Cancer Treatments Subcommittee of PTAC
Meeting held 24 Mach 2017

(minutes for web publishing)

Cancer Treatments Subcommittee minutes 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 Treatments Subcommittee meeting; only the relevant portions of the minutes relating to Cancer Treatments Subcommittee discussions about an application or PHARMAC staff proposal that contains a recommendation are generally published.

The Cancer Treatments Subcommittee may:

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

These Subcommittee minutes were reviewed by PTAC at its meeting 10 & 11 August 2017.

1. Correspondence and Matters arising

Bendamustine for CLL

1.1. The Subcommittee noted that PHARMAC had received correspondence from a consultant haematologist responding to the September CaTSoP minutes for bendamustine for CLL which suggested the term "GFR >50" be removed from the Special Authority (SA) criteria and requested clarification on the recommendation to fund bendamustine in combination with rituximab as the combination was recommended in consensus guidelines.

1.2. The Subcommittee noted that the inclusion of the term "GFR >50" was made in error. The Subcommittee **recommended** that "GFR >50" was removed from its earlier Special Authority criteria recommendation for bendamustine for naïve CLL. The Subcommittee considered that removing the term from the SA criteria would not have a significant adverse fiscal impact.

1.3. The Subcommittee considered that bendamustine for CLL was best used in conjunction with rituximab to achieve the best clinical outcome. The Subcommittee **recommended** that if a decision was made to fund bendamustine, the rituximab SA criteria should be amended to allow it to be used in combination with bendamustine for patients with treatment naïve CLL.

Definition of remission duration in rituximab CLL criteria

1.4. The Subcommittee noted that PHARMAC had received feedback from a clinician following consultation on the Roche Bundle in late 2016 requesting amendment to the definition of remission duration in the rituximab for CLL renewal (retreatment) SA criteria.

1.5. The Subcommittee noted that the criteria in question stated "The patient has had a rituximab treatment-free interval of 36 months or more" which implied the interval started from the end of the treatment period rather than from the start of the treatment period.

1.6. The Subcommittee noted that in Tam et al. (Blood 2014;124:3059-64) the first remission duration (REM1) was defined as the time period from the first date of FCR therapy to the date of disease progression. The trial considered that for patients with a REM1 of greater than 3 years a FCR rechallenge represents a reasonable standard of care.

1.7. The Subcommittee noted that given the likely timings of clinical review, this is unlikely to result in any significant fiscal impact.

1.8. The Subcommittee **recommended** the following change to the rituximab CLL renewal criteria:

> 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:
> All of the following:
> 1. The patient's disease has relapsed following no more than one prior line of treatment with rituximab for CLL; and
> 2. The patient has had a**n** ~~rituximab treatment-free~~ interval of 36 months or more **since commencement of FCR treatment**; and
> 3. The patient does not have chromosome 17p deletion CLL; and

4. It is planned that the patient receives full dose fludarabine and cyclophosphamide (orally or dose equivalent intravenous administration); and
5. Rituximab to be administered in combination with fludarabine and cyclophosphamide for a maximum of 6 treatment cycles.

1.9. ld seek advice regarding how the discontinuation would be managed internationally.

Pertuzumab correspondence

1.10. The Subcommittee noted that PHARMAC had received a query from clinicians stating that the Special Authority criteria for pertuzumab were ambiguous with regards to the definition of “treatment-free interval”.

1.11. The Subcommittee noted that the current Special authority criteria for pertuzumab require patients to have ‘a treatment free interval of at least 12 months between prior (neo)adjuvant chemotherapy treatment and diagnosis of metastatic breast cancer’. Members noted that clinicians had indicated there was uncertainty regarding whether this should be interpreted as being from the last adjuvant dose of trastuzumab or the last chemotherapy dose.

1.12. The Subcommittee considered that it would be appropriate to amend the pertuzumab Special Authority criteria to clarify that the treatment-free interval should be measured from the end of prior adjuvant cytotoxic chemotherapy treatment to the diagnosis of metastatic disease. The Subcommittee considered that this amendment would not have a significant impact on the number of patients being treated and would improve clarity regarding the patient population for funded pertuzumab.

1.13. The Subcommittee noted that PHARMAC had also received a request for clarification of the use of pertuzumab for HER-2 positive breast cancer patients who had been referred for either adjuvant or neoadjuvant treatment with suspected metastatic disease, but who require longer follow-up in order to confirm diagnosis.

1.14. The Subcommittee noted that when diagnosis of metastatic disease was uncertain, it was standard practice to treat patients with the standard adjuvant regimen and once metastatic disease was confirmed switch to pertuzumab treatment.

1.15. The Subcommittee noted that use of pertuzumab for patients without metastatic disease was not currently a registered indication in New Zealand and published evidence to support its use in this setting had not been considered by CaTSoP. The Subcommittee considered it was inappropriate for patients to commence treatment with pertuzumab prior to confirmation of metastatic disease.

1.16. The Subcommittee noted that where patients had commenced adjuvant chemotherapy prior to confirmation of a metastatic diagnosis this meant they no longer met the pertuzumab criteria as it is currently worded due to the required treatment-free interval since prior adjuvant chemotherapy.

1.17. The Subcommittee considered that approximately 5% of patients may have an uncertain but subsequently confirmed metastatic diagnosis. The Subcommittee considered that these patients were part of the patient group intended to be eligible for funded pertuzumab treatment.

1.18. The Subcommittee considered that amending the Special Authority criteria for pertuzumab to allow for treatment in circumstances where metastatic disease was ambiguous would be with significant fiscal risk.

1.19. The Subcommittee considered that the most appropriate mechanism to provide funded access to pertuzumab for these patients would be via the Special Authority waiver mechanism. Members noted that the waiver process required manual completion of the relevant Special Authority form including the reason why a waiver was sought. Members considered that waiver applications should be accompanied by clinic letters and imaging reports; which would be required to demonstrate the patient's clinical circumstances met the intent of the pertuzumab Special Authority criteria.

1.20. The Subcommittee considered that there was a lack of awareness regarding the waiver process. The Subcommittee considered that it would be beneficial for PHARMAC to contact all oncology departments to inform them with regards to the expectations regarding these patients and the requirements of the waiver process.

1.21. The Subcommittee considered that the number of pertuzumab waiver applications received and therefore the continued appropriateness of the waiver mechanism for these patients should be reviewed at its next meeting.

Aminolevulinic acid hydrochloride (Gliolan) access criteria

1.22. The Subcommittee noted the PHARMAC sought the Subcommittee's advice on proposed Special Authority criteria for aminolevulinic acid hydrochloride (Gliolan).

1.23. The Subcommittee noted that the application for aminolevulinic acid hydrochloride had been previously considered by CaTSoP and PTAC in October 2014 and November 2014, respectively, and that both committee's had recommended funding aminolevulinic acid hydrochloride with high priority.

1.24. The Subcommittee noted that CaTSoP's previous recommendation in 2014 was for aminolevulinic acid hydrochloride to be funded for patients same patient group enrolled in the Stummer et al 2006 trial (Lancet Oncol 2006; 7:392-401).

1.25. The Subcommittee noted that since previous consideration Gliolan was now Medsafe registered for use in New Zealand indicated in adult patients for visualisation of malignant tissue during surgery for malignant gliomas that are glioblastoma multiforme on preoperative imaging, and who are intended for resection of the tumour.

1.26. The Subcommittee **recommended** that aminolevulinic acid be funded subject to the following clinical criteria:

> Initiation—high grade malignant glioma
> Both:
> 1. Patient has newly diagnosed, untreated, glioblastoma multiforme; and
> 2. Treatment to be used as adjuvant to fluorescence-guided resection

Erlotinib and Gefitnib for NSCLC access criteria

1.27. The Subcommittee noted that advice was sought regarding whether it was appropriate to amend the Special Authority criteria to allow for patients with EGFR positive NSCLC to switch TKI treatment due to intolerance developed following an extended period of time on treatment.

