukaemia (AML) is a haematopoietic neoplasm involving clonal proliferation of myeloid precursor cells, leading to

increased production of immature malignant cells and a reduction in mature myeloid cells. The Subcommittee noted that AML is a highly symptomatic, rapidly progressing disease that results in a variety of systemic consequences (e.g. anaemia, bleeding, and an increased risk of infection) due to bone marrow failure or the presence of AML blasts in the bone marrow, peripheral blood or other organs, with poor overall survival.

4.9. The Subcommittee noted that patients with AML spend a substantial amount of time in hospital for disease management, treatment administration, supportive care and investigations; this inpatient duration may be weeks or months for patients who receive intensive chemotherapy. The Subcommittee noted evidence where the caregivers of patients with AML, in addition to patients themselves, experienced post-traumatic stress (Leunis et al. Eur J Haematol. 2014;93:198-206, Jia et al. Psychooncology. 2015;24:1754-60). Members considered the impact on family and whānau is due to the need to support the patient with AML through this long and difficult illness.

4.10. The Subcommittee noted that AML is the most common acute leukaemia diagnosed in New Zealand adults, with incidence estimated to be 6-9 per 100,000 in the population in 2016 (Global Burden of Disease Cancer Collaboration. JAMA Oncol. 2018;4:1553-68). However, Members estimated that if AML secondary to prior haematological malignancy or previous treatment of malignant disease is excluded, the incidence of *de novo* AML in New Zealand is lower, closer to 3.5 per 100,000. The Subcommittee noted that AML incidence increases with age and that the median age at diagnosis is between 65 to 70 years.

4.11. The Subcommittee noted that Māori have an increased risk of AML relative to New Zealand Caucasians (Tracey et al. Am J Hematol. 2005;79:114-8) and that Māori have reduced chances of finding suitable stem cell donors from international registries, leading to disproportionately less stem cell transplantation as part of therapy for AML.

4.12. The Subcommittee considered that standard of care diagnostic investigation of patients with AML includes bone marrow sampling, molecular testing and immunophenotyping via flow cytometry; the latter of which would detect the cell surface antigen CD33 that is present for approximately 85–90% of patients with AML.

4.13. The Subcommittee noted that the health need and probability of survival for patients with AML is predominantly influenced by age and cytogenetic risk profile which can be categorised as favourable or intermediate (combined, these account for about 70% of *de novo* AML) or as adverse (~30% of cases). The Subcommittee noted that molecular testing identifies a range of genetic mutations in AML which occur in different patterns and combinations, contributing to a patient's cytogenetic risk:

4.13.1. The Subcommittee noted that the FLT3 (FMS-like tyrosine kinase 3) mutation occurs in about one-third of patients with AML. The Subcommittee considered that patients with FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) experience more frequent and earlier disease relapse leading to poor survival.

4.13.2. The Subcommittee noted that patients with acute promyelocytic leukaemia (APL) have a particular, mutation, that is associated with good outcomes from current treatment, therefore patients with APL were considered out of scope for the current funding applications.

4.14. The Subcommittee noted that cytogenetic testing is routinely available across New Zealand and that results are generally available within 48 to 72 hours. The Subcommittee considered it important for cytogenetic results to be available before treatment commences to ensure therapy is optimal with regard to the patient's cytogenetics, however, unavoidable delays (e.g. due to public holidays) are known to lead to additional supportive care requirements while results are pending.

4.15. The Subcommittee noted that approximately half to three-quarters of younger patients (generally defined as those aged less than 60 years) with AML are suitable for intensive induction and consolidation chemotherapy with anthracycline (e.g. daunorubicin) and cytarabine, both which are currently funded without restriction and remain the backbone of intensive treatment for AML.

4.16. The Subcommittee noted that many New Zealand patients with AML have participated in UK-based clinical trials, most recently the AML-19 trial; a randomised, factorial design, open-label, phase III trial comparing several different treatment strategies (including gemtuzumab ozogamicin and midostaurin) in adults with *de novo* AML who are suitable for intensive chemotherapy. Members considered that early data from the AML-19 trial suggests an improvement in long-term survival in younger patients.

4.17. The Subcommittee noted that azacitidine is not used to treat patients with AML who are deemed suitable for treatment with intensive chemotherapy. The Subcommittee considered that azacitidine is generally used in patients of older age, those who are frail, have low AML blast cell counts and have adverse cytogenetics. As a result, the Subcommittee considered that any widening of access to azacitidine for patients with AML would not affect the treatment paradigm for patients with AML who are suitable candidates for intensive chemotherapy.

4.18. The Subcommittee noted that disease relapse, which is accompanied by a return of symptoms due to blast cell re-emergence, is of high unmet clinical need for patients with AML as there are limited subsequent treatment options and often very shortened survival post-relapse. The Subcommittee noted that younger patients with AML who receive intensive treatment have 5 year-survival rates of about 50% at 5 years and this rate has improved over past decades, predominantly driven by improved understanding of the disease, therapeutic approaches and molecular testing in clinical trials; however, patients over 60 have a lower rate of survival (about 25% at 5 years) and this has not improved substantially over past decades.

4.19. Members noted that patients with AML with intermediate or adverse disease risk that is in remission after intensive chemotherapy treatment may be fit enough to undergo allogenic stem cell transplant, leading to better outcomes for such patients; however, older patients (e.g. patients over 60 years of age) may not be suitable candidates for transplant and therefore are unable to receive this additional benefit.

Gemtuzumab ozogamicin

4.20. The Subcommittee noted that in February 2015, PHARMAC received a clinician application to fund gemtuzumab ozogamicin in New Zealand for favourable and intermediate-risk AML within the context of the UK Medical Research Council (UK MRC) cooperative group trial, AML-19. The Subcommittee noted that the AML-19 clinical trial was discussed by CaTSoP in March 2015 and that the clinician application was reviewed by PTAC in May 2015, who noted gemtuzumab ozogamicin was not commercially available and recommended it be declined due to insufficient evidence to support funding it on the Pharmaceutical Schedule; subsequently, an

exemption to the Hospital Medicines List was granted, enabling gemtuzumab ozogamicin use within the AML-19 clinical trial, for a maximum of three years.

4.21. The Subcommittee noted that gemtuzumab ozogamicin is a monoclonal antibody to CD33 linked to a cytotoxic agent that selectively targets CD33-positive AML blast cells and induces cell death while selectively minimising the impact on cells and tissues that do not express CD33.

4.22. The Subcommittee noted that a regulatory application for gemtuzumab ozogamicin was submitted to Medsafe in May 2020, and at this review this application was considered to meet PHARMAC's criteria for consideration under the parallel assessment pathway which provides for consideration of cancer medicines at the same time as they are assessed by Medsafe.

4.23. The Subcommittee noted that gemtuzumab ozogamicin is available as 5 mg powder concentrate for infusion in a single-use vial and the applicants state it would be administered at a dose of 3 mg per m^2, capped at 5 mg per dose, in combination with standard intensive anthracycline and cytarabine chemotherapy.

4.24. The Subcommittee noted that the supplier requested funding for three doses during induction therapy and up to two doses for consolidation therapy (total of five doses), however, the clinician applicants' requested that gemtuzumab ozogamicin be funded for one or two doses for induction therapy only.

4.25. The Subcommittee noted that the supplier additionally defined the patient group being considered for treatment with gemtuzumab ozogamicin as those who have CD-33 positive disease, whereas the clinician applicants defined the target patient group as those with good, intermediate or unknown cytogenetic risk treated with curative intent.

4.26. The Subcommittee noted that the key clinical trial evidence for gemtuzumab ozogamicin comes from the randomised (1:1), phase III, open-label ALFA 0701 trial, which investigated standard induction (daunorubicin 60 mg/m^2 and cytarabine 200 mg/m^2), consolidation therapy (daunorubicin 60 mg/m^2 cytarabine 1 g/m^2) with or without gemtuzumab ozogamicin 3 mg per m^2 on days 1, 4, and 7 of induction and day 1 of consolidation courses (total of 5 doses) in 280 patients aged 55 to 70 years with previously untreated de novo acute AML (Castaigne et al. Lancet. 2012;379:1508-16).

4.27. The Subcommittee noted the primary outcome of ALFA 0701 was event free survival (EFS, defined as time from randomisation to relapse, death [any cause], or failure to achieve complete remission [CR] or complete remission with incomplete haematological recovery [CRp]) and that following a relapse event, patients could undergo salvage treatment. The Committee noted that 177 of 280 patients tolerated the treatment well enough to receive the entire regimen.

4.28. The Subcommittee noted that the ALFA 0701 trial results report an improvement in EFS (HR 0.58, 95% CI: 0.43-0.78; P=0.0003) and a lesser improvement in overall survival (OS) (HR for death 0.69, 95% CI: 0.49-0.98; P=0.0368). The Subcommittee considered that salvage treatment of patients post-relapse could have resulted in some of the reported OS benefit. The Subcommittee noted that the rates of death due to major toxicity were similar between the treatment groups.

4.29. The Subcommittee noted that persistent grade 4 thrombocytopenia was reported in in 22 patients (16%) receiving gemtuzumab ozogamicin in the ALFA 0701 trial compared with 4 patients (3%) in the control group (P<0.0001), longer treatment-

induced neutropenia was reported in patients receiving gemtuzumab ozogamicin, and there were generally increased rates of grade 3 and 4 adverse events in patients receiving gemtuzumab ozogamicin.

