Cancer Treatments Subcommittee of PTAC
Teleconference held 20 May 2016

(minutes for web publishing)

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

The Cancer 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.

These Subcommittee minutes were reviewed by PTAC at its meeting 11 & 12 August 2016.

1 Ibrutinib for chronic lymphocytic leukaemia and mantle cell lymphoma

Application

1.1 The Subcommittee considered an application from Janssen-Cilag Pty Ltd for the funding of ibrutinib (Imbruvica) for the treatment of patients with high risk chronic lymphocytic leukaemia (CLL) (chromosome del(17p) or TP53 mutation at diagnosis or relapse, CLL relapsed within 24 months of prior therapy, and CLL refractory to prior therapy (progressed within 12 months)), and patients with relapsed and/or refractory mantle cell lymphoma (MCL) that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy (rituximab-based therapy).

1.2 The Subcommittee also noted correspondence from the supplier, clinicians and other parties in response to the November 2015 PTAC minute regarding the application for ibrutinib.

Recommendation

1.3 The Subcommittee **recommended** that ibrutinib be funded with a medium priority for the treatment of CLL with chromosome del(17p) or TP53 mutation at diagnosis or relapse subject to the following Special Authority criteria:

> IBRUTINIB – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (17p deletion or TP53 mutation CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Either:
> 1.1. Patient has treatment naïve CLL; or
> 1.2. Patient has previously treated CLL with relapsed disease; and
> 2. There is documentation confirming that patient has 17p deletion by FISH testing or TP53 mutation by sequencing; and
> 3. Patient has good performance status; and
> 4. The patient has adequate renal function (creatinine clearance ≥ 30ml/mm); and
> 5. Ibrutinib is to be given with curative intent.
>
> Renewal application (17p deletion or TP53 mutation CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment; and

1.4 The Subcommittee **recommended** that ibrutinib be funded with a low priority for the treatment of relapsed CLL (within 24 months of prior therapy) subject to the following Special Authority criteria:

> IBRUTINIB – Retail Pharmacy - Specialist
> Initial application (relapsed 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 previously treated CLL; and

2. There is documentation confirming that patient does not have 17p deletion by FISH testing or TP53 mutation by sequencing; and
3. Patient disease has relapsed within 24 months of previous treatment; and
4. Patient has good performance status; and
5. The patient has adequate renal function (creatinine clearance ≥ 30ml/mm); and
6. Ibrutinib is to be given with curative intent

Renewal application (relapsed CLL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment;

1.5 The Subcommittee **recommended** that ibrutinib be funded with a medium priority for the treatment of refractory CLL (progressed within 12 months) subject to the following Special Authority criteria:

IBRUTINIB – Retail Pharmacy - Specialist
Initial application (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:
All of the following:
1. Patient has previously treated CLL; and
2. There is documentation confirming that patient does not have 17p deletion by FISH testing or TP53 mutation by sequencing; or
3. Patient has refractory disease that has progressed within 12 months of previous treatment; or
4. Patient has good performance status; and
5. The patient has adequate renal function (creatinine clearance ≥ 30ml/mm); and
6. Ibrutinib is to be given with curative intent

Renewal application (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:
All of the following:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment;

1.6 The Subcommittee **recommended** that ibrutinib be funded with a medium priority for the treatment of relapsed and/or refractory MCL (that has progressed within 24 months of allograft or chemotherapy or chemo-immunotherapy) subject to the following Special Authority criteria:

IBRUTINIB – Retail Pharmacy - Specialist
Initial application (relapsed or refractory MCL) - 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 previously treated CLL; and
2. There is documentation confirming that patient does not have 17p deletion by FISH testing or TP53 mutation by sequencing; or
3. Patient has relapsed or refractory MCL confirmed by a haematologist that has progressed within 24 months of allograft or previous treatment; and
4. Patient has good performance status; and
5. The patient has adequate renal function (creatinine clearance ≥ 30ml/mm); and
6. Ibrutinib is to be given with curative intent

Renewal application (relapsed or refractory MCL) - only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Treatment remains clinically appropriate and the patient is benefitting from and tolerating treatment;

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

Discussion

1.8 The Subcommittee noted that CLL is generally an indolent disease with variable clinical course, and that treatment is generally delayed until the patient's clinical symptoms or blood counts indicate that the disease has progressed to a point where it may affect the patient's quality of life. The Subcommittee noted that MCL generally follows an aggressive course with rapid progression and generally requires treatment at diagnosis or at relapse.