1.28. The Subcommittee noted that the current Special Authority criteria for erlotinib and gefitinib for NSCLC allowed switching due to intolerance, provided there was no evidence of disease progression, but only within the first 12 weeks of commencing treatment.

1.29. The Subcommittee considered that a very low number of patients would develop intolerance to treatment beyond 12 weeks of treatment. The Subcommittee considered that it was reasonable for such patients to switch TKI treatment due to intolerance at any time provided there was no evidence of disease progression.

1.30. The Subcommittee **recommended** that the Special Authority criteria for erlotinib and gefitinib for NSCLC be amended to remove the 12 week timeframe for switching due to intolerance.

2. Dexrazoxane for Cardioprotection in Conjunction with Anthracycline Chemotherapy

Recommendation

2.1. The Subcommittee reaffirmed its **recommendation** that dexrazoxane be funded for paediatric cancer patients participating in a randomised clinical trial with high priority. Members noted that funded access was currently provided via HML exemption.

2.2. The Subcommittee **recommended** that dexrazoxane be listed on the Pharmaceutical Schedule for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults who are not participating in a randomised clinical trial, with a medium priority. Members considered that the evidence addressed safety concerns, but noted that the priority was influenced by uncertainty regarding the long-term clinically meaningful benefit and harm of dexrazoxane in this population.

Discussion

2.3. The Subcommittee noted that the funding of dexrazoxane for cardioprotection in conjunction with anthracycline chemotherapy in children and young adults had been considered by both PTAC and CaTSoP on a number of occasions.

2.4. The Subcommittee noted that at its meeting in May 2013 PTAC had recommended funding of dexrazoxane for paediatric cancer patients participating in a randomised clinical trial, despite considering dexrazoxane itself to have no clear benefit and some evidence of potential harm in terms of an increased relative risk of secondary malignancies. The Subcommittee noted that PTAC had also recommended that the funding of dexrazoxane for adult patients and for paediatric cancer patients not participating in a randomised clinical trial, including those treated as per trial protocols, be declined.

2.5. The Subcommittee noted that, at its meeting September 2013, CaTSoP had agreed with PTAC's recommendations and considered that overall there was insufficient evidence at the time to support the use of dexrazoxane outside of clinical trials.

2.6. The Subcommittee noted that an HML exemption had been put in place for the use of dexrazoxane for cancer patients enrolled in a paediatric oncology clinical trial, which meant that currently the final decision on its use in this population was a matter of discretion for each DHB.

2.7. The Subcommittee noted that until recently the evidence for cardioprotective effect had been in the adult population, particularly women with breast cancer receiving adjuvant anthracycline containing chemotherapy. Members noted the meta-analysis published by van Dalen et al (2011 Cochrane Database Syst Rev. 2011 Jun 15;(6):CD003917. doi:10.1002/14651858.CD003917.pub4.) of randomised controlled trials which compared any cardioprotective agent to no additional therapy or placebo in cancer

patients (children and adults) receiving anthracyclines. Members noted that the 10 included studies had enrolled 1619 patients and had shown a statistically significant benefit for the use of dexrazoxane in preventing heart failure (risk ratio 0.29, 95% CI 0.20-0.41), however there was no evidence for a difference in cancer response rate or overall survival benefit.

2.8. The Subcommittee noted that anthracycline cardiotoxicity is not as significant an issue as it was 20 or 30 years ago, when the main trials into the use of dexrazoxane were undertaken, as current practice was to use shorter courses of anthracyclines.

2.9. The Subcommittee considered with respect to the paediatric oncology practice, anthracycline-induced cardiotoxicity remains a clinically significant issue with long-term consequences. Members considered that in this population there is a higher rate of death from late cardiac causes than second malignancy. The Subcommittee noted that an important factor increasing the risk of cardiac toxicity is the cumulative anthracycline dose received. Members noted that there is no established 'safe' dose of anthracycline but risk of morbidity is higher with higher cumulative doses.

2.10. The Subcommittee noted that anthracyclines are an important class of anticancer drugs that are used to treat many childhood malignancies. The Subcommittee considered that patients receiving treatment for osteosarcoma, Ewing's sarcoma, rhadbomyosarcoma, acute myeloid leukaemia (AML) and nephroblastoma would likely receive high dose anthracycline treatment with cumulative doses in excess of 250 mg/m2 doxorubicin equivalence. The Subcommittee considered that patients receiving doses of anthracycline at this level would be most at risk of anthracycline-induced cardiotoxicity.

2.11. The Subcommittee noted that dexrazoxane is not approved for use in Europe for children under the age of 16 years due to safety concerns, however, in the USA there is no restriction on the use of dexrazoxane in children where it is routinely used in Children's Oncology Group trials using anthracyclines.

Updated Evidence Review

2.12. The Subcommittee noted that further evidence regarding the use of dexrazoxane in the paediatric and adolescent oncology population had recently been published:

2.13. The Subcommittee noted evidence from Chow et al. (J Clin Oncol. 2015 20;33:2639-45) which reported long-term outcomes of 1008 patients enrolled in three Children's Oncology Group randomised controlled trials: P9404 (T cell acute lymphoblastic leukaemia/lymphoma; n=537), P9425 (intermediate/high-risk Hodgkin lymphoma (HL); n= 216), and P9426 (low-risk HL; n=255).

2.14. The Subcommittee noted that each trial randomised patients to doxorubicin (cumulative protocol-specified dose of 100-360mg/m2) with or without dexrazoxane at a dose ratio of 10:1. The Subcommittee noted that the trials ran from 1996-2008 and, while formal reporting of data from two trials was to 2008, one trial is ongoing with data reported from cut-off 31 December 2011.

2.15. The Subcommittee noted that with a median follow-up of 12.6 years (range 0-15.5 years), overall it was reported that dexrazoxane exposure was not associated with an increased hazard of relapse (HR 0.81; 95% CI 0.60-1.08) or death (HR 1.03; 95% CI 0.73-1.45). Members noted no deaths from a primary cardiovascular event were reported and heart failure was not seen.

2.16. The Subcommittee noted the authors concluded that dexrazoxane did not appear to interfere with cancer treatment efficacy, in terms of original cancer mortality or overall risk of relapse. The Subcommittee noted there were 18 deaths from a secondary cancer, mainly as a result of AML/MDS, however the overall number of events was too small to identify a statistically significant difference.

2.17. The Subcommittee noted evidence from Asselin et al. (J Clin Oncol. 2016 10;34:854-62) which reported outcomes of 573 patients, aged between 1 and 21 years, with newly diagnosed T-cell acute lymphoblastic leukaemia or advanced-stage lymphoblastic NHL treated on Paediatric Oncology Group Protocol POG9404 which included random assignment to treatment with or without dexrazoxane at a dose ratio of 10:1. Members noted that serum cardiac troponin-T concentrations and echocardiograms were performed during treatment, then 3 and 6 years after diagnosis.

2.18. The Subcommittee noted that the protocol specified a cumulative doxorubicin dose of 360 mg/m2 and allowed dose reduction. The Subcommittee noted that it was reported that neither event-free survival or overall survival at 5 and 10 years were reported to differ between groups (p=0.9). Members considered that the 10 year event-free survival of 74% was comparable with other studies. Members noted that troponin concentrations were lower in the dexrazoxane group and, at three years follow up, surrogate echocardiogram features were significantly worse in the group that did not receive dexrazoxane. Members considered that a limitation of this data was that too few patients (<10%) had echocardiograms at six years follow up.

2.19. The Subcommittee noted that the authors concluded that the addition of dexrazoxane to a doxorubicin containing regimen did not compromise antileukemic efficacy and had cardioprotective effect sustained at the 3-year follow-up; and that the incidences of toxicity and secondary malignancy were not significantly increased in patients who received dexrazoxane.