4.30. The Subcommittee noted the ALFA 0701 trial final OS results, which reported a modest improvement in OS (although not statistically significant) with median OS 27.5 months (95% CI: 21.4-45.6) with gemtuzumab ozogamicin compared with 21.8 months (95% CI: 15.5-27.4) in the control group (HR 0.81, 95% CI: 0.60-1.09; 2-sided *P*=0.16) (Lambert et al. Haematologica. 2019;104:113-9). The Subcommittee noted that OS analysis in patient subsets indicated that younger patients and patients with favourable and intermediate cytogenetic risk receive a survival benefit (HR: 0.46, 95% CI: 0.31-0.68; *P*<0.0001); however, the data indicated that patients with unfavourable cytogenetics (irrespective of mutation e.g. FLT3, NPM1 or other type) did not benefit from the addition of gemtuzumab ozogamicin (HR: 1.11, 95% CI: 0.63-1.95;P=0.72). Members noted that the trial population included more patients with intermediate cytogenetic risk than favourable cytogenetic risk (Castaigne et al. Lancet. 2012;379:1508-16). Members considered despite the limited trial data for patients with favourable cytogenetic risk it was likely that they also benefitted from treatment with gemtuzumab ozogamicin.

4.31. The Subcommittee noted the results of a meta-analysis of five randomised controlled trials, in which gemtuzumab ozogamicin was used at a dose of 3 mg per m^2 (single or multiple doses) or at 6 mg per m^2 as part of intensive induction therapy in a total of 3,325 adult patients with AML (Hills et al. Lancet Oncol. 2014;15:986-96). The Subcommittee noted that this meta-analysis included the open-label, randomised AML-15 trial in patients with AML (excluding APL) who were mostly less than 60 years of age (Burnett et al. J Clin Oncol. 2011; 29:369-77).

4.32. The Subcommittee noted that the meta-analysis by Hills et al. reported that the rate of remission was unchanged, the risk of relapse was reduced (odds ratio [OR]: 0.81, 95% CI: 0.73 – 0.90, *P*=0.0001) and OS at five years was increased (OR: 0.90, 95% CI: 0.82 – 0.98, *P*=0.01) with gemtuzumab ozogamicin in intensively treated patients. The Subcommittee noted that after treatment with gemtuzumab ozogamicin, 20.7% (OR: 0.47) more patients with favourable cytogenetic risk and 5.7% (OR: 0.84) more patients with intermediate risk respectively remained alive after 6 years than those who did not receive gemtuzumab ozogamicin, however, those with adverse risk cytogenetics did not benefit from gemtuzumab ozogamicin.

4.33. The Subcommittee also noted the applicant-submitted data for gemtuzumab ozogamicin from the AAML0531 trial in patients aged 0 to 29 years with newly diagnosed AML (Gamis et al. J Clin Oncol. 2014;32:3021-32).

4.34. The Subcommittee considered that approximately 88 patients with AML would be fit for intensive chemotherapy each year in New Zealand, of which approximately three-quarters (66 patients) would have favourable, intermediate or undetermined cytogenetics and would therefore be potentially eligible for gemtuzumab ozogamicin. The Subcommittee considered this estimate was sufficiently close to that of the applicants (45 patients per year).

4.35. The Subcommittee considered that gemtuzumab ozogamicin would provide a treatment benefit for the group of patients with AML with favourable, intermediate or undetermined cytogenetic risk and therefore the funded benefit would reach many people with AML. The Subcommittee considered that the use of gemtuzumab ozogamicin, if funded, would not change usage of other funded medicines used to treat AML, however there may be additional platelet transfusion requirements as

more patients would achieve complete remission with incomplete platelet recovery after treatment with gemtuzumab ozogamicin.

4.36. The Subcommittee considered that the Special Authority criteria for gemtuzumab ozogamicin should include favourable and intermediate, but not unknown, cytogenetic risk; treatment with gemtuzumab ozogamicin should be commenced after cytogenetic testing results are made available.

4.37. The Subcommittee considered that, based on the mature published evidence and unpublished emerging evidence (i.e. AML 19 trial data) for gemtuzumab ozogamicin at this time, a single dose of gemtuzumab ozogamicin would likely provide sufficient benefit in terms of relapse rate and survival compared with two or five doses for patients with favourable, intermediate or undetermined risk AML, noting the risk of liver toxicity or thrombocytopenia that may develop as a result of additional doses during intensive treatment, and which may preclude subsequent transplant, as well as the incremental cost of additional doses. The Subcommittee considered that it was reasonable to specify a maximum of one dose of gemtuzumab ozogamicin in the Special Authority criteria based on this assessment.

Midostaurin

4.38. The Subcommittee noted that midostaurin is a multi-targeted kinase inhibitor that inhibits FLT3 receptor signalling, inducing cell death in leukaemic cells that express mutated FLT3 receptors and overexpressed wild-type receptors.

4.39. The Subcommittee noted that midostaurin is approved by Medsafe for use in combination with standard anthracycline and cytarabine induction and cytarabine consolidation chemotherapy, followed in patients with complete response by single agent maintenance therapy for adult patients with newly diagnosed AML who are FLT3 mutation-positive.

4.40. The Subcommittee noted that midostaurin is available as 25 mg capsule and would be administered in combination with standard intensive chemotherapy containing anthracycline and cytarabine, with midostaurin taken orally at a dose of 50 mg twice daily on days 8 to 21 of each 21-day cycle (14 days of treatment).

4.41. The Subcommittee considered that the target patient population for midostaurin (FLT3 mutation positive disease) is a subset of the target patient population for gemtuzumab ozogamicin (AML with favourable or intermediate cytogenetic risk). The Subcommittee noted that the supplier had requested midostaurin be funded for induction and consolidation therapy, and then as maintenance for twelve 28-day cycles, however, the clinician applicants had requested funding for induction and consolidation therapy only.

4.42. The Subcommittee noted that the key clinical trial evidence for midostaurin comes from the phase III, randomised (1:1), double-blind, placebo-controlled multicentre RATIFY trial which included 717 patients aged 18 to 59 years with newly diagnosed, untreated AML (excluding APL) with TKD or ITD (high or low) FLT3-mutations (Stone et al. N Engl J Med. 2017;377:454-64). The Subcommittee noted that the study investigated standard induction with daunorubicin 60 mg/m^2, cytarabine 200 mg/m^2 plus midostaurin or placebo; then standard consolidation therapy with high-dose cytarabine 3 g/m^2 twice daily plus midostaurin or placebo; then if in remission, maintenance midostaurin or placebo. Patients received midostaurin 50 mg orally twice daily or placebo taken for a fortnight within each 21-day treatment cycle during induction and consolidation (total of five or six cycles), then midostaurin 50 mg orally

twice daily or placebo alone (according to initial randomisation) for twelve 28-day cycles during maintenance therapy. The Subcommittee noted that 36% (896) of patients screened for the RATIFY trial (3,277) had FLT3 mutations and that over half of the patients in each arm received stem cell transplant in the first line of therapy.

4.43. The Subcommittee noted that the RATIFY trial reported median event-free survival (EFS) of 8.2 months (95% CI: 5.4 to 10.7) with midostaurin compared with 3.0 months (95% CI: 1.9 to 5.9) with placebo (HR for event 0.78, 95% CI: 0.66 to 0.93, P=0.002). The Subcommittee noted that the median OS in the RATIFY trial was 74.7 months (95% CI: 31.5 to not reached) with midostaurin compared with 25.6 months (95% CI: 18.6 to 42.9) with placebo (HR for death 0.78, 95% CI: 0.63 to 0.96, P=0.009). The Subcommittee considered that this evidence showed a benefit of midostaurin treatment with respect to EFS and OS in patients with AML with FLT3 mutations, and noted that subgroup analysis according to ITD or TKD status reported similar hazard ratios for OS although these were not statistically significant.

4.44. The Subcommittee noted that the RATIFY trial reported higher rates of grade 3 to 5 anaemia (92.7% with midostaurin compared with 87.8% with placebo, *P*=0.03) and rash (14.1% with midostaurin compared with 7.6% with placebo, *P*=0.008). Overall, the Subcommittee considered that the rates of serious adverse events (SAEs) were similar between the groups and that midostaurin was well tolerated, although tolerance was lower in patients who received midostaurin post-transplant.

4.45. The Subcommittee noted that the comparative evidence for midostaurin maintenance following intensive chemotherapy came from the RATIFY trial; however, RATIFY participants who received intensive chemotherapy without midostaurin were unable to cross over to receive midostaurin in the maintenance phase, therefore the trial did not provide appropriate evidence indicating additional benefit from the addition of midostaurin as maintenance. The Committee considered that there is currently limited trial evidence of benefit from midostaurin maintenance, and that the ongoing clinical trials would contribute to this understanding.

4.46. The Subcommittee noted evidence from the phase II, open-label, hypothesis-generating AMLSG 16-10 trial, which investigated use of midostaurin during induction (50 mg twice daily, starting on day 8, until 48 hours before the start of the subsequent chemotherapy cycle) with daunorubicin 60 mg/m^2 and cytarabine 200 mg/m^2, in consolidation with either allogenic stem cell transplant or high-dose cytarabine 3 g/m^2 (starting on day 6, until 48 hours before the start of conditioning therapy for stem cell transplant or the start of subsequent consolidation chemotherapy) and as maintenance therapy (midostaurin alone, 50 mg orally twice daily for twelve 28-day cycles) in 284 patients with newly diagnosed AML (including secondary AML but excluding APL) with FLT3-ITD mutation (Schlenk et al. Blood. 2019;133:840-51).