1.9 The Subcommittee noted that MCL is generally characterised by the chromosomal translocation t(11;14) and accounts for 3%-10% of all non-Hodgkin's lymphoma. The Subcommittee noted that the currently funded treatment options for patients with MCL in New Zealand included R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone), combination chemotherapy with high dose cytarabine, fludarabine combination chemotherapy, or chlorambucil/ other oral chemotherapy. Members considered that MCL patients who relapse or are refractory following treatment have limited effective treatment options in the current New Zealand setting.

1.10 The Subcommittee noted that CLL is the most common type of leukaemia with around 200 patients diagnosed each year with 10% to 20% identified as having p53 gene mutations. Members noted that the incidence of these mutations in CLL increases with each relapse and that detection of 17p deletion by FISH testing was routinely available in New Zealand.

1.11 The Subcommittee noted that the application was for high risk CLL groups including those with relapsed and refractory disease and patients with p53 gene deletion or mutation who generally have a poorer prognosis and response to currently funded therapy than CLL patients without these aberrations. Members noted that 17p deletion CLL has a 3 year overall survival of 37% compared to 83% for the general CLL patient population.

1.12 The Subcommittee noted that in New Zealand CLL patients with 17p deletion are not eligible for rituximab funding and that funded treatment options for these patients are FC (fludarabine and cyclophosphamide), chlorambucil, or supportive therapy. Members noted that funded treatments for CLL patients with relapsed disease or those refractory to treatment are FC, FC-R (fludarabine, cyclophosphamide and rituximab), (if they did not receive it in a first line setting), chlorambucil, or supportive therapy. Members noted that full dose FC-R chemotherapy was generally only tolerated by younger patients or patients with

few comorbidities but that some patients received reduced dose FCR chemotherapy.

1.13 The Subcommittee considered that there was an unmet health need for better treatment options for patients with relapsed, refractory and 17p deletion CLL.

1.14 The Subcommittee noted that most new treatments for CLL are not available in NZ, which is noted in much of the correspondence received in response to the November PTAC minute for ibrutinib. Members noted that funding applications for bendamustine and obinutuzumab have been considered recently by CaTSoP.

1.15 The Subcommittee noted that ibrutinib is an orally administered, selective and covalent inhibitor of Bruton's tyrosine kinase (BTK) targeting B-cell malignancies. Members noted that ibrutinib has been available in New Zealand on compassionate grounds and for research purposes for relapsed CLL and more recently MCL patients.

1.16 The Subcommittee noted that the application had previously been considered by PTAC in November 2015 where the Committee recommended that the applications for all CLL indications be declined noting that there was considerable uncertainty about the benefits of ibrutinib in a New Zealand setting, that long-term survival data could not be determined based on currently available evidence and, given the high price being sought, poor cost-effectiveness. Members noted that this was in line with international recommendations from NICE in the UK, PBAC in Australia, and CADTH in Canada.

1.17 The Subcommittee noted that PTAC had recommended funding ibrutinib for relapsed/refractory MCL with low priority noting the aggressive course of this disease but uncertainty regarding the magnitude of the potential benefit of ibrutinib for the treatment of MCL.

1.18 The Subcommittee noted that PTAC further recommended that the applications be referred to the Cancer Treatments Subcommittee for consideration.

Evidence for use in CLL

1.19 The Subcommittee noted that the main evidence for the use of ibrutinib for the treatment of CLL was from three open-label randomised controlled trials (RESONATE, RESONATE-2 and RESONATE-17). The Subcommittee noted that RESONATE-17 had not yet been published in a peer-reviewed journal.

RESONATE

1.20 The Subcommittee reviewed evidence from RESONATE a phase 3, randomised, multicentre, open-label study in patients with relapsed or refractory CLL or SLL (Byrd et al. NEJM, 2014;371:213-23).