2.20. The Subcommittee noted evidence from Seif et al. (Pediatr Blood Cancer. 2015;62:704-9) which reported secondary AML risk in a retrospective cohort of 15,532 paediatric cancer patients with newly identified malignancies (excluding AML) receiving anthracyclines of which 1,406 received dexrazoxane.

2.21. The Subcommittee noted that the rate of secondary AML was 0.52% for the entire cohort; incidence of secondary AML 0.21% (3 patients) in the dexrazoxane exposed group and 0.55% (77 of 14126 patients) in the unexposed group. The Subcommittee noted that the authors concluded that these data support dexrazoxane's safety in the general paediatric population.

General comments

2.22. The Subcommittee considered that overall there was good randomised evidence of improvement in surrogate markers for cardioprotective effect with the use of dexrazoxane with no observed difference in risk of relapse, death or secondary malignancy rate.

2.23. The Subcommittee considered that the currently available evidence supported the long-term safety of dexrazoxane for the primary prevention of cardiotoxicity in conjunction with chemotherapy in children and young adults.

2.24. The Subcommittee considered that there remained limited information regarding a clinically meaningful, long-term cardioprotective effect of dexrazoxane. However, based on currently available evidence, the Subcommittee considered there was

evidence of a benefit from the use of dexrazoxane in preventing anthracycline-induced cardiac toxicity in children and young adults. Members noted that the magnitude of this clinical benefit was uncertain.

2.25. The Subcommittee considered the use of dexrazoxane should be limited to those treated with high dose anthracyclines given with curative intent, and with an anticipated cumulative lifetime dose of anthracycline of 250 mg/m2 doxorubicin equivalent or greater.

3. Pembrolizumab for Advanced Non-Small Cell Lung Cancer

Application

3.1. The Subcommittee reviewed funding proposals from Merck Sharpe and Dohme (MSD) for the funding of pembrolizumab (Keytruda) for treatment of two groups of advanced non-small cell lung cancer (NSCLC) patients:

- as first-line treatment for EGFR wildtype patients and second-line for EGFR positive patients whose tumours express programmed death ligand 1 (PD-L1) at a level of ≥ 50%
- as second-line treatment for EGFR wildtype patients and third-line for EGFR positive patients whose tumours express PD-L1 at a level of ≥ 1%.

Recommendation

3.2. The Subcommittee **recommended** that pembrolizumab be funded for the first-line treatment of patients with previously untreated advanced NSCLC whose tumours express PD-L1 at a level of ≥ 50% with a low priority, subject to the following Special Authority criteria:

> PEMBROLIZUMAB - Special Authority for Subsidy – PCT only
>
> Initial application - (NSCLC first-line) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
>
> All of the following:
> 1. Patient has unresectable stage III or IV non-small cell lung cancer; and
> 2. Patient has an ECOG 0-1; and
> 3. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 50% as determined by a validated Dako-based diagnostic test; and
> 4. The patient has not had prior treatment for their metastatic disease; and
> 5. There is documentation confirming that the disease does not express activating mutations of EGFR tyrosine kinase; and
> 6. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks for a maximum of 12 weeks; and
> 7. Baseline measurement of overall tumour burden is documented.
>
> Renewal – (NSCLC first line) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:
>
> 1. Any of the following:
>   1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
>   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
>   1.3. Patient has stable disease according to RECIST criteria; and
> 2. Response to treatment in target lesions has been determined by radiologic assessment (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. Pembrolizumab to be used at a maximum dose of 200 mg every 3 weeks for a maximum of 12 weeks; and
6. Treatment to be discontinued at disease progression, unacceptable toxicity or after a total duration of 24 months from commencement.

3.3. The Subcommittee **recommended** that pembrolizumab be funded for the second or third-line treatment of patients with previously treated advanced NSCLC whose tumours express PD-L1 at a level of ≥ 1% with a low priority, subject to the following Special Authority criteria:

Initial application - (NSCLC second-line) only from a medical oncologist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:
1. Patient has unresectable stage III or IV Non-Small Cell Lung Cancer; and
2. Patient has an ECOG 0-1; and
3. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 1% as determined by a validated Dako-based diagnostic test; and
4. The patient has documented disease progression following treatment with platinum based chemotherapy; and
5. Either:
    5.1. There is documentation confirming that the disease does not express activating mutations of EGFR tyrosine kinase; or
    5.2. Both:
        5.2.1. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
        5.2.2. The patient has documented disease progression following treatment with erlotinib or gefitinib; and
6. Pembrolizumab to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks; and
7. Baseline measurement of overall tumour burden is documented.

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

1. Any of the following:
    1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
    1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
    1.3. Patient has stable disease according to RECIST criteria; and
2. Response to treatment in target lesions has been determined by radiologic assessment (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. Pembrolizumab to be used at a maximum dose of 2 mg/kg every 3 weeks for a maximum of 12 weeks; and
6. Treatment to be discontinued at disease progression, unacceptable toxicity or after a total duration of 24 months from commencement.

3.4. The Subcommittee noted that the priority of its recommendations were influenced by the health need of the patient population, the high level of uncertainty regarding the utility of PD-L1 as a biomarker, complexity surrounding PD-L1 testing, and the high price sought by the supplier.

3.5. The Subcommittee noted that the cost-effectiveness of pembrolizumab in the previously treated population would likely increase at higher PD-L1 expression thresholds which, if significant, would increase the priority of its recommendation in this setting.

Discussion

3.6. The Subcommittee noted that in 2013 lung cancer was the fifth most common cancer registered in New Zealand, accounting for 9.2% of all cancer registrations, and was the leading cause of cancer death overall and by gender.

3.7. The Subcommittee noted that registration and mortality rates for lung cancer are consistently 2-4 times higher for Maori than for non-Maori.

3.8. The Subcommittee noted that survival for lung cancer patients with currently funded treatments was poor for patients with locally or distally advanced disease, with a relative survival at 1 year of around 30%.

3.9. The Subcommittee noted that pembrolizumab is currently registered in New Zealand for locally advanced or metastatic melanoma and previously treated advanced NSCLC, and was currently being assessed by Medsafe for registration in the first-line setting.

3.10. The Subcommittee noted that pembrolizumab and nivolumab are currently funded for the treatment of patients with locally advanced or metastatic melanoma.

3.11. The Subcommittee noted that at its meeting in November 2016 PTAC had considered an application for pembrolizumab as monotherapy for the second or third-line treatment of locally advanced, or metastatic, unresectable NSCLC whose tumours express PD-L1 at a level of ≥ 1%. The Subcommittee noted that PTAC had recommended funding in this setting with low priority due to: the significant immaturity of currently available data, uncertainty that the observed trial-based improvements translate to long-term clinically meaningful overall survival gains, and significant uncertainty regarding the optimal duration of treatment.

3.12. The Subcommittee noted that PTAC had further recommended the application for pembrolizumab be referred to CaTSoP for advice and the application was on the agenda for consideration at this meeting.

3.13. The Subcommittee noted that applications for nivolumab as monotherapy for the treatment of locally advanced or metastatic squamous and non-squamous NSCLC in second/third-line settings for patients who have progressed on or after prior platinum based chemotherapy were considered by CaTSoP at its meeting in April 2016 and PTAC in May 2016. The Subcommittee noted that funding for nivolumab for advanced NSCLC had been recommended with low priority noting the immaturity of data and limited and uncertain benefit over current treatments.

3.14. The Subcommittee noted that it had previously proposed access criteria for nivolumab for NSCLC which did not require patients to undergo testing for PD-L1 expression or any other biomarker.