4.47. The Subcommittee noted that the AMLSG 16-10 trial allowed allogenic transplant at investigator discretion and included patients up to 70 years of age. The Subcommittee noted that the trial used historical controls from five prospective AMLSG trials of induction and consolidation, recruiting from 1993-2008, and considered that these controls were of limited quality for comparison.

4.48. The Subcommittee noted that median EFS in AMLSG 16-10 was 13.2 months (95% CI: 10.0-18.3 months), and that EFS at two years was 39% (95% CI: 33-47%) in younger patients aged 18 to 60 years and 53% (95% CI: 46-61%) in older patients aged 61 to 70 years. The Subcommittee noted that median OS was 26.0 months (95% CI: 18.9-37.0 months) and that OS at 2 years was 34% (95% CI: 24-47%) in

younger patients and 46% (95% CI: 35-59%) in older patients. The Subcommittee considered that midostaurin provided good outcomes for patients aged over 60.

4.49. The Subcommittee noted additional evidence provided by the supplier regarding midostaurin in AML, including the following from phase I-IIb clinical trials:

- Cooper et al. Clin Lymphoma Myeloma Leuk. 2015;15:428-32
- Stone et al. Leukaemia. 2012;26:2061-8
- Fischer et al. J Clin Oncol. 2010;28:4339-45
- Strati et al. Am J Hematol. 2015;90:276-81

4.50. The Subcommittee considered that approximately 88 patients with AML would be fit for intensive chemotherapy each year in New Zealand, of which approximately three-quarters (66 patients) would have favourable or intermediate cytogenetics (and would therefore be potentially suitable for gemtuzumab ozogamicin); approximately one third of those patients would have mutation in FLT3 that would make them potentially suitable for treatment with midostaurin.

4.51. The Subcommittee considered that midostaurin would provide a treatment benefit for the group of patients with AML with favourable or intermediate cytogenetic risk who have FLT3 mutation positive disease. The Subcommittee considered that the use of midostaurin, if funded, would not change usage of other funded medicines used to treat AML.

4.52. Members considered that there is no evidence to suggest that patients with AML have an unmet need for maintenance treatment after intensive chemotherapy or as a bridge to transplant, noting that transplant requires disease remission and the current evidence indicates that neither maintenance therapy or treatment used as a bridge to transplant improves remission rates in AML.

4.53. The Subcommittee considered that, based on the mature published evidence for midostaurin at this time, four cycles of midostaurin given with intensive chemotherapy would provide sufficient survival benefit compared with six cycles for patients with FLT3 mutation positive AML, and noted the incremental cost of the additional two doses. In addition, the Subcommittee considered that the available evidence did not support maintenance therapy with midostaurin in this patient population. The Subcommittee considered that it was reasonable to specify a maximum of four cycles of midostaurin with intensive therapy, without maintenance, in the Special Authority criteria based on this assessment.

5. Atezolizumab for the treatment of first-line NSCLC as monotherapy and combination therapy

Application

5.1. The Subcommittee considered an application from Roche Products (New Zealand) Ltd for atezolizumab monotherapy for the first-line treatment of adult patients with metastatic squamous or non-squamous non-small cell lung cancer (NSCLC) with high (>50%) expression of programmed death ligand 1 (PD-L1).

5.2. The Subcommittee considered updated information from Roche Products (New Zealand) Ltd regarding the application for atezolizumab in combination with paclitaxel

and carboplatin (with or without bevacizumab) for the first-line treatment of adult patients with metastatic non-squamous NSCLC.

5.3. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering these agenda items.

Recommendation

5.4. The Subcommittee **recommended** atezolizumab monotherapy for the first-line treatment of adult patients with metastatic squamous or non-squamous NSCLC with high expression of PD-L1 be funded with high priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

> ATEZOLIZUMAB – PCT only
> Initial application (NSCLC first-line monotherapy) only from a medical oncologist or any relevant 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 not received prior treatment with an immune checkpoint inhibitor for NSCLC; and
> 2. Patient has locally advanced or metastatic non-small cell lung cancer (NSCLC); and
> 3. The patient has not had prior chemotherapy treatment for their disease; and
> 4. There is documentation confirming that the disease does not express driver mutations of EGFR tyrosine kinase or ALK gene rearrangements; and
> 5. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 50% as determined by a validated test;
> 6. Patient has ECOG performance score of 0-1; and
> 7. Baseline measurement of overall tumour burden is documented; and
> 8. Treatment is to be administered as first-line monotherapy.
>
> Renewal application (NSCLC first-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 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. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
> 3. No evidence of disease progression according to RECIST criteria; and
> 4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
> 5. Atezolizumab to be discontinued at signs of disease progression.

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

Discussion

5.6. The Subcommittee noted that lung cancer is the fifth most 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.

5.7. 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.

5.8. 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).

5.9. The Subcommittee considered that under-representation of minority groups with high health needs, such as the Māori population, in randomised clinical trials is an ongoing issue for the interpretation of likely benefit of treatments for these populations from clinical trial data.

5.10. The Subcommittee also noted that the incidence and mortality rates for lung cancer are both higher in geographical areas of New Zealand with a higher deprivation index.

5.11. 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.

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

5.13. The Subcommittee noted that there are currently targeted agents available for only some of these alterations (e.g. EGFR, ALK, ROS1, BRAF) and not all of these are currently funded; and that there are a number of agents under development for other oncogenic genetic alterations (e.g. RET, NTRK, HER2, MET, KRAS).

5.14. The Subcommittee noted that standard clinical practice for NSCLC, in New Zealand DHB Cancer Centres, is to test all newly diagnosed locally advanced or metastatic patients for EGFR and ALK driver mutations. The Subcommittee considered that currently PD-L1 testing was not routinely undertaken or funded by all DHBs.

5.15. The Subcommittee noted that, for NSCLC patients without ALK or EGFR driver mutations, first-line funded treatment would be 4 to 6 cycles of platinum-based doublet chemotherapy with or without maintenance pemetrexed depending on histology. Following disease progression, second line chemotherapy including docetaxel would be considered, depending on performance status.

5.16. The Subcommittee noted that atezolizumab is currently Medsafe-approved for locally advanced and metastatic NSCLC either in combination with other agents in the first-line, or following prior therapies, and is currently being evaluated by Medsafe for first-line monotherapy for NSCLC. The Subcommittee noted that at the time of submission, the application for use as monotherapy was considered to meet PHARMAC's criteria for consideration under the parallel assessment pathway, which provides for consideration of cancer medicines at the same time as they are assessed by Medsafe.

Atezolizumab in combination with chemotherapy

5.17. The Subcommittee noted that in April 2019, CaTSoP had reviewed an 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 NSCLC and had recommended it be declined. The Subcommittee noted that at the time it had considered the currently available evidence was insufficient to support a positive recommendation for the specific combination regimen requested.

5.18. The Subcommittee noted that the preclinical rationale for atezolizumab in combination with paclitaxel and carboplatin, with bevacizumab, for the treatment of NSCLC is based on likely synergistic activity of an anti-angiogenic (bevacizumab) with an immune checkpoint inhibitor (atezolizumab). Members noted that anti-angiogenics are associated with increased haemorrhage in squamous NSCLC and therefore considered squamous disease was appropriately excluded.

5.19. The Subcommittee noted that in February 2020, the supplier had provided additional information to support its application and in response to issues raised in CaTSoP's April 2019 consideration.

5.20. The Subcommittee noted updated evidence in the form of the final analysis of the phase III, randomised, double-blind, IMpower150 trial (the key evidence supporting the supplier's initial application).

5.20.1. The Subcommittee noted that IMpower150 was a three-arm clinical trial which investigated atezolizumab with carboplatin and paclitaxel (ACP) compared with atezolizumab with carboplatin, paclitaxel and bevacizumab (ABCP) compared with carboplatin, paclitaxel and bevacizumab (BCP) as first line therapy in 1,202 patients with stage IV non-squamous NSCLC.

5.20.2. The Subcommittee noted that IMpower150 participants received four or six cycles of chemotherapy then maintenance therapy (no crossover permitted); patients randomised to an arm receiving atezolizumab could continue this until disease progression (according to RECIST v 1.1), and similarly those randomised to bevacizumab could continue until disease progression (RECIST v1.1).

5.20.3. The Subcommittee noted that the IMpower150 statistical analysis plan prespecified hierarchical testing with alpha spending across sequential analyses, initially analysing ABCP versus BCP; then if significant for progression-free survival (PFS), analysing overall survival (OS) in these two groups; then if significant, analysing PFS and OS for ACP versus BCP. The Subcommittee considered that the trial therefore did not compare benefit with ABCP versus ACP; and as a consequence, statistical analysis of the benefit from the addition of bevacizumab to the triplet of ACP was not forthcoming from IMpower150.