1.21 The Subcommittee noted that patients (n=391) were randomised 1:1 to receive either ibrutinib (420mg once daily) or ofatumumab (300mg in week 1 followed by 2,000 mg weekly for 7 weeks then 4 weekly for 16 weeks) until either disease progression or unacceptable toxicity with patients able to crossover to the other

treatment arm following confirmed disease progression. Members noted that 31% of enrolled patients had chromosome 17p deletion and that patients in the ibrutinib group had more bulky disease (64% vs. 52%), more previous therapies (median 3 vs. 2), and a shorter time from last therapy (median 8 vs. 12 months).

1.22 The Subcommittee noted that after a median follow-up of 9.4 months median progression free survival (PFS), the primary end-point of the study, was not reached in the ibrutinib group (88% remained in PFS at 6 months) compared with a median PFS of 8.1 months in the ofatumumab group (hazard ratio (HR) for progression or death 0.22; 95% confidence interval (CI), 0.15 to 0.32; p<0.001). Members noted that at 12 months, 90% of the patients in the ibrutinib group were still alive compared with 81% in the ofatumumab group (HR 0.43; 95% CI, 0.24 – 0.79; P=0.005) and that similar effects were observed regardless of whether patients had chromosome 17p deletion or resistance to purine analogues.

1.23 The Subcommittee noted that 43% of participants in the RESONATE trial had previously received treatment with bendamustine and 21% with alemtuzumab, neither of which are funded in New Zealand. Members also noted that ofatumamab is not currently funded in New Zealand.

RESONATE-2

1.24 The Subcommittee reviewed evidence from RESONATE-2 a randomised, multicentre, open-label, phase 3 trial in treatment naïve patients with CLL/SLL who were 65 years of age or older (Burger et al. NEJM 2015;373(25):2425-37). Members noted that 269 patients were randomised to receive either ibrutinib (420mg daily) until disease progression or unacceptable toxicity, or chlorambucil (0.5mg-0.8mg) for a maximum of 12 cycles.

1.25 The Subcommittee noted that median PFS, the primary endpoint of the study, was not reached in the ibrutinib arm, and was 18.9 months for the chlorambucil arm (HR 0.16, 95% CI 0.09 – 0.28, p<0.0001) and that median OS was not reached in either of the treatment arms, however, ibrutinib was reported to significantly reduced the risk of death by 84% (HR=0.16, 95% CI 0.05 – 0.56, p=0.001).

1.26 The Subcommittee noted that overall response rate was 82.4% for the ibrutinib arm and 35.3% for the chlorambucil arm (p<0.0001). Members noted that treatment emergent adverse events were reported in 65.9% in the ibrutinib arm and grade ≥3 adverse events were reported in 35.6% of subjects treated with ibrutinib.

RESONATE-17

1.27 The Subcommittee reviewed evidence from RESONATE-17 an unpublished open label, single arm, study of ibrutinib (420mg daily until progression) in 144 patients with del(17p) CLL who had failed at least one previous therapy (O'Brien et al. ASH 2014 abstract 327; Stilgenbauer et al. ASH 2013 Oral presentation abstract 833). The Subcommittee noted that after a median follow-up of 11.5 months, 65% of patients had a treatment response and at 12 months 79.3% were still alive. Members noted that median PFS and OS were not reached.

1.28 The Subcommittee considered that because this was a single-arm non-randomized or controlled study it was not possible to determine with certainty the magnitude of the potential benefits of ibrutinib within the New Zealand context.

1.29 The Subcommittee requested that evidence from the RESONATE-17 study be brought back for review following publication.

1.30 The Subcommittee also reviewed evidence for ibrutinib in the treatment of CLL from a number of other open label non-randomised single arm Phase 1b-2 studies and results from the 17p deletion patient subgroup of the RESONATE trial. In a single arm NIH study of ibrutinib in 51 patients with untreated/relapsed 17p deletion/TP53 mutated CLL, the estimated PFS and OS at 24 months was 80% without differences between untreated and relapsed patients (Farooqui et al. Lancet Oncol 2015; 16(2): 169-176).

Evidence for use in MCL

1.31 The Subcommittee reviewed data from the RAY (MCL-3001) study an open label randomised phase 3 trial comparing ibrutinib (560mg daily until disease progression) with temsirolimus (175mg IV day 1,8,15 of first 21 day cycle, then 75mg IV day 1,8,15 until disease progression) in 280 patients with relapsed (70%) or refractory (30%) MCL (Dreyling et al. Lancet 2016, 387; 770-8). Members noted that all patients had received at least one prior rituximab-containing treatment regime, with a median of 2 previous lines of treatment.