First line evidence

3.15. The Subcommittee noted that the key evidence for pembrolizumab for previously untreated patients with advanced NSCLC comes from KEYNOTE-024; a randomised, open-label, phase 3 study of pembrolizumab (fixed dose 200 mg every 3 weeks) compared with investigators choice of platinum chemotherapy in 305 patients with previously untreated stage IV NSCLC with high PD-L1 positive (PD-L1 expression ≥50%) without EGFR mutation or ALK translocation (Reck et al. NEJM 2016;375:1823-33).

3.16. The Subcommittee noted that eligibility criteria included no prior systemic therapy for metastatic disease, ECOG 0-1, a life expectancy of at least 3 months, and at least one measurable lesion according to RECIST.

3.17. The Subcommittee noted that patients were randomly assigned 1:1 to receive treatment with either pembrolizumab (n=154) for 35 cycles of the investigator's choice of the following five platinum-based chemotherapy for 4-6 cycles (n=151); carboplatin or cisplatin plus pemetrexed, carboplatin or cisplatin plus gemcitabine, or carboplatin plus paclitaxel. The Subcommittee noted that pemetrexed is not currently funded in New Zealand, however, considered that the non-pemetrexed treated study population was comparable to the New Zealand setting.

3.18. The Subcommittee noted that 30.2% of the screened population had PD-L1 ≥50% but that only 18.4% went onto trial. The Subcommittee considered it was unclear from the published study data the reason why approximately 200 screened patients with PD-L1 status ≥50% did not progress to randomisation. Members considered this likely represented a patient cohort who were too sick to progress on study and, if this was the case, meant the study population would be a preselected 'fitter' population than would be seen in clinical practice.

3.19. The Subcommittee noted that per protocol study treatment continued for the specified number of cycles or until the patient had radiologic disease progression as per RECIST, or treatment-related adverse events of unacceptable severity, or until investigator decided to withdraw the patient, whichever occurred first. The Subcommittee noted that patients in either treatment group who were in clinically stable condition and were considered by the investigator to be deriving clinical benefit could continue therapy after disease progression. The Subcommittee noted that median duration of treatment was 7.0 months or 10.5 cycles in pembrolizumab arm and 3.5 months or 4 cycles in the chemotherapy arm.

3.20. The Subcommittee noted that study protocol allowed patients in the chemotherapy group who had disease progression to cross over to receive pembrolizumab. Members noted that crossover was not permitted from pembrolizumab to the chemotherapy group and there were no guidelines regarding therapy after disease progression from the pembrolizumab arm. The Subcommittee noted that at the time of data cutoff, 35.4% of the enrolled patients had died, 57.6% were still receiving pembrolizumab, and 43.7% of the patients in the chemotherapy arm had crossed over to receive pembrolizumab after disease progression.

3.21. The Subcommittee noted that at a median follow-up of 11.2 months (6.3-19.7), median progression-free survival (PFS), the primary end-point, was 10.3 months (95% CI, 6.7-NR) in the pembrolizumab arm and 6.0 months (95% CI, 4.2-6.2) in the chemotherapy arm (HR for disease progression or death, 0.50; 95% CI, 0.37-0.68; p<0.0001).

3.22. The Subcommittee noted that the estimated percentage of patients who were alive at 6 months was 80.2% (95% CI, 72.9-85.7) in the pembrolizumab arm and 72.4% (95% CI 64.5-78.9) in the chemotherapy arm.

3.23. The Subcommittee considered that there was uncertainty regarding the durability of response to pembrolizumab as 50% patients remained on treatment at data cut-off. Members noted that it would not be appropriate to extrapolate durability of response in the NSCLC population based on data from melanoma patients.

3.24. The Subcommittee noted that during treatment with the initially assigned therapy, treatment-related adverse events occurred in 73.4% of the patients in the

pembrolizumab arm and in 90.0% of the patients in the chemotherapy arm. The Subcommittee noted that grade 3 or greater treatment-related adverse events occurred in 26.6% of patient in the pembrolizumab arm and in 53.3% in the chemotherapy arm. Members noted the most common treatment-related adverse events were diarrhoea (in 14.3% of the patients), fatigue (10.4%), and pyrexia (10.4%) in the pembrolizumab group and anaemia (44.0%), nausea (43.3%), and fatigue (28.7%) in the chemotherapy group.

Second-line evidence

3.25. The Subcommittee noted that the key evidence for pembrolizumab for previously treated NSCLC comes from KEYNOTE-010; a randomised, open-label, phase 2/3 study of pembrolizumab (2 mg/kg every 3 weeks (n=345) or 10 mg/kg every 3 weeks (n=346)) compared to docetaxel (75 mg/kg every 3 weeks, n=343) in 1034 patients with previously treated, PD-L1 positive (PD-L1 expression >1%), advanced NSCLC (Herbst et al. Lancet 2016;387:1540-50).

3.26. The Subcommittee noted that patients were treated for 24 months or until confirmed disease progression, intolerable toxic effect, physician decision, patient withdrawal or other reasons. Members noted that there appeared to be a high level of withdrawal due to physician decision which was a highly subjective criterion.

3.27. The Subcommittee noted that eligibility criteria included confirmed disease progression after two or more cycles of platinum-doublet chemotherapy and a tyrosine kinase inhibitor for EGFR-positive or ALK-positive patients, no active brain metastases, ECOG 0-1. Members noted that patients had received prior treatment with PD-1 inhibitors or docetaxel, interstitial lung disease or history of pneumonitis requiring systemic steroids were excluded.

3.28. The Subcommittee noted the protocol was amended to require fresh biopsy material for PD-L1 testing.

3.29. The Subcommittee noted that patients in the docetaxel arm were not permitted to cross over to receive pembrolizumab, however, 16% received subsequent treatment with other immunotherapies. Members noted that 40% of patients in the pembrolizumab 2 mg/kg group, 38% of patients in the pembrolizumab 10 mg/kg group, and 44% of patients in the docetaxel group received additional antineoplastic treatment after discontinuation of study treatment.

3.30. The Subcommittee noted that, at a median follow-up of 13.1 months (IQR 8.6-17.7), median overall survival (OS) for patients with a PD-L1 tumour proportion score (TPS) of 50% or greater was 14.9 months (95% CI 10.4–not reached) for the pembrolizumab 2 mg/kg group, 17.3 months (11.8–not reached) for the pembrolizumab 10 mg/kg group, and 8.2 months (6.4–10.7) for the docetaxel group.

3.31. The Subcommittee noted that for patients with a TPS of 1% or greater median OS was 10.4 months (95% CI 9.4–11.9) for the pembrolizumab 2 mg/kg group, 12.7 months (10.0–17.3) for the pembrolizumab 10 mg/kg group, and 8.5 months (95% CI, 7.5–9.8) for the docetaxel group.

3.32. The Subcommittee noted that OS was similar in the two pembrolizumab groups both in patients with a PD-L1 TPS of 50% or greater (HR for 2 mg/kg vs 10 mg/kg 1.12, 95% CI 0.77–1.62) and in the total population; TPS 1% or greater (HR 1.17, 0.94–1.45).

3.33. The Subcommittee noted updated results for KEYNOTE-010 were presented at the 17th World Conference on Lung Cancer in 2016 which reported, at a median follow-up of 2.1 years (1.5-3.0), the median OS was 10.5 months in the pembrolizumab 2mg/kg group, 13.4 months in the 10mg/kg group, and 8.6 months in the docetaxel group.

PD-L1 as a biomarker

3.34. The Subcommittee considered that currently published literature was conflicted regarding the predictive value of PD-L1 expression and that nominating a threshold to reflect a target population was essentially arbitrary and may change with evolving clinical data.

3.35. The Subcommittee noted that based on KEYNOTE-001 data the response rate to pembrolizumab in NSCLC differs depending on PD-L1 tumour proportion score (TPS) and that patients with a TPS less than 1% had the potential to respond to treatment with pembrolizumab. Members considered the response rate in patients with TPS <1% was similar in patients with TPS 1%-24% (10.3% and 12.6% respectively) and it was unclear why these patients had been excluded from further studies.