5.20.4. The Subcommittee noted that it had previously reviewed results from IMpower150, where it was reported that OS in the intention-to-treat population of 45.1% with ABCP compared with 35.5% with BCP (HR 0.76; 95% CI: 0.63 to 0.93) and noted that an additional 10% of patients were alive at 2 years with ABCP (Reck et al. Lancet Respir Med. 2019;7:387-401). The Subcommittee considered that the 3% difference in landmark survival between ACP (38.3%) compared with BCP (35.5%, HR 0.85; 95% CI: 0.71 to 1.03) at two years was not statistically meaningful, and noted that no further analyses had been provided.

5.21. The Subcommittee noted the additional evidence provided from the final, unpublished and embargoed IMpower150 study report, which included updated hazard ratios and median OS results for the ITT and ITT-wild type populations. The Subcommittee considered there was no meaningful difference between these results and those of the data previously reviewed by CaTSoP (i.e. paragraphs 4.14 and 4.16 of the April 2019 CaTSoP meeting record), therefore this updated data did not alter the Subcommittee's previous assessment and advice.

5.22. The Subcommittee noted the subgroup analyses according to EGFR and/or ALK mutation status, liver metastases and PD-L1 status. The Subcommittee considered

that this new data indicated a modest benefit of ABC compared with BCP in patients with sensitising EGFR or ALK mutations, and in those with liver metastases, noting that these patient groups were small (less than 10% and 13% of ITT, respectively) which differed to CaTSoP's previous assessment of earlier data in these patient groups (i.e. paragraph 4.15 of the April 2019 CaTSoP meeting record).

5.23. The Subcommittee considered that the evidence suggests that the addition of bevacizumab into the atezolizumab-containing regimen may improve the response to atezolizumab, and that this positive interaction may have a beneficial impact for patients (e.g. if accompanied by improvement in symptom control), however, the significance of this could not be determined due to IMpower150's hierarchical analysis plan. Members further noted that use of bevacizumab is only relevant for patients with non-squamous NSCLC, and even in that population it is associated with a known modest increase in toxicities (e.g. pulmonary haemorrhage, elevated blood pressure).

5.24. The Subcommittee noted the supplier-proposed control data from several phase III Roche clinical trials (IMpower110, IMpower130, IMpower132) and the PRONOUNCE trial (Zinner et al. J Thorac Oncol. 2015;10:134-42), and considered that this data was reasonable for cross-trial comparison, given the nature of such comparisons. In particular, the Subcommittee considered that the control arm data from Keynote-189 was reasonable, noting platinum and pemetrexed is standard of care for this patient population in New Zealand.

5.25. The Subcommittee considered that in addition to the modest increase in toxicities compared with standard of care, there are practical concerns of an extended infusion duration and additional reconstitution resource of the treatment regimen as compared to a regimen without bevacizumab.

5.26. The Subcommittee also noted the expert review of the first-line atezolizumab combination regimen (Reck et al. Expert Rev Respir Med. 2020;14:125-36) provided by the supplier. The Subcommittee noted that the reviews of international bodies (NCCN, EMA) consider ABCP to be a standard of care treatment option but not the only standard of care treatment.

5.27. Overall, the Subcommittee considered that the additional information provided by the supplier was not sufficient to alter its previous assessment such that a different recommendation could be made. Therefore, The Subcommittee reiterated its previous recommendation that the application for the specific regimen of atezolizumab in combination with paclitaxel and carboplatin, with or without bevacizumab in patients with NSCLC be declined.

5.28. The Subcommittee considered that, in reference to the role of bevacizumab, that the four-drug combination regimen at the proposed pricing represented a high cost-to-benefit ratio, was accompanied by an increased toxicity profile as well as additional infusion duration and resource for an uncertain gain.

Atezolizumab monotherapy

5.29. The Subcommittee noted that a funding application for pembrolizumab as first-line monotherapy in patients with previously untreated NSCLC, PD-L1 positive ≥50% had been previously considered on a number of occasions, most recently by PTAC in February 2019 and CaTSoP in April 2019, with funding recommended with a medium and high priority respectively. The Subcommittee noted that this was the same population as being considered in this atezolizumab application.

5.30. The Subcommittee noted the primary evidence for the health benefits of atezolizumab as monotherapy for the first-line treatment of locally advanced or metastatic (advanced) NSCLC in patients with PD-L1 expression of 50%, is from two clinical trials: IMpower110 and BIRCH.

5.31. The Subcommittee noted that IMPower110 is a phase III, open label, randomised trial (n=572) in which chemotherapy naïve, metastatic (stage IV) NSCLC patients (of both squamous or non-squamous histologies) received atezolizumab 1200 mg IV (Arm A) or platinum-based chemotherapy (4 or 6 21-day cycles, Arm B).

5.31.1. The Subcommittee noted that it appeared the results of this trial were yet to be published and currently available evidence was provided as a conference abstract (Spigel DR, et al. Ann Oncol 2019; 30(Suppl_5):mdz293) and two sets of European Society of Medical Oncology (ESMO) conference presentation slides.

5.31.2. The Subcommittee noted that participants were categorised by PD-L1 expression (evaluated via VENTANA SP142 IHC assay for IMpower110 trial inclusion) in tumour-infiltrating immune cells (IC) and tumour cells (TC) as follows:

- TC3/IC3 = TC ≥50% or IC ≥10% PD-L1 expressing cells
- TC2/3 or IC2/3 = TC or IC ≥5% PD-L1 expressing cells
- TC1/2/3 or IC 1/2/3 = TC or IC ≥1% PD-L1 expressing cells

5.31.3. The Subcommittee noted that patients were treated until disease progression or loss of clinical benefit in Arm A, but only until disease progression in Arm B. The Committee considered that this may have allowed patients in Arm A to continue atezolizumab even with RECIST (v 1.1) defined disease progression if it were deemed to be having a clinical benefit, which could artificially inflate the arm favouring atezolizumab.

5.31.4. The Subcommittee noted that the issues regarding PD-L1 testing had been previously discussed and documented in records of previous CaTSoP meetings.

5.31.5. The Subcommittee noted that the IMpower110 investigators had also evaluated PD-L1 expression in the study population using both the Ventana SP263 assay and the Dako 22C3 assay for evaluation of clinical efficacy in biomarker subgroups. The Subcommittee noted that of the SP142 High PD-L1 classified patients, 9% would not have been classified as high using the Dako assay, and therefore would not have been considered study eligible if the Dako assay had been used.

5.31.6. The Subcommittee considered that, of specific relevance to this application is that several of the PD-L1 assays used in New Zealand were local lab-developed, and as such the results obtained from these assays may not be in concordance with the Ventana assay used in the trial, meaning that stratification and categorisation of patients in New Zealand may differ to that presented in the trial.

5.31.7. The Subcommittee noted that median OS for the high PD-L1 expression group was 20.2 months in Arm A versus 13.1 months in Arm B (HR: 0.595 [95% CI: 0.34 to 0.890] P=0.011). The Subcommittee also noted that OS was higher with atezolizumab (17.5 months) compared to Arm B (14.1 months) for all PD-L1 positive subgroups (TC1/2/3 or IC1/2/3; HR 0.832 [95% CI: 0.65 to 1.067], P=0.15). The Subcommittee considered that the increase in OS reported in Arm A, especially in the high PD-L1 expression group, was clinically meaningful.

5.31.8. The Subcommittee noted that treatment-related serious adverse events occurred in 8.4% of patients in Arm A and 15.6% of patients in Arm B, and that adverse events of special interest requiring use of corticosteroids was 7.7% in Arm A and 0.4% in Arm B.

5.32. The Subcommittee considered that the statistical analysis plan for the IMpower 110 trial as described in the study protocol provided by the applicant was complex. The Subcommittee considered that it was difficult to determine the final outcome assessments chosen for the trial, also noting that the protocol was amended at the end of the trial. The Subcommittee considered that review of the final study report published fully in a peer reviewed journal was critical to confidence in the statistical methods and resulting data.

5.33. The Subcommittee noted that the BIRCH trial is a multicentre, phase II, single-arm trial (n=667) in which patients with non-squamous locally advanced or metastatic NSCLC received atezolizumab (fixed dose 1200 mg) via IV every 3 weeks (Peters et al. J Clin Oncol. 2017;35:2781-9).

5.33.1. The Subcommittee noted that in BIRCH patients were split into 3 cohorts:

- Cohort 1: First line atezolizumab, no prior chemotherapy (n=142)
- Cohort 2: Second line atezolizumab, one prior platinum-based chemotherapy treatment (n=271)
- Cohort 3: ≥ Third line (at least two prior chemotherapies including one platinum-based chemotherapy treatment (n=254).

5.33.2. The Subcommittee noted that participants were selected based on tumour PD-L1 expression (TC2/3 and/or IC2/3), using the Ventana SP 142 platform and that only 46% of patients (n=65) in Cohort 1 had high PDL1 expression of 50% or greater and so relevant to consideration of the requested population in this application.

5.33.3. The Subcommittee noted that the median OS for Cohort 1 participants was 23.5 months (95% CI: 18.1 to not estimable), and that Cohort 1 participants with high PD-L1 expression had an overall survival of 26.9 months (95% CI: 12.0 to not estimable), and that this did not change at the 34.3 month survival follow-up.

5.34. The Subcommittee considered the quality of evidence provided for the use of atezolizumab as monotherapy for advanced NSCLC to be of moderate strength and quality, but considered that data is currently limited by the lack of maturity in follow up and a peer-reviewed journal publication for the phase III RCT IMpower110.