1.32 The Subcommittee noted that after a median follow-up of 20 months, median PFS, the primary endpoint of the study, was 14.6 months in the ibrutinib arm compared with 3.2 months in the temsirolimus arm (HR=0.43, CI 0.32-0.58, p<0.0001).

1.33 The Subcommittee reviewed evidence from a phase 2, open label, single arm study of ibrutinib (560mg daily) for the treatment of patients with relapsed or refractory MCL (Wang et al. NEJM 2013;369:507-16). Members noted that patients had received a median of 3 previous treatments, 43% had previous been treated with bortezomib, which is not funded in New Zealand for MCL, and 86% of patients had intermediate risk or high risk disease. Members noted following a median follow-up period of 15.3 months overall response rate, the primary endpoint of the study, was 68% (comprising 21% complete response and 47% partial response).

1.34 The Subcommittee noted long term follow up of patients in this study (Poster ASH 2014, Wang et al. Blood 2015;126:739-45) reporting that at a median follow-up of 26.7 months, the median duration of response was 17.5 months (95% CI 14.9- not estimable (NE)), median PFS was 13 months (95% CI 7.0-17.5) and a median OS was 22.5 months (95% CI 13.7-NE).

General Comments

1.35 The Subcommittee considered that, overall, the evidence for the use of ibrutinib was promising but the data from all studies was immature as OS benefit over current treatment had not yet been demonstrated and was confounded by

crossover. Members noted that surrogate endpoints such as PFS did not always correlate to survival gains.

1.36 The Subcommittee considered that use of comparator treatments that were not currently funded in New Zealand meant there was uncertainty about the benefits ibrutinib may provide for patients with CLL and MCL in a New Zealand setting; however, the Subcommittee considered that the comparator treatments used in the RESONATE studies were appropriate in the context of international CLL treatment paradigms and clinical practice which are more advanced than those in New Zealand.

1.37 The Subcommittee considered that ibrutinib would likely provide a level of benefit for relapsed/refractory CLL and MCL patients over currently funded treatments particularly due to its oral administration but noted that the magnitude and durability of clinical benefit was uncertain as was the duration of treatment. Members considered that longer follow-up data would likely provide greater certainty regarding the durability of response.

1.38 The Subcommittee considered the ibrutinib appeared to be generally well tolerated with a manageable side effect profile and therefore that patients would likely commence treatment with ibrutinib earlier in the disease course than they would with standard chemotherapy options which have significant toxicity.

2 Crizotinib for ALK-positive advanced and/or metastatic non-small cell lung cancer

Application

2.1 The Subcommittee considered an application from Pfizer NZ Limited for the funding of crizotinib (Xalkori) for the treatment of locally-advanced and/or metastatic (Stage IIIB and IV) non-small cell lung cancer (NSCLC) patients who test positive for an anaplastic lymphoma kinase (ALK) gene rearrangement in first line (treatment naïve) and second line (following treatment with at least one platinum-based chemotherapy regimen) settings.

2.2 The Subcommittee also noted correspondence from the supplier in response to the November 2015 PTAC minute regarding the application for crizotinib.

Recommendation

2.3 The Subcommittee **recommended** that crizotinib be funded as a first line treatment for ALK positive locally-advanced and metastatic NSCLC with a low priority, subject to the following Special Authority restrictions:

> CRIZOTINIB – Retail Pharmacy - Specialist
> Special Authority for Subsidy
> Initial application (treatment naïve advanced NSCLC) - only from an oncologist. Approvals valid for 6 months for applications meeting the following criteria:
> All of the following:
> 1. Patient has treatment-naïve locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and

2. There is documentation confirming that patient has an ALK tyrosine kinase gene rearrangement using FISH testing.

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

2.4 The Subcommittee **recommended** that crizotinib be funded as a second line treatment for ALK positive advanced and metastatic NSCLC with a low priority, subject to the following Special Authority restrictions:

CRIZOTINIB – Retail Pharmacy - Specialist
Special Authority for Subsidy
Initial application (relapsed advanced NSCLC) - only from an oncologist. Approvals valid for 6 months for applications meeting the following criteria:
All of the following:
1. Patient has locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and
2. There is documentation confirming that patient has an ALK tyrosine kinase gene rearrangement using FISH testing; and
3. Patient has documented disease progression following first-line treatment with platinum-based chemotherapy.