3.36. The Subcommittee considered that current literature suggested there was a high level of heterogeneity of PD-L1 expression between tumour cell types. Members also noted that not only tumour cell types but also tumour-infiltrating immune cells express PD-L1, and it was uncertain whether PD-L1 expression on immune cells could be more relevant to the PD-1 inhibitor response than its expression on tumour cells, in some instances.

3.37. The Subcommittee considered it was uncertain whether biopsied tissue would be representative of PD-L1 expression of the tumour as a whole. The Committee considered that any test result would be highly dependent on the cells biopsied rather than PD-L1 expression of the overall tumour.

3.38. Members considered the literature was also unresolved regarding the variability of PD-L1 expression over time and modulation by previous treatment.

3.39. Members considered that based on currently published evidence it remained uncertain whether PD-L1 expression was a definitive predictive biomarker in response to immune checkpoint inhibitors for patients with NSCLC, and noted that several other candidate predictive biomarkers for response to immune checkpoint inhibitors in NSCLC were currently being investigated including gene expression and tumour mutational load.

3.40. The Subcommittee considered that there were significant outstanding issues with regards to the reliability of PD-L1 expression testing and its utility in defining eligibility for treatment, particularly at a threshold of 1% or greater. Members considered the use of a 1% threshold cast doubt on the value of undergoing PD-L1 expression testing given the similarity of response in patients with TPS<1% and 1%-24%. Members considered there may be value in PD-L1 testing with higher thresholds, such as 50% or greater, as the response rate to pembrolizumab was significantly higher than at lower thresholds. Members considered that the cost-effectiveness of various PD-L1 expression thresholds should be investigated.

3.41. The Subcommittee considered that if PD-L1 were to be used to determine eligibility for funded treatment, there would be incentive for patients to undergo multiple biopsies and/or assays to achieve a PD-L1 test result that reaches the defined 'positive' threshold. The Subcommittee noted that the supplier's proposed treatment paradigm

included only upfront PD-L1 testing. The Subcommittee considered patients would likely be tested prior to commencing second-line treatment. The Subcommittee considered that the supplier's estimates of the number of PD-L1 tests undertaken per year was underestimated for this reason.

3.42. Members considered that in NSCLC tissue availability for biopsy was a limiting factor. Member considered it was likely a small number of patients may not have tissue available to undergo PD-L1 testing which could exclude patients with the potential to respond.

3.43. The Subcommittee considered estimates of PD-L1 expression in the literature vary widely and it was uncertain whether this would translate to a New Zealand population. The Subcommittee considered that the percentage seen in New Zealand populations in clinical practice could potentially be influenced by the testing methodology adopted by providers in New Zealand.

PD-L1 expression testing platform

3.44. The Subcommittee noted that it did not appear there was a globally accepted testing mechanism for PD-L1 expression.

3.45. The Subcommittee noted that PD-L1 expression testing in KEYNOTE-024 was undertaken on a Dako-based immunohistochemistry companion diagnostic staining platform. Members were not aware of any providers of a Dako-based platform in New Zealand and considered that setting up this facility would require notable investment.

3.46. The Subcommittee considered that most immunohistochemistry tests are optimised to provide binary outcomes whereas PD-L1 expression was a continuum.

3.47. The Subcommittee noted that the supplier had indicated a test protocol would need to be established in New Zealand along with training for pathologists in the quantification of PD-L1 expression. The Subcommittee noted that the test protocol would likely be lab-developed and would require ongoing validation against the companion diagnostic assay from the registration trial. The Subcommittee considered the costs associated with this could be significant.

3.48. The Subcommittee noted there did not currently appear to be any planned standardisation or regulation of the testing platform development in New Zealand and it was likely this would lead to variation between testing providers. The Subcommittee considered, based on a study comparing the performance of PD-L1 platforms (Rimm et al JAMA Oncol. 2017; doi:10.1001/jamaoncol.2017.0013), it was possible there would be a high level of variability between results returned on different testing platforms. Members considered it was likely that the difference in platform used could also lead to variation in interpretation of PD-L1 status by pathologists.

3.49. The Committee considered that there were a number of technical and methodological issues with PD-L1 expression testing which appeared to have a strong impact on the outcome of PD-L1 test results.

3.50. The Subcommittee considered that if PD-L1 were used to determine eligibility for funded treatment it would be appropriate to specify the PD-L1 testing platform in the access criteria.

General comments

3.51. The Subcommittee considered that there was good evidence that pembrolizumab provided a benefit in the first and second-line treatment of patients with advanced NSCLC over current chemotherapy options but noted the open-label study designs and lack of data maturity.

3.52. The Subcommittee considered that pembrolizumab appeared to be relatively tolerable compared with chemotherapy, but that due to the data being early it was likely adverse events were under-reported in both the first and second-line settings.

3.53. The Subcommittee considered that, given the improved tolerability profile of pembrolizumab when compared with chemotherapy, it was likely some patients who were not fit for platinum regimens would receive treatment with pembrolizumab. Members noted that if pembrolizumab were to be funded in both the first and second-line settings, around 80% of NSCLC patients would be eligible for treatment with this agent as some point in their disease course. Members considered if pembrolizumab were funded in a second-line setting, prescribers treating all existing patients would seek treatment for them within the first year of listing.

3.54. The Subcommittee considered that funding of pembrolizumab for patients with advanced NSCLC would represent an additional line of therapy in both the first and second-line setting.

3.55. The Subcommittee noted that a change to the 200 mg fixed dose for all indications was possible in future. The Subcommittee considered that the 200 mg fixed dose, as opposed to the 2 mg/kg dosing currently registered in the second-line NSCLC and melanoma settings, would result in a significant increase in the number of milligrams administered per patient. Members noted the clinical reason for this change was unclear given previously published data indicated there was no statistical difference between the 2 mg/kg and 10 mg/kg dosings.

3.56. The Subcommittee noted that a change in the presentation of pembrolizumab to 100 mg vial was possible in future and considered that this would likely result in increased wastage compared to the 50 mg vial presentation currently supplied.

3.57. The Subcommittee considered that based on data from KEYNOTE-024 and KEYNOTE-010 it would be appropriate to limit the duration of treatment to 2 years from commencement of therapy with pembrolizumab, however, considered this should be reviewed once further data was available.

3.58. The Subcommittee noted that the KEYNOTE-042 trial was currently being undertaken to investigate the use of pembrolizumab in treatment naïve NSCLC with PD-L1 expression of 1% or greater.

3.59. The Subcommittee noted that there were a number of other PD-1 or PD-L1 inhibitors in development for use in the treatment of patients with NSCLC either as monotherapy or in combination with other treatments.

4. [Withheld]

5. Teniposide for Multiply Relapsed Multiple Myeloma

Application

5.1. The Subcommittee considered a clinician funding application from a Haematologist for the use of teniposide in multiply relapsed/refractory multiple myeloma, specifically for patients who have progressed following a proteasome inhibitor, such as bortezomib, and lenalidomide. The Subcommittee noted the applicant requested teniposide be funded for use in combination therapy with cyclophosphomide and steroids for 6 cycles.

Recommendation

5.2. The Subcommittee **recommended** that the funding application for the listing of teniposide for multiply relapsed multiple myeloma be declined due to a lack of evidence for a health benefit.

Discussion

5.3. The Subcommittee noted multiple myeloma (MM) is an incurable disease characterised by the neoplastic proliferation of plasma cells in the bone marrow that produce a monoclonal immunoglobulin. Most patients with MM present with signs or symptoms related to the infiltration of plasma cells into the bone or other organs or to kidney damage from excess light chains. Anaemia is present in almost three quarters of new presentations, with bone pain and elevated creatinine a feature in about half.