5.35. The Subcommittee considered that while mature data was preferred to support funding applications, given that this was not a first in class assessment (as data from atezolizumab and other ICI agents had been previously considered), the Subcommittee considered that atezolizumab as monotherapy in the first-line advanced NSCLC setting could be considered to demonstrate the class effect.

6. Immune checkpoint inhibitors for advanced NSCLC review

Discussion

6.1. The Subcommittee considered that there were a number of monoclonal antibodies that target PD-1 or PD-L1 inhibitors, previously considered for funding, and in development for use in the treatment of patients with advanced NSCLC either as monotherapy or in combination with other treatments.

6.2. The Subcommittee noted that advice was sought by PHARMAC staff regarding the current landscape for ICI agents for NSCLC, including agents currently being considered by PHARMAC and agents that may be considered by PHARMAC in the future.

6.3. The Subcommittee noted that it had considered the broader lung cancer treatment paradigm including anti PD-1/anti PD-L1 and targeted agents at its April 2019 meeting.

6.4. The Subcommittee considered that the treatment paradigm for advanced NSCLC continues to evolve due to the number and rate of new lung cancer treatments being developed. However, since the April 2019 meeting, there have been no major new trials published regarding the efficacy of combination anti-CTLA4/anti PD1 agents in the treatment of advanced NSCLC.

6.5. The Subcommittee considered that while toxicity related adverse events are less common with anti PD-1/anti PD-L1 agents than with chemotherapy, there was a small portion of patients treated with ICI agents who experience significant immune-mediated adverse events, which require intensive management and monitoring often over a long period of time and often entailed increased clinic visits, treatment with steroids and ongoing immunosuppressants.

6.6. The Subcommittee noted that ESMO/ACSO guidelines support use of anti PD-1/anti PD-L1 agents (pembrolizumab, atezolizumab, nivolumab) in the treatment of NSCLC in first and second-line settings, either monotherapy or in combination with chemotherapy and other agents depending on patient and cancer characteristics.

6.7. The Subcommittee considered that, based on the totality of currently available data, anti PD-1/anti PD-L1 agents appear to provide the same (or similar) effect in the treatment of advanced NSCLC.

6.8. The Subcommittee considered that currently pembrolizumab and atezolizumab have the strongest data for use in the first-line setting for advanced NSCLC; and that data is comparable for atezolizumab, pembrolizumab and nivolumab in the second-line. The Subcommittee considered that there is currently a lack of supportive data for avelumab in advanced NSCLC in any setting and for nivolumab in the first-line setting.

6.9. The Subcommittee noted a meta-analysis comparing trials of anti PD-1/anti PD-L1 agents as monotherapy or in combination with chemotherapy across NSCLC histologies and biomarker expression (Lantuejoul et al. J Thorac Oncol. 2020; 15:499-519). The Subcommittee considered that the studies presented heavily overlapped in patient characteristics and outcomes, indicating a similar level of benefit across the various trial agents and populations. It was also considered that diagnostic thresholds for PD-L1 expression were broadly consistent with 50% and 1% thresholds.

6.10. The Subcommittee noted a review of first-line anti PD-1/anti PD-L1 agent trials for NSCLC, in which approximately half of the studies reviewed had hazard ratios for overall survival whose confidence intervals crossed 1, indicating no statistically significant improvements with anti PD-1/anti PD-L1 treatment (Remon et al. J Thorac Oncol. 2020;15:914-47).

6.11. The Subcommittee reiterated that based on the currently available evidence (across multiple trials and agents) the overall survival gain for NSCLC patients with anti PD-1/anti PD-L1 agents was approximately 3 months irrespective of treatment line. The Subcommittee considered that to date it remained the case that published evidence for the use of anti PD-1/anti PD-L1 agents does not indicate there is a 'tail' of long-term survivors with advanced NSCLC.

6.12. The Subcommittee considered a letter 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). The Subcommittee noted that, while not unanimous, based on the currently available evidence for use of various agents there was majority support for a class effect for monoclonal antibodies targeting PD-1/PD-L1 in treatment for advanced NSCLC.

6.13. The Subcommittee considered that while there is variability between trials for anti PD-1/anti PD-L1 agents (atezolizumab, pembrolizumab, durvalumab, nivolumab) in how they stratify by PD-L1 expression, participants are generally grouped based on PD-L1 tumour expression of ≥ 50% (high expression), PD-L1 tumour expression of ≥ 1% (PD-L1 positive), and PD-L1 expression <1% (PD-L1 negative).

6.14. The Subcommittee considered that although stratification of patients in clinical trials based on PD-L1 expression is relatively consistent across studies, at the current time it is difficult to determine what the downstream immune effects of PD-L1 blockade are and so PD-L1 expression may not be biologically meaningful in defining a patient population for exclusion of benefit of anti PD-1/anti PD-L1 treatment.

6.15. The Subcommittee considered that published data indicates that a higher expression of PD-L1 on tumour cells or surrounding immune stromal cells correlates to a higher response rate from ICI agents.

6.16. The Subcommittee considered that although patients with high PD-L1 expression appear to benefit most, those with lower expression may also benefit, with a statistically significant and clinically meaningful improvement in overall survival.

6.17. The Subcommittee considered that use of different assays, tumour proportion scores, and PD-L1 expression thresholds may lead to problems with reproducibility and standardisation of testing and by extrapolation the benefits observed in trial populations.

6.18. The Subcommittee considered that lab-developed tests used in New Zealand may not have the same sensitivity as the tests used in the clinical trials. As a variety of PD-L1 testing platforms are in use in New Zealand, the Subcommittee considered that the true rates of PD-L1 expression in NSCLC for patients in New Zealand may be difficult to estimate.

6.19. 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 driver mutations (e.g. EGFR-negative, ALK-negative). Therefore, the Subcommittee considered there continued to be a lack of data to support efficacy

of anti PD-1/anti PD-L1 agents in patients with known driver mutations, such that inclusion of these populations in any funding criteria for anti PD-1/anti PD-L1 agents could not currently be supported.

6.20. The Subcommittee considered that similarly patients with uncontrolled brain metastases were not included in trial populations, and that in NSCLC this is considered an unfavourable prognostic factor such that it would be appropriate to exclude these patients from funding of these agents.

6.21. The Subcommittee considered it remained appropriate to limit patients to a single line of treatment with anti PD-1/anti PD-L1 agents which could be administered at any point in the treatment sequence for patients with EGFR wild-type or ALK-negative advanced NSCLC.

6.22. The Subcommittee considered that it would be appropriate to limit the total duration for a course of anti PD-1/anti PD-L1 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 anti PD-1/anti PD-L1 pre-treated NSCLC patients, and that treatment should cease at signs of disease progression (whether this occurred during continuous treatment or in a period when 'off' treatment).

6.23. The Subcommittee considered that, while funding for all advanced NSCLC would be the preferred outcome, if targeting was required for fiscal reasons then use of PD-L1 expression would be reasonable.

6.24. The Subcommittee considered there were benefits and shortfalls of a Special Authority criteria mandating PD-L1 testing to determine eligibility for anti PD-1/anti PD-L1 agents for advanced NSCLC.

6.25. The Subcommittee considered that, if anti PD-1/anti PD-L1 agents were to be funded in New Zealand, subject to criteria irrespective of PD-L1 expression (i.e. where PD-L1 level did not determine eligibility for funding) that this would allow clinicians to prescribe anti PD-1/anti PD-L1 agents according to patient needs and clinical judgement. The Subcommittee considered that in this situation it was likely that the majority of patients would receive treatment as a combination regimen with chemotherapy, and only those considered unfit for chemotherapy would likely receive monotherapy.

6.26. The Subcommittee considered that, conversely, if anti PD-1/anti PD-L1 agents were to be funded in New Zealand subject to criteria that mandated PD-L1 expression (i.e. where PD-L1 level was a required determinant of eligibility for funding) use of a 50% threshold would likely be appropriate. The Subcommittee considered that this could target funded treatment to those that may benefit most and limit the overall resource impact for DHBs.

6.27. The Subcommittee considered that if first-line treatment were to be funded for all advanced NSCLC patients (rather than only a high PD-L1 expression population), PD-L1 level would likely be used to determine treatment regimen. The Subcommittee considered that any patients whose disease had high PD-L1 expression (50% or greater) would likely receive anti PD-1/anti PD-L1 monotherapy, with patients whose disease had PD-L1 expression less than 50% who are 'fit' receiving the combination regimen. The Subcommittee considered that in this scenario patients who are 'unfit'

to receive chemotherapy and did not have disease with high expression of PD-L1 may not be eligible to receive funded anti PD-1/anti PD-L1 treatment.

6.28. The Subcommittee considered that mandating PD-L1 testing would require DHBs to fund and provide tests but may create inequities for patients who are unfit for chemotherapy and may not meet the specified PD-L1 expression threshold.

6.29. The Subcommittee considered that if PD-L1 testing was not used to specify eligibility for funding, it was uncertain whether testing would be implemented equitably by DHBs. The Subcommittee considered this may result in more patients receiving combination chemotherapy regimens with the additional toxicities and resourcing requirements when comparable benefit could likely be achieved without this.

6.30. The Subcommittee considered that, given these points, it would be reasonable to progress funding for anti PD-1/anti PD-L1 agents in the treatment of advanced NSCLC subject to criteria with or without specification of PD-L1 based on assessment of the most favourable cost-effectiveness taking in to account the health system impacts.