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

2.5 The Subcommittee noted that the priority ratings in these recommendations were influenced by the high health need of the population, lack of long-term data and high price being sought by the supplier.

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

Discussion

2.7 The Subcommittee noted that lung cancer is the leading cause of cancer death in New Zealand. The Subcommittee noted that lung cancer can be broadly categorised into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with NSCLC being the most common type (~80%) in New Zealand and adenocarcinoma accounting for around half of NSCLC cases.

2.8 The Subcommittee noted that lung cancer incidence and mortality are higher in Maori compared with non-Maori. Members noted a correlation between lung cancer and social deprivation. Members noted that the most common age for presentation was in the 60 to 70 year old age group and 81% had documented medical co-morbidity. Members noted that 70% of NSCLC is locally advanced or metastatic at presentation.

2.9 The Subcommittee noted that current treatment for locally-advanced and/or metastatic NSCLC are platinum-based regimens which are highly toxic and/or the oral tyrosine kinase inhibitors, gefitinib or erlotinib, for patients who have tested

positive for epidermal growth factor receptor (EGFR) tyrosine kinase activating mutations. The Subcommittee noted that survival rates for patients with advanced NSCLC either with or without anaplastic lymphoma kinase (ALK) mutation were poor with currently funded treatments with two year survival rates of approximately 20%.

2.10 The Subcommittee noted that mutations of ALK gene are mutually exclusive to other lung cancer mutations and are more common in a younger population and never-smokers but noted that these factors are not used as prognostic determinants. Members considered that patients with ALK positive NSCLC represent a different cohort to other forms of lung cancer and that there was a high health need for patients inthis population.

2.11 The Subcommittee noted that the method of ALK testing differed between centres. The Subcommittee noted the Royal College of Pathologists of Australasia guideline would be released in the near future. Members noted that current testing in Australia for adenocarcinoma of the lung started with EGFR mutation testing, if this was negative then immunohistochemistry ALK testing was performed and any positivity confirmed with fluorescence in situ hybridisation (FISH) testing. Members noted that ALK testing could represent a significant additional cost in the treatment of these patients.

2.12 The Subcommittee noted that crizotinib is an orally administered selective small molecule inhibitor of the ALK receptor tyrosine kinase and its oncogenic variants MET and ROS1. Members noted that crizotinib dosing is 250 mg twice daily, irrespective of a patient's body mass index, and continued until disease progression.

2.13 The Subcommittee noted that this application had previously been considered by PTAC at its meeting in November 2015 where it recommended that the application be declined noting that evidence of long term efficacy was lacking and, given the high price being sought, that the treatment was poorly cost-effective. The Subcommittee noted that PTAC further recommended that the application be referred to the Cancer Treatments Subcommittee for consideration.

2.14 The Subcommittee noted PTAC's comments regarding possible variability of dosing due to body weight and concern about poor penetration of the Central Nervous System (CNS). The Subcommittee noted that CNS metastases are common in ALK positive NSCLC and expressed concern that patients may continue to receive crizotinib beyond disease progression if the clinician felt that they were still receiving a clinical benefit.

2.15 The Subcommittee noted that in 2013 the National Institute for Health and Care Excellence (NICE) in the UK did not recommend crizotinib for previously treatment ALK positive advanced NSCLC due to its low cost effectiveness.

First-line treatment

2.16 The Subcommittee reviewed evidence from a phase 3, open label, randomised trial of crizotinib versus first-line pemetrexed and platinum chemotherapy

(pemetrexed/cisplatin or pemetrexed/carboplatin) in treatment naïve patients with advanced ALK-positive non-squamous NSCLC (Study A8081014 (PROFILE 1014) published as Solomon et al. NEJM 2014:371:2167-77).

2.17 The Subcommittee noted that patients were randomly assigned to receive crizotinib at a dose of 250 mg twice daily or chemotherapy (pemetrexed, 500 mg per square meter of body-surface area, plus ether cisplatin, 75 mg per square meter, or carboplatin, target are under the curve of 5 to 6 mg per mL per minute) administered every 3 weeks for up to six cycles.