5.4. While the applicant requested use of teniposide in patients progressive through treatment with a proteasome inhibitor as well as lenalidomide, the Subcommittee noted that, in 2017, transplant eligible patients will have progressed through a bone marrow transplant procedure and through two lines of immunomodulating agents - thalidomide and lenalidomide. Thus the application would be essentially for use of teniposide as part of fourth line therapy in a group of patients who are very unwell.

5.5. The Subcommittee noted that refractory MM patients may have pain and be at risk of fracture with a life expectancy measured in short months. The Subcommittee noted that the primary goal of therapy for these patients is symptom improvement and to improve quality of life, with survival (prolongation of life) as a secondary goal.

5.6. The Subcommittee noted the risk of MM is approximately 40% higher in males than females, and that Māori and Pacific Islanders have a substantially higher risk of being diagnosed with, and dying from, MM than non-Māori. It is not clear why there is a higher risk of MM in Māori and Pacific Islanders.

5.7. The Subcommittee noted that teniposide is a very old drug which does not currently have Medsafe approval. It is delivered via intravenous infusion.

5.8. The Subcommittee noted that PHARMAC had received a number of Named Patient Pharmaceutical Assessment (NPPA) applications for teniposide for multiply relapsed MM. The Subcommittee noted that at their meetings in March 2013 and March 2015, they had recommended that PHARMAC seek a clinician funding application for its use in this indication.

5.9. The Subcommittee noted that in April 2016, PHARMAC decided to change its approach and no longer consider teniposide for the group of multiply relapsed MM patients under the NPPA pathway. This was based on both the historical number of applications and clinical advice received indicating that this group would be more appropriate to consider via the Pharmaceutical Schedule application process.

5.10. The Subcommittee noted that the most widely used funded treatment options for MM include bortezomib, thalidomide, lenalidomide, melphalan and autologous haematopoietic stem cell transplantation in eligible patients, with the choice of treatment driven by patient fitness/comorbidities and eligibility for transplantation.

5.11. The Subcommittee noted the applicant sought teniposide in the multiply relapsed MM population which have few treatment options and typically have progressive bone disease with pain and bone fractures and a poor prognosis of weeks to months. The Subcommittee considered that the health need of this population was high.

5.12. The Subcommittee noted that in 2017, the alternative unfunded treatments for this patient group in a New Zealand context would be compassionate access carfilzomib, a clinical trial with either an antiCD38 or anti PD-1 therapy, or supportive care. Members noted that they had previously recommended pomalidomide for funding for patients in this setting but it remains unfunded.

5.13. The Subcommittee noted the report from Tirelli et al (Am J Clin Oncol. 1985;8:329-31) dating from 1985 - a single agent phase II trial of 30 patients. Of the study population only 25 were evaluable for response due to loss of follow-up due to early death. Members noted that the authors concluded that the drug has some activity - with 7 responses in the study population using Myeloma Task Force definitions of response (half of whom were previously untreated). The responses were of short duration - median 4 months. Toxicity was not well reported. Emesis appeared to be the primary toxicity contributed to the combination. The Subcommittee noted that in 2017 emesis regimens would be significantly improved so this was unlikely to be such a therapeutic issue.

5.14. The Subcommittee noted the report from Leoni et al. (Leuk Lymphoma. 1992;7:481-7), who published a combination study of teniposide in 43 patients with refractory MM, 37 evaluable (again due to loss to follow-up due to early death). Prior therapy was by 2017 standards historic - as current patients will be more heavily pre-treated so the therapeutic response may be overestimated. Teniposide was used in combination with cyclophosphamide and dexamethasone. Response was assessed using levels of myeloma protein or marrow indices which is usual in myeloma studies. A Major response was achieved in 18 patients (50% of the patient cohort) and a minor response in a further 9 patients. The report does describe that almost all patients receiving teniposide in combination with cyclophosphamide and dexamethasone experienced relief of bone pain and "an amelioration of their performance status" which is encouraging. Toxicity was deemed acceptable by the authors but is not described in any detail, and with two early deaths is concerning.

5.15. The Subcommittee noted two abstract presentations detailing the responses of 23 heavily pre-treated MM patients receiving teniposide, cyclophosphamide and prednisone chemotherapy at North Shore Hospital, Auckland between January 2012 and July 2014. Twelve patients (52.2%) completed 4-6 cycles chemotherapy containing tenoposide. Treatment response could be calculated in 20 out of the 23 patients in the cohort. Although responses were reported differently in the abstracts, it appears that an overall response rate of 27% was observed. This represents the three patients with a partial response and three having a very good partial response. The median time to progression/next treatment for the 17 patients with partial response or stable disease was 5.2 months. During the follow-up period, 12 of the 23 patients died (52.2%). Toxicity is not described in any detail with the authors reporting that the chemotherapy was fairly-well tolerated with more than half the patients completing 4 to 6 cycles, and only one dying from chemotherapy related toxicity.

5.16. The Subcommittee noted a review of the comparative analysis of single-agent drug activity in MM (Kortuem et al. Clin Lymphoma Myeloma Leuk. 2014;14:284-90). Based on the activity of teniposide in the Tirelli et al study, Korteum et al. rated teniposide response as just above their proposed threshold of interest of >22%.

5.17. The Subcommittee considered that the evidence shows that teniposide does have some limited activity in multiple myeloma. However the level of evidence to support the funding application for use in combination therapy in a heavily pre-treated population, in a 2017 context, is very poor. All the papers suffer from major quality issues, but were published at a time when there was lower publication rigor. All report non-randomised data. The definitions of response and durability of response are unclear, the clinical benefit is unclear and the toxicity impacts are poorly reported. The Subcommittee considered that the applicability of both the Tirelli and Leoni et al. trials to current practice was limited. It is clear that it may add toxicity and as the patient population in 2017 is more heavily pre-treated it could be argued that the potential for toxicity (eg myelosuppression and neurotoxicity) is higher now than at the time of the Tirelli and Leoni papers. There is no quality of life data to support its use and the overall clinical benefit analysis cannot be proven. There is uncertainty as to how much additional benefit teniposide adds to high dose steroids and cyclophosphamide in this population.

5.18. There are now several additional options for prior lines of treatment and the single-agent regimen in Tirelli et al with a large proportion of previously untreated patients is not relevant in the setting applied for.

5.19. The Subcommittee considered it remained unclear whether reported symptom improvement was observed due to the concomitant administration of high-dose steroids.

5.20. The Subcommittee noted that the PEP-C regimen (prednisone, etoposide, procarbazine and cyclophosphamide) was funded and being used in this multiply relapsed MM population as a last-line palliative treatment option. The Subcommittee considered that this was likely a more suitable treatment, that would be preferred by most clinicians, as it was an oral regimen.

5.21. The Subcommittee noted that the fiscal risk of funding teniposide was low, given that only approximately 20 patients per annum would be likely to access this treatment if available. The Subcommittee considered that while there would be additional infusions and management of toxicity (including issues related to myelosuppression), this is likely to be of little impact to Day and Inpatient units, so Health Sector impact was considered minimal.

5.22. The Subcommittee considered that although patients with multiply relapsed MM were likely very unwell, symptomatic and had a life-expectancy of only a few months, the evidence for the use of teniposide in this indication was of poor quality and weak strength, particularly for quality of life gains or a durable response, and additional toxicity was a concern. The Subcommittee concluded that the evidence of a net health benefit remained insufficient at this time to recommend funding.

6. Dasatinib for Philadelphia Chromosome-Positive Acute Lymphoid Leukaemia (ALL) and Chronic Myeloid Leukaemia (CML) access changes

Application

6.1. The Subcommittee reviewed a clinician application for widened access to dasatinib to specifically include Philadelphia chromosome-positive (Ph+) ALL, PHARMAC staff proposed changes to the Panel application process and distribution mechanism, and whether restricting dasatinib funding to second-line in all new patients diagnosed with chronic-phase CML would be appropriate for cost reasons.