6.31. The Subcommittee considered that appropriate criteria in each scenario would be:

<u>PD-L1 defined population</u>

Initial application - (NSCLC first-line) only from a medical oncologist or any relevant 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 not received prior treatment with an immune checkpoint inhibitor for non-small cell lung cancer (NSCLC); and
2. Either:
   - 2.1. All of the following:
     - 2.1.1. Patient has locally advanced or metastatic, unresectable, NSCLC; 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 driver 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 diagnostic test; and
     - 2.1.5. Patient has an ECOG 0-1; and
     - 2.1.6. Patient does not have uncontrolled brain metastases; and
     - 2.1.7. [Chemical] to be used as monotherapy at a maximum dose of [dose] for a maximum of 12 weeks; and
     - 2.1.8. Baseline measurement of overall tumour burden is documented; or
   - 2.2. All of the following:
     - 2.2.1. Patient has metastatic, unresectable, NSCLC; 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 driver mutations of EGFR or ALK tyrosine kinase; and
     - 2.2.4. Patient has an ECOG 0-1; and
     - 2.2.5. Patient does not have uncontrolled brain metastases; and
     - 2.2.6. [Chemical] to be used in combination with chemotherapy at a maximum dose of [dose] for a maximum of 12 weeks; and
     - 2.2.7. Baseline measurement of overall tumour burden is documented.

Initial application- (NSCLC second-line) only from a medical oncologist or any relevant 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 locally advanced or metastatic non-small cell lung cancer (NSCLC); and
2. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
3. Patient has an ECOG 0-1; and
4. Patient does not have uncontrolled brain metastases; and

5. Patient has documented disease progression following treatment with platinum-based chemotherapy; and
6. Patient has not had prior treatment with immune checkpoint inhibitors for NSCLC; and
7. [Chemical] is to be used as monotherapy at a dose of [dose] for a maximum of 12 weeks; and
8. Baseline measurement of overall tumour burden is documented as per RECIST criteria.

Renewal – (NSCLC first or second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:
All of the following
6. Any of the following:
   6.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
   6.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
   6.3. Patient has stable disease according to RECIST criteria; and
7. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
8. No evidence of disease progression according to RECIST criteria; and
9. The treatment remains clinically appropriate and patient is benefitting from treatment; and
10. [chemical] to be used at a maximum dose of [dose] (or equivalent); and
11. [chemical] to be discontinued at signs of disease progression; and
12. Treatment with [chemical] to cease after a total duration of 24 months from commencement.

Irrespective of PD-L1 (regimen/dose not defined either)

Initial application - (NSCLC first-line) only from a medical oncologist or any relevant 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 not received prior treatment with an immune checkpoint inhibitor for non-small cell lung cancer (NSCLC); and
2. Patient has locally advanced or metastatic, unresectable, NSCLC; and
3. The patient has not had prior chemotherapy treatment for their disease; and
4. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
5. Patient has an ECOG 0-1; and
6. Patient does not have uncontrolled brain metastases; and
7. Baseline measurement of overall tumour burden is documented.

Initial application- (NSCLC second-line) only from a medical oncologist or any relevant 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 locally advanced or metastatic non-small cell lung cancer (NSCLC); and
2. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
3. Patient has an ECOG 0-1; and
4. Patient does not have uncontrolled brain metastases; and
5. Patient has documented disease progression following treatment with platinum-based chemotherapy; and
6. Patient has not had prior treatment with immune checkpoint inhibitors for NSCLC; and
7. Baseline measurement of overall tumour burden is documented as per RECIST criteria.

Renewal – (NSCLC first or second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 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. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3. No evidence of disease progression according to RECIST criteria; and
4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
5. [Chemical] to be discontinued at signs of disease progression; and
6. Treatment with [chemical] to cease after a total duration of 24 months from commencement.

7. Chronic lymphocytic leukaemia (CLL) treatments review

Applications

7.1. The Subcommittee noted that there were three interrelated applications for treatments for chronic lymphocytic leukaemia (CLL). The Subcommittee considered:

7.1.1. an application for ibrutinib for relapsed/refractory chronic lymphocytic leukaemia with or without del 11q mutation and previously untreated chronic lymphocytic leukaemia with del 17p mutation;

- This included: patients intolerant to venetoclax; patients who progress on or relapse after treatment with venetoclax and patients unsuitable for treatment with venetoclax

7.1.2. an application for ibrutinib for previously untreated CLL for whom chemoimmunotherapy is inappropriate;

7.1.3. an application for venetoclax for previously untreated chronic lymphocytic leukaemia patients for whom fludarabine-based chemoimmunotherapy is inappropriate and who are immunoglobulin heavy chain variable region (IGHV) unmutated.

7.2. The Subcommittee took into account, where applicable, PHARMAC's relevant decision-making framework when considering these agenda items

Recommendations

7.3. The Subcommittee **recommended** ibrutinib as an alternative option to venetoclax containing regimens in previously untreated patients and relapsed refractory patients, for whom ibrutinib is a more appropriate option, be listed with a medium priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application (previously untreated chronic lymphocytic leukaemia (CLL) with 17p deletion or TP53 mutation*) - 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 treatment-naïve CLL requiring therapy; and
2. There is documentation confirming that patient has 17p deletion or TP53 mutation; and
3. Patient has an ECOG performance status of 0-2

Renewal application (previously untreated chronic lymphocytic leukaemia with 17p deletion or TP53 mutation*) - 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. No evidence of clinical disease progression; and
2. The treatment remains appropriate and the patient is benefiting from treatment.

Initial application (relapsed/refractory chronic lymphocytic leukaemia (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. Patient has received at least one prior immunochemotherapy for CLL; and

2. Patient has not previously received funded ibrutinib; and
3. The patient's disease has relapsed within 36 months of previous treatment.

Renewal application (relapsed/refractory 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:

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

7.4. The Subcommittee **recommended** ibrutinib as a subsequent line of therapy (relapsed/refractory or intolerance) to venetoclax containing regimens be listed with a high priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application (relapsed/refractory chronic lymphocytic leukaemia (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. Patient has not previously received funded ibrutinib; and
2. Patient's CLL has relapsed within 36 months of previous treatment with venetoclax or a venetoclax containing regimen.

Renewal application (relapsed/refractory 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:

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

7.4.1. The Subcommittee considered that those patients refractory to, or intolerant of venetoclax had the highest unmet health need and therefore the greatest priority for treatment with ibrutinib of the CLL groups considered at this meeting.

7.5. The Subcommittee **recommended** ibrutinib for the treatment of relapsed/refractory del11q CLL be declined, within the context of treatment of malignancy.

7.5.1. The Subcommittee considered there to be no clear evidence that ibrutinib confers additional benefit in patients with the del11q mutation compared with the wider CLL patient population when making this recommendation.

7.6. The Subcommittee **recommended** ibrutinib for previously untreated CLL patients, for whom fludarabine-based chemoimmunotherapy is inappropriate with or without immunoglobulin heavy chain (IGHV) mutation be listed with a low priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application (chronic lymphocytic leukaemia) - 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 is treatment naive; and
2. Treatment with fludarabine-based chemoimmunotherapy is not considered appropriate due to patient comorbidities; and
3. Patient has a score of >6 on the Cumulative Illness Rating Scale (CIRS) or reduced renal function (creatinine clearance < 70ml/min); and
4. Patient has an ECOG performance status of 0-2.

Renewal application (chronic lymphocytic leukaemia) - 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:
Both:

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

7.7. The Subcommittee **recommended** venetoclax in combination with obinutuzumab as a first-line treatment option for previously untreated CLL patients, for whom fludarabine-based chemoimmunotherapy is inappropriate, without immunoglobulin heavy chain (IGHV) mutation, be listed with a low priority within the context of treatment of malignancy, subject to the following Special Authority criteria:

Initial application (chronic lymphocytic leukaemia) - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months.
All of the following:

1. Patient has previously untreated CLL; and
2. Treatment with fludarabine-based chemoimmunotherapy is not considered appropriate due to patient comorbidities; and
3. Patient has a score of >6 on the Cumulative Illness Rating Scale (CIRS) or reduced renal function (creatinine clearance < 70ml/min); and
4. Patient's disease is not immunoglobulin heavy chain (IGHV) mutated; and
5. Patient has an ECOG performance status of 0-2.

Renewal application (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:
Both:

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

Discussion

7.8. The Subcommittee noted that the current treatment options for patients ineligible for fludarabine based chemoimmunotherapy (fludarabine ± cyclophosphamide and rituximab) were obinutuzumab-chlorambucil or bendamustine-rituximab, and noted that bendamustine-rituximab was not funded in the relapsed/refractory setting. The Subcommittee noted that if the patient had the 17p deletion or the TP53 mutation, that they would be eligible for venetoclax monotherapy as first line treatment. The Subcommittee noted that patients who relapse within 36 months of treatment with obinutuzumab-chlorambucil or bendamustine-rituximab would be eligible for venetoclax-rituximab. The Subcommittee noted that after venetoclax-rituximab, if patients have not received obinutuzumab, they would be eligible for this as third line treatment.