Recommendation

6.2. The Subcommittee **recommended** that dasatinib be funded for the treatment of Ph+ ALL with a low priority, due to a lack conclusive evidence supporting the theoretical benefits of dasatinib in this population.

6.3. The Subcommittee **recommended** that dasatinib be transitioned from a Panel application process managed by PHARMAC to the standard Special Authority and retail pharmacy distribution system.

6.4. The Subcommittee deferred making a recommendation on changes proposed by PHARMAC staff in regards to making dasatinib second-line to imatinib in all new patients diagnosed with chronic-phase CML until PHARMAC consulted with haematologists regarding any possible changes, and it was discussed again at the next CaTSoP meeting.

Discussion

6.5. The Subcommittee noted dasatinib is indicated for the treatment of adults aged 18 years or over with newly diagnosed CML, and CML in chronic, accelerated or myeloid or lymphoid blast phase with resistance or intolerance to prior therapy including imatinib. Dasatinib is also indicated for the treatment of adults aged 18 years or over with Ph+ ALL with resistance or intolerance to prior therapy.

6.6. The Subcommittee noted that currently applications for dasatinib are made directly to the CML coordinator at PHARMAC. The CML coordinator then approves applications, collects prescriptions and sends those prescriptions to a central pharmacy who dispenses dasatinib with a waived patient co-payment. Distribution is then arranged via a contracted logistics provider to their nominated delivery point. This direct distribution system was implemented by PHARMAC at the time of dasatinib listing, given the mechanism was in place for imatinib, which had a similar cost.

Ph+ ALL

6.7. The Subcommittee noted that Ph+ ALL is a biologically and clinically distinct variant of ALL, classified as ALL with a t(9;22)(q34;q11.2);BCR-ABL1 mutation. While abnormalities in the Philadelphia chromosome are a characteristic feature of CML, they are also the most frequent cytogenetic abnormality in adults presenting with ALL. Ph+ ALL accounts for approximately 20 to 30 percent of ALL in adults and 2 to 3 percent of ALL in children. The Subcommittee considered that 5-10 patients were likely to present with Ph+ ALL per year.

6.8. The Subcommittee noted the increased potency of dasatinib against BCR-ABL Tyrosine Kinase and its broader spectrum of activity against other potentially important mutations that feature in Ph+ ALL. The Subcommittee also noted dasatinib has proven central nervous system penetration, and this is a site where Ph+ ALL commonly relapses.

6.9. The Subcommittee noted in a recent case series (Foa et al. Blood. 2011;18:6521-8), all 53 evaluable patients treated with dasatinib achieved a complete hematologic remission, a result also observed in a previous series using imatinib monotherapy in elderly patients.

6.10. The Subcommittee noted that there was evidence for a faster achievement of complete haematological and molecular remissions and a deeper molecular response with dasatinib compared to imatinib. Although there are no head-to-head clinical trials comparing dasatinib and imatinib in Ph+ ALL, the Subcommittee considered, based on evidence of weak strength, that it was plausible that the theoretical benefits may translate into a small incremental survival gain for some patients.

6.11. The Subcommittee noted that dasatinib treatment would continue until relapse or excessive toxicity or until allogenic stem cell transplant in fit patients aged less than 65 years. The Subcommittee noted that only three to four months' treatment may be required as preparation for allogenic stem cell transplant in eligible patients, and it is possible that the occasional good-responder may not need to proceed to transplant. Dasatinib post-transplant is frequently recommended, but often dose-reduced or given for a short treatment period because of toxicity or tolerability issues.

6.12. The Subcommittee noted that switching between tyrosine kinase inhibitors in the treatment of Ph+ ALL would occur because of treatment limiting toxicity, or be considered if there was disease progression, but responses are likely limited.

6.13. The Subcommittee noted that given the rapid progression and high mortality rates if remission is not achieved in Ph+ ALL, it would not be clinically appropriate to require a trial of imatinib as a first-line treatment and then restrict dasatinib to those with a documented treatment failure or treatment limiting toxicity.

6.14. The Subcommittee noted the differentiation of Ph+ ALL and CML blast-crisis are often not separable at diagnosis, and in many cases, cannot be differentiated with full results unless they are known to have pre-existing CML that transforms on treatment.

6.15. The Subcommittee considered that almost all patients with Ph+ ALL were currently accessing funded dasatinib under the CML blast crisis criterion and as such the budget impact of explicitly funding this group as part of the Special Authority restrictions would be small or negligible.

Panel application process and distribution mechanism

6.16. The Subcommittee noted feedback from clinicians that the current application system involves unnecessary additional administration. The Subcommittee considered transitioning to funded access via the standard Special Authority and retail pharmacy distribution system would be preferable.

Dasatinib for CML – proposed requirement to trial imatinib first

6.17. The Subcommittee noted PHARMAC made a decision to fund dasatinib from 1 August 2009 for the treatment of CML in chronic phase, accelerated phase and blast crisis. Because the commercial arrangement negotiated with the supplier at that time resulted in the net cost of dasatinib being lower than that for imatinib, PHARMAC decided that funding could be made available to all CML patients, not just those who had previously failed imatinib treatment as per the funding application, registered indication and the clinical advice that was received.

6.18. The Subcommittee noted, because of the major price differential between dasatinib and generic imatinib, PHARMAC staff now requested advice on whether it would be appropriate to require all patients with newly diagnosed chronic-phase CML to have an adequate trial of imatinib as a first-line treatment, and restrict dasatinib to those with a documented treatment failure or treatment limiting toxicity with imatinib.

6.19. The Subcommittee noted a cost comparison and of imatinib and dasatinib, including the preferred bid price for imatinib in the currently unresolved 2016/17 Invitation to Tender. The Subcommittee considered the cost-differential was considerable and considered the relative prices warranted further consideration of the comparative benefits. The Subcommittee noted the high and increasing expenditure on dasatinib.

6.20. The Subcommittee noted although it was assumed at the time of listing dasatinib that imatinib would be the first-line treatment in most newly diagnosed patients with chronic-phase CML, PHARMAC staff presented data to the Subcommittee showing that almost half of patients who were prescribed dasatinib for the first time in the 2016 financial year had not received prior therapy with imatinib in the preceding 12 months.

6.21. The Subcommittee noted the introduction of imatinib for the treatment of CML resulted in high rates of haematologic and cytogenetic response, although it is recognised that some patients are unable to tolerate imatinib or eventually develop imatinib-resistant forms of CML.

6.22. The Subcommittee noted that NICE, in its consideration of dasatinib for patients with imatinib-resistant or intolerant CML (NICE technology appraisal guidance ta245 and ta246, December 2016), reported that approximately 60% of people observe a satisfactory response to standard-dose imatinib, and that these people will continue to receive the treatment for life and have a normal life expectancy. NICE's clinical experts considered that more than 50% of people with imatinib-resistant CML who have dasatinib or nilotinib, achieve a good response to treatment and that this response is usually as good as the initial response to standard-dose imatinib.

6.23. The Subcommittee noted that NICE was to review its recommendation for dasatinib and nilotinib as options for untreated chronic-phase CML in 2 years' time, when the price of standard-dose imatinib will be affected by the entry of new competitive products.

6.24. The Subcommittee noted the DASISION study funded by the dasatinib supplier, (Cortes et al. J Clin Oncol. 2016;34:2333-40) for which the 5-year results are now available, is the key study to date evaluating long-term efficacy and safety outcomes of patients with chronic phase CML treated with first-line dasatinib or imatinib.

6.25. The Subcommittee noted that despite a higher rate of achievement of early surrogate measures, being Molecular Response and Major Molecular Response, the 5-year PFS and OS were comparable between the treatment arms. The Subcommittee noted that the imatinib PFS and OS plots in Figure 3 were very similar to the corresponding dasatinib plots. Progression-free survival (85% vs. 86%, HR, 1.06; 95% CI, 0.68 to 1.66) and overall survival at 5 years (91% vs 90%, HR, 1.01; 95% CI, 0.58 to 1.73) remained high and similar across both dasatinib and imatinib treatment arms respectively.