7.9. The Subcommittee noted that the current treatment options for patients eligible for fludarabine based chemoimmunotherapy (fludarabine ± cyclophosphamide and rituximab) was FCR, unless the patient had the 17p deletion or the TP53 mutation, in which case they would be eligible for venetoclax monotherapy. The Subcommittee noted that that patients who relapse within 36 months of treatment with FCR would be eligible for venetoclax-rituximab. The Subcommittee noted that after venetoclax-rituximab, if patients have not received obinutuzumab, they would be eligible for this as third line treatment.

Ibrutinib for patients with previously untreated del17p/TP53 chronic lymphocytic leukaemia (CLL) for whom ibrutinib is a more appropriate option

7.10. The Subcommittee noted ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK), a protein found in B cells that plays a role in oncogenic signalling. The Subcommittee noted that ibrutinib blocks B cell receptor signalling, which drives cells into apoptosis and/or disrupts cell migration and adherence to protective tumour microenvironments, and that this helps to limit the survival of cancerous B cells and thus may slow the progression of CLL or small lymphocytic lymphoma (SLL).

7.11. The Subcommittee noted that ibrutinib is an oral therapy that can be dispensed in community and carries a low risk of leucocytosis and tumour lysis syndrome (TLS) on initiation. The Subcommittee noted that ibrutinib is a continuous therapy used until progressive disease.

7.12. The Subcommittee noted that venetoclax monotherapy is currently funded for the first-line treatment of patients with previously untreated CLL with 17p deletion or TP53 mutation. The Subcommittee noted that venetoclax treatment involves a four week regimen of increasing doses of oral venetoclax, with TLS prophylaxis.

7.13. The Subcommittee noted the results of a single-arm, open-label phase II study that investigated the use of ibrutinib in patients with del 17p or TP53 mutation (Farooqui et al. Lancet Oncol. 2015;16(2):169-76). The Subcommittee noted that 97% (95% confidence interval (CI): 86-100) of previously untreated patients achieved an objective response, including partial response, in 55% of patients.

7.14. The Subcommittee noted the results of a multicentre, retrospective cohort study of CLL patients treated with ibrutinib in the front-line setting (Mato et al. Am J Hematol. 2018;93:1394-401). The Subcommittee noted the objective response rate (ORR) for patients with both del17p and TP53 mutation was 91% and that, at a median follow-up of 13.8 months, the median progression free survival and overall survival end points had not been reached.

7.15. The Subcommittee noted that international guidelines recommended the use of ibrutinib for upfront treatment of 17p-/TP53 mutated CLL.

7.16. The Subcommittee noted there are currently no published head-to-head trials comparing venetoclax and ibrutinib in this population. The Subcommittee considered that there is more evidence and a longer follow up for ibrutinib than venetoclax in the first-line treatment of 17p and TP53 CLL.

7.17. The Subcommittee noted that if ibrutinib were funded for previously untreated patients with 17p deletion/TP53 CLL, there would be no change to the currently available diagnostic testing. The Subcommittee considered that there would be a reduction in the requirement for TLS prophylactic regimens and associated hospital admissions.

7.18. The Subcommittee considered that, if ibrutinib and venetoclax were both funded for this indication, patient co-morbidity and patient preference would likely drive clinician choice. The Subcommittee considered that if ibrutinib were funded, it would be preferred for patients with bulky nodal disease or difficulties with hospital attendance for monitoring. However, the Subcommittee considered that venetoclax would be preferred for patients with primarily blood- and marrow-based CLL/SLL, when fixed term therapy was desired, or if anticoagulation was needed.

Ibrutinib for patients with CLL/SLL who progress during or relapse after venetoclax treatment, are intolerant of venetoclax, or for whom venetoclax is inappropriate

7.19. The Subcommittee noted that venetoclax in combination with rituximab is currently funded as treatment for a fixed two-year duration for patients with relapsed/refractory CLL that has relapsed within 36 months of previous treatment. The Subcommittee also noted that obinutuzumab-chlorambucil and chlorambucil monotherapy are also funded in this setting, depending on previous treatment received.

7.20. The Subcommittee considered that while venetoclax meets the health need for the majority of previously untreated del17p/TP53 mutated CLL patients and patients that relapse within 36 months, that there remains an unmet health need for patients who are intolerant of venetoclax, refractory to venetoclax, relapse after treatment with venetoclax, or for whom treatment with venetoclax is inappropriate. The Subcommittee considered that patients intolerant or refractory to venetoclax containing regimens had the highest unmet health.

7.21. With regards to patients with intolerance to venetoclax; the Subcommittee noted that in a retrospective cohort study where patients had received a median of three prior therapies, venetoclax was reportedly discontinued by 29% of patients, 21% of which were due to toxicity (Mato et al. Haematologica. 2018;103:1511-7). The Subcommittee noted that there are currently limited treatment options for patients who are intolerant of venetoclax.

7.22. The Subcommittee considered that approximately 20% of patients with del17p/TP53 mutation would not respond to treatment with venetoclax, based on the findings of a phase II trial in patients relapsed or refractory chronic lymphocytic leukaemia with 17p deletion (Stilgenbauer et al. Lancet Oncology. 2016;17:768-78). The Subcommittee also noted the results of the Murano trial of patients with relapsed/refractory CLL treated with venetoclax-rituximab, in which, 16.5% of patients experienced progression or death and there was a 2 year progression free survival (PFS) of 84.9% (Seymour et al. N Engl J Med. 2018;378:1107-1120). The Subcommittee noted that there are currently limited treatment options for patients who have progressed on venetoclax with or without rituximab, and that these options include obinutuzumab-chlorambucil (if not received previously), allogenic transplant or methyl prednisone. The Subcommittee considered that, in this setting, the appropriate comparator for ibrutinib would be obinutuzumab-chlorambucil.

7.23. The Subcommittee noted the results of the RESONATE trial, a randomised, multicentre, open-label, phase III study, which investigated the use of ibrutinib compared with ofatumumab in patients with previously treated CLL or SLL (Munir et al. Am J Hematol. 2019;94(12):1353-63). The Subcommittee noted the progression free survival benefit of ibrutinib over ofatumumab in the genomic high-risk population with del(17p), TP53 mutation, del(11q), and/or unmutated IGHV status (median progression free survival 44.1 vs 8.0 months; hazard ratio (HR): 0.110; 95% CI: 0.080-0.152). The Subcommittee also noted that approximately 30% of patients on this trial continued to receive treatment after five years. The Subcommittee noted that in the RESONATE-2 trial, 58% of patients continued to receive ibrutinib at 60 months follow up (Burger et al. Leukemia 2020;34:787–98). The Subcommittee noted that the results of the RESONATE and RESONATE 2 trials could be used to inform the expected median duration of ibrutinib treatment.

7.24. The Subcommittee considered that as an alternative therapy, there was good evidence supporting ibrutinib in the relapsed/refractory group and that the outcome data were more mature than that of venetoclax. The Subcommittee considered that as a subsequent line of therapy, given that ibrutinib has a different mechanism of action to venetoclax, patients refractory to venetoclax could respond to ibrutinib. The Subcommittee noted the recent publication of an observational retrospective consecutive case series, in which ibrutinib was reported to be effective for patients with CLL who progressed on venetoclax after a remission period of greater than 24 months, 91% of whom obtained an objective response (OR) (Lin et al. Blood. 2020;135:2266-70). The Subcommittee noted that patients who progressed quickly on venetoclax have been reported to have poorer outcomes when treated with a BTK inhibitor, however considered that this may be due to the higher risk disease in these patients.

7.25. The Subcommittee considered that if ibrutinib were funded in the relapsed/refractory setting that it would be unlikely to significantly change the first line treatment that patients would receive. However, the Subcommittee considered that there would be less pressure to use effective but potentially toxic therapies in first line, and therefore it would be important to specify the definition of relapsed/refractory and ensure that patients had undergone appropriate first line therapy such as receiving at least two cycles of chemoimmunotherapy in first line.

7.26. The Subcommittee considered that if ibrutinib were funded in the relapsed/refractory setting, there would be a reduction in the requirement for TLS prophylactic regimens and associated hospital admissions. The Subcommittee considered that treatment is required until progression for ibrutinib, unlike venetoclax and this would result in ongoing clinic requirements for surveillance of toxicity as well as progression, but that the associated costs would be minimal.

7.27. With regards to patients with bulky disease; the Subcommittee noted results suggesting reduced complete response (CR) rate and shorter duration of response in patients with bulky CLL/SLL treated with venetoclax (Roberts et al. Blood 2019 134(2) 111-122). The subcommittee noted that if both ibrutinib and venetoclax were funded there may be a clinician preference for the use of ibrutinib in patients with bulky nodal CLL/SLL.

7.28. With regards to patients who are challenged by inequity of access to hospital services; the Subcommittee noted that venetoclax is associated with an increased risk of TLS, with reports that 35.8% and 19.4% of patients on venetoclax treatment were at an intermediate or high TLS risk, respectively; with 80% of patients requiring hospitalisation during dose escalation (Mato et al. Haematolgica. 2018;103:1511-7). The Subcommittee noted that patients receiving treatment with venetoclax require monitoring for TLS. The Subcommittee noted the need to admit high risk, and some intermediate risk, patients and the need for outpatient laboratory monitoring of low risk patients. The Subcommittee considered that there can be difficulties obtaining timely laboratory results for regional patients whose blood must be sent to a main centre for analysis. The Subcommittee considered that for patients living in rural areas, where local laboratory monitoring may not be readily available, ibrutinib would provide a more suitable treatment option than venetoclax. The Subcommittee considered that while ibrutinib would be more convenient in these circumstances, the majority of patients can be managed appropriately with a TLS prophylactic strategy in place.