6.26. The Subcommittee noted an analysis of expected life span by age at diagnosis, showing both arms of the DASISION study approached that of an external, non-CML population.

6.27. The Subcommittee noted the KISS (Kinase Inhibition with Sprycel Start-up) clinical trial led by Professor Peter Browett was due to begin shortly. This study sought to establish whether there is an advantage to commencing dasatinib as an initial treatment for newly-diagnosed CML, then switching them to imatinib if they have a major molecular response within one year of treatment. The Subcommittee noted that the proposed changes would likely have a significant impact on the KISS study, and further engagement on this issue would be important. Members noted that the Leukaemia and Blood Cancer NZ charity has made a significant contribution to initiate this study.

7. Bisphosphonates for Adjuvant Use in Postmenopausal Women with Early Breast Cancer

Application

7.1. The Subcommittee considered updated evidence in support of the funding of zoledronic acid for adjuvant use in postmenopausal women with early breast cancer to reduce the risk of recurrence with bone metastases and to improve survival.

Recommendation

7.2. The Subcommittee **recommended** that zoledronic acid be funded for adjuvant use in woman with early breast cancer with a medium priority based on updated evidence of a modest benefit from treatment in this patient population.

Discussion

7.3. The Subcommittee noted that the application from the New Zealand Breast Cancer Special Interest Group (NZBCSIG) for funding of zoledronic acid for adjuvant use in postmenopausal women with early breast cancer had previously been considered by both PTAC and CaTSoP in 2015.

7.4. The Subcommittee noted that, at its meeting in March 2015, CaTSoP had recommended that zoledronic acid be funded in this setting with low priority noting that there were challenges determining with any certainty the benefits of zoledronic acid as well as the risk of recurrence and/or effect on survival. The Subcommittee also noted that in 2015 CaTSoP considered it was likely there was a bisphosphonate class effect rather than a specific effect of zoledronic acid itself; and that there was no evidence to support zoledronic acid being more effective than other bisphosphonates in this setting.

7.5. The Subcommittee noted that at its meeting in November 2015, PTAC had accepted CaTSoP's recommendations in relation to zoledronic acid for breast cancer and noted that a recently published meta-analysis be referred to the Subcommittee for consideration.

7.6. The Subcommittee noted the recently published Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of individual patient data from 18,766 participants in 26 unconfounded randomised trials of 2-5 years that compared breast cancer outcomes in those allocated adjuvant bisphosphonate versus those who were not (EBCTCG Lancet 2015;386:1353-61, and Brufsky & Mathew Lancet 2015;386:1319-20 editorial).

7.7. The Subcommittee noted that eligible trials included those that began before 2008 and randomly assigned women between a bisphosphonate of any type (zoledronic acid, ibadronate, pamidronate, clodronate), dose, and schedule versus a control group,

either open label or placebo with no bisphosphonate, all other treatments being similar in both groups. Members noted that trials were mainly in zoledronic acid and clodronate and that the dose regimens and intensity varied.

7.8. The Subcommittee noted that, with a median follow up of 5.6 years, it was reported that overall the reductions in recurrence (24.9% bisphosphonate groups vs 25.9% control groups, 10-year absolute reduction 1.1%, RR 0.94, 95%CI 0.87-1.01;2p=0.08), distant recurrence (20.4% vs 21.8%, 1.4% reduction, 0.92, 0.85-0.99; 2p=0.03) and breast cancer mortality (16.6% vs 18.4%, 1.7% reduction, 0.91, 0.83-0.99, 2p=0.04) were of borderline significance, but the reduction in bone recurrence was considered more definite (7.8% vs. 9.0%, 1.1% reduction, 0.83, 0.73-0.94, 2p=0.004).

7.9. The Subcommittee noted that various subgroup analyses to investigate the effects of bisphosphonates on any recurrence, distant recurrence, bone recurrence, and breast cancer mortality were undertaken. The Subcommittee noted that it was reported that the efficacy of bisphosphonates in reducing bone recurrence was barely significant by menopausal status (2p=0.06 for trend with menopausal status) or age (2p=0.03 for trend with age in treatment effect) and it was non-significant by bisphosphonate class, treatment schedule, oestrogen receptor status, nodes, tumour grade, or concomitant chemotherapy.

7.10. The Subcommittee noted that sensitivity analyses of the possible relevance of age and menopausal status that omitted the hypothesis-generating ABCSG-12 (Gnant et al. NEJM 2009;360679-91) and AZURE (Coleman et al. Lancet Oncol. 2014;15:997-1006, Coleman et al. NEJM 2011;365:1396-405) studies reported significant (2p=0.004) benefit only in post-menopausal women. The Subcommittee noted that no differences were reported in non-breast cancer mortality but bone fractures were reduced (RR 0.85, 95%CI 0.75-0.97;2p=0.02).

7.11. The Subcommittee noted that it was reported that the benefits appeared to be similar in trials of low-intensity anti-osteoporosis schedules and in trials of more intensive schedules such as those approved for use in metastatic bone disease, as well as for different durations of treatment and in the presence or absence of chemotherapy.

7.12. The Subcommittee noted that it was reported there were significant reductions in bone recurrence during years 0–1 and years 2–4 after randomisation but there appeared to be no further reduction thereafter. However, the authors noted that this difference over time was not significant (trend 2p=0.11) and may have been due to the limited follow-up post the first 5 years.

7.13. The Subcommittee noted that in the postmenopausal subgroup for bone recurrence the absolute gain from treatment was 2.2% (95% CI 0·6–3·8) (10-year risks 6.6% vs 8.8%; RR 0.72, 95% CI 0.60–0.86; 2p=0.0002), whereas for breast cancer mortality the absolute gain was 3.3% (95% CI 0·8–5·7) (10-year risks 14.7% vs 18.0%; RR 0.82, 0.73–0.93; 2p=0.002).

7.14. The Subcommittee noted that the authors conclude that these trials have shown that some years of adjuvant bisphosphonate treatment can reduce breast cancer recurrence rates in bone and improve breast cancer survival, but have provided clear evidence of benefit only in women who are postmenopausal (natural or induced) at the time bisphosphonates are started.

7.15. The Subcommittee considered that, based on the currently available evidence, there was evidence of a modest but significant effect from treatment with bisphosphonates although only in post-menopausal women. Members considered that the statistical

significance was greater in older women and those who were post-menopausal, however, it was uncertain which factor had more relevance.

7.16. The Subcommittee considered that age restrictions had been used in trials as a surrogate for defining a post-menopausal population but that it would be appropriate to restrict funded access to women who had been amenorrhoeic for 12 months or greater or where amenorrhea had been chemotherapy induced for at least 2 years.

7.17. The Subcommittee considered that while the currently published evidence for the use of bisphosphonates came from trials using multiple regimens and various bisphosphonates; the majority of published evidence was for use of zoledronic acid. Members considered there was limited evidence for the use of clodronate and ibadronate and no evidence for the use of other bisphosphonates such as risidronate. The Subcommittee considered that it is difficult to determine if the different bisphosphonate regimens have different effects and that much more reliable comparisons will likely emerge from ongoing trials comparing them directly.

7.18. The Subcommittee considered that based on the currently available evidence of efficacy and adverse effects, the most appropriate treatment regimen would be 6-monthly zoledronic acid for a period of two years. Members considered that the greatest benefit from bisphosphonate treatment was derived from the initial doses and that the incremental benefit of subsequent doses was uncertain. Members considered that in other disease settings there was a trend for increasing dose intervals and that further data for its use in breast cancer patients would likely inform whether a dosing interval of greater than 6-monthly would be appropriate.