Ibrutinib for previously untreated CLL, fludarabine-based chemoimmunotherapy-inappropriate with or without immunoglobulin heavy chain variable region (IGHV) mutation

7.29. The Subcommittee noted that approximately 50% of CLL is IGHV unmutated, and that unmutated IGHV CLL is associated with shorter progression free survival and higher relapse risk when treated with traditional chemotherapy. The Subcommittee noted that currently, patients with unmutated IGHV have poorer outcomes on currently available therapy. The Subcommittee noted that some international guidelines provide separate recommendations for patients with mutated vs unmutated IGHV.

7.30. The Subcommittee noted the results of the ALLIANCE trial, which investigated the use of ibrutinib, ibrutinib with rituximab, and bendamustine-rituximab in patients aged over 65 years with previously untreated CLL (Woyach et al. N Eng J Med. 2018;379:2517-28). The Subcommittee noted that, in patients treated with ibrutinib, there was a significantly higher proportion of patients with progression free survival at two years compared with those treated with bendamustine-rituximab (HR: 0.39, 95% CI: 0.26-0.58,

p<0.001), however that there was no difference in overall survival advantage at two years for patients treated with ibrutinib compared with bendamustine-rituximab.

7.31. The Subcommittee noted that the RESONATE-2 trial reported that patients with mutated IGHV treated with ibrutinib experienced greater progression free survival compared with those treated with chlorambucil (HR: 0.153, 95% CI: 0.067-0.346); a similar result was also reported in patients with unmutated IGHV (HR: 0.105, 95% CI: 0.058-0.190) (Burger et al. Leukemia 2020;34:787–98). The Subcommittee noted that the comparator in RESONATE-2, chlorambucil, is a less potent treatment than other treatment options currently available for this patient group in New Zealand.

7.32. The Subcommittee noted results of the ECOG E1912 trial comparing FCR with ibrutinib and rituximab (Shanafelt et al. N Engl J Med. 2019;381:432-43), which showed that after a median follow up of 33.6 months, that the ibrutinib-rituximab showed improved progression free survival compared with FCR (89.4% vs. 72.9% at 3 years; hazard ratio for progression or death, 0.35; 95% confidence interval [CI], 0.22 to 0.56; P<0.001) and an overall survival (98.8% vs. 91.5% at 3 years; hazard ratio for death, 0.17; 95% CI, 0.05 to 0.54; P<0.001).

7.33. The Subcommittee considered that the appropriate comparator for ibrutinib in this setting would be obinutuzumab-chlorambucil. The Subcommittee considered that if ibrutinib was funded in this setting, it would reduce the infusion requirements associated with obinutuzumab-chlorambucil.

7.34. The Subcommittee considered that if ibrutinib were to be funded for previously untreated CLL where fludarabine-based chemoimmunotherapy is inappropriate, that the most likely treatment in the relapsed/refractory setting would be venetoclax with rituximab.

7.35. The Subcommittee considered that while ibrutinib may offer an improved treatment option compared with current standard of care, this would come at a substantial cost. The Subcommittee considered that defining groups by eligibility for chemoimmunotherapy may create inequities within the wider CLL patient population, by giving an unfair advantage to those patients less physically/physiologically fit, and that it would not be appropriate to determine eligibility for ibrutinib based on eligibility for and appropriateness of FCR treatment.

Ibrutinib for patients with relapsed/refractory del11q CLL

7.36. The Subcommittee noted that the current Special Authority for venetoclax in combination with rituximab includes patients with relapsed/refractory del 11q CLL. The Subcommittee noted that ibrutinib has not been specifically reviewed in this subpopulation previously.

7.37. The Subcommittee noted that the del11q mutation is present in 10-20% of patients with CLL, and that patients with del11q were considered to have shorter progression free survival (i.e. faster progression) that those without. The Subcommittee noted that data from the CLL8 trial reported this risk of faster progression is reversed with immunochemotherapy (Fischer et al. Blood. 2016;127:208-15). The Subcommittee considered that, when treated with FCR, the overall survival of patients with the del11q mutation is not adversely reduced compared with patients with normal cytogenetics. The Subcommittee considered that there was little evidence that the del11q subgroup is a high risk subgroup with greater unmet health need when compared with the wider CLL population.

7.38. The Subcommittee noted the results of a pooled analysis of the randomised RESONATE, RESONATE-2 and HELIOS trials, which reported that ibrutinib-treated patients with del11q had a significantly longer progression free survival than ibrutinib-treated patients without del11q (42-month progression free survival rate 70% vs. 65%, p=0.02) (Kipps et al. Clin Lymphoma Myeloma Leuk. 2019;19(11):715-22). The Subcommittee noted that the comparators in these trials (ofatumumab, chlorambucil and bendamustine-rituximab then placebo or ibrutinib) were less effective treatment regimens. The Subcommittee considered that there was no clear evidence that ibrutinib conferred an additional benefit for patients with del11q above the general CLL population.

7.39. The Subcommittee noted that ibrutinib with rituximab has reported favourable outcomes compared with FCR in patients with the del11q mutation (HR: 0.24; 95% CI: 0.10-0.62), however that this does not appear to differ substantially compared with all patients (HR:0.35, 95% CI: 0.22-0.56) (Shanafelt et al. N Engl J Med. 2019;381:432-43). The Subcommittee also noted that compared with bendamustine-rituximab, patients with del17 or del11q treated with ibrutinib were less likely to experience disease progression or death (HR: 0.26; 95% CI: 0.12-0.56) (Shanafelt et al. N Engl J Med. 2019;381:432-43). The Subcommittee noted that this result was also similar to the benefit observed in all patients in the study (HR: 0.37; 95% CI: 0.25-0.56).

7.40. The Subcommittee noted that testing for the del11q mutation (FISH) is routinely offered by all New Zealand District Health Boards. The Subcommittee considered that del17p, TP53 and IGHV mutational status are more significant prognostic risk factors than del11q.

7.41. The Subcommittee noted that there is emerging evidence that the residual ATM allele, located on chromosome 11q may be responsible for some of the adversity experienced by these patients, and considered that differentiating the del 11q subgroup from the wider population may be inappropriate as del 11q may be an oversimplification of a determinant of cellular response to treatment.

Venetoclax in combination with obinutuzumab for previously untreated patients, for whom fludarabine-based chemoimmunotherapy is inappropriate without IGHV mutation

7.42. The Subcommittee noted that venetoclax is an orally bioavailable small-molecule inhibitor of B-cell lymphoma BCL-2, an antiapoptotic protein that is overexpressed in CLL cells. The Subcommittee noted obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype, administered via intravenous infusion.

7.43. The Subcommittee considered that there was good evidence that patients with unmutated IGHV have worse clinical outcomes. The Subcommittee noted the results of the CLL-14 trial, a phase III, open-label randomised control trial that investigated the use of venetoclax in combination with obinutuzumab in patients with previously untreated B-lymphocyte antigen CD20 and CLL (Fischer et al. N Engl J Med. 2019;380:2225-36). The Subcommittee noted the estimated investigator assessed progression free survival at 36 months was 81.9% for venetoclax-obinutuzumab compared with 49.5% for the obinutuzumab-chlorambucil treated group (Al-Sawaf O et al. J Clin Oncol. 2020;38(suppl):abstr 8027) but that the median PFS for IGHV mutated and unmutated groups had not been reached. The Subcommittee noted that there was no difference in overall survival between the two groups in the study after a median follow up of 39.6 months.

7.44. The Subcommittee considered there to be no issues with the use of obinutuzumab outside of its Medsafe approved indication (in combination with chlorambucil).

7.45. The Subcommittee noted that the dosing titration schedule of venetoclax-obinutuzumab used in the trial was devised to reduce the risk of TLS by gradually decreasing the leukaemia cell tumour burden. The Subcommittee considered that commencing treatment with obinutuzumab prior to venetoclax was the most likely cause of the observed reduction in TLS incidence.

7.46. The Subcommittee considered the appropriate comparators for this population to be obinutuzumab-chlorambucil and bendamustine-rituximab. The Subcommittee considered that the appropriate comparator for venetoclax-obinutuzumab in this setting based on the proposed Special Authority criteria would be obinutuzumab-chlorambucil.

7.47. The Subcommittee noted that IGHV testing is not currently conducted in New Zealand, and is sent to Australia at a cost of approximately $400 per test. The Subcommittee considered that testing could be established locally, as commercial kits and software are available. The Subcommittee also considered that this mutation is stable, unlike 17p, and therefore only needs to be tested once.

7.48. The Subcommittee considered that there would be approximately 40-45 incident IGHV unmutated patients each year who would be eligible for treatment with venetoclax and obinutuzumab.

7.49. The Subcommittee considered that if this treatment option was only available for patients for whom fludarabine based chemoimmunotherapy was inappropriate, this may create inequities, as patients able to tolerate chemoimmunotherapy, who may also likely benefit from venetoclax-obinutuzumab treatment, would be excluded, however the Subcommittee noted that no trial had compared venetoclax-obinutuzumab to FCR. The Subcommittee considered that such a restriction could cause an increase in patients classified as inappropriate for chemoimmunotherapy in order to receive venetoclax-obinutuzumab treatment.