2.18 The Subcommittee noted that treatment was continued until RECIST-defined disease progression, development of unacceptable toxic effects, death, or withdrawal of consent. Members noted that patients in the chemotherapy group who had disease progression as confirmed by independent radiologic review could cross over to crizotinib treatment if safety screening criteria were met. Members considered that imaging in clinical practice would likely be less frequent than carried out in the clinical trial and therefore there was a risk that treatment would continue beyond disease progression. Members noted that patients in the crizotinib arm were allowed to continue crizotinib beyond disease progression if they were perceived to be having a clinical benefit.

2.19 The Subcommittee noted that 94% of patients enrolled had an Eastern Cooperative Oncology Group (ECOG) score of 0-1 with the remaining patients ECOG 2 and that patients with treated brain metastases were eligible if metastases were neurologically stable for 2 weeks prior to enrollment and had no ongoing requirement for glucocorticoids. Members noted that 98% of patients had metastatic disease, including 26.8% that had cerebral metastases. The Subcommittee noted that this is a group of patients with a very poor prognosis.

2.20 The Subcommittee noted that median progression-free survival (PFS), the primary endpoint of the study, was 10.9 months in the crizotinib treatment arm versus 7.0 months in the chemotherapy arm (Hazard Ratio (HR) 0.45; 95% confidence interval (CI), 0.35 to 0.60; $p<0.001$) and that median overall survival (OS) was not reached, after 36 months follow-up, in either group (HR 0.82; 95% CI, 0.54 to1.26; P=0.36). Members noted that OS results were complicated by 70% of patients in the chemotherapy arm crossing over. The Subcommittee noted that there was a marked divergence in PFS after 7 months, with 30% of patients in the crizotinib arm looking to have a sustained PFS.

2.21 Members noted that the median duration of response was 11.3 months and 5.3 months in the crizotinib and chemotherapy arms, respectively, and the objective response rate was 74% (95% CI, 67 to 81) in the crizotinib arm compared to 45% (95% CI, 37 to 53) in the chemotherapy arm ($P<0.001$). Members noted that the median number of chemotherapy cycles completed was six.

2.22 The Subcommittee noted that pemetrexed is not currently funded in New Zealand for patients with advanced NSCLC, but cisplatin and gemcitabine are funded for this indication. The Subcommittee noted that an indirect comparison of crizotinib with non-pemetrexed platinum based chemotherapy had been provided by the supplier using a phase 3 non-inferiority study in chemotherapy naïve patients with Stage IIB or Stage IV NSCLC comparing first-line pemetrexed/cisplatin with

gemcitabine/cisplatin (Scagliotti et al. J Clin Oncol 208;26:3543-51). Members noted that this trial showed that OS for cisplatin/pemetrexed was non-inferior to gemcitabine/cisplatin. Members noted that indirect comparisons were inherently problematic but considered most clinicians would accept this analysis.

Second-line treatment

2.23 The Subcommittee reviewed evidence from a phase 3, open-label, randomised trial comparing crizotinib with single agent chemotherapy (pemetrexed or docetaxel) in patients with locally advanced or metastatic ALK-positive NSCLC that had receive one prior platinum-based regimen (Study 8081107 Shaw et al. NEJM 2013:368;25:2385-94).

2.24 The Subcommittee noted that eligibility criteria included patients with stable brain metastases that had been treated previously or were untreated and asymptomatic. The Subcommittee noted that patients in the chemotherapy arm with progressive disease were able to crossover to receive crizotinib.

2.25 The Subcommittee noted that at with a median follow-up of 12.2 months, median PFS, the primary endpoint of the study, was 7.7 months in the crizotinib group compared with 3.0 months in the chemotherapy group (HR 0.49; 95% CI, 0.37 to 0.64; P<0.001). Members noted that 64% of patients in the chemotherapy arm crossed over to receive crizotinib, and there was no significant difference between the treatment groups in OS, which was 20.3 with crizotinib and 22.8 months with chemotherapy (HR 1.02; 95% CI, 0.68 to 1.54; P=0.54).

2.26 The Subcommittee noted that the most common adverse events with crizotinib were visual impairment, photopsia and blurred vision which were reported in 60% of patients treated with crizotinib. Members noted that limited information was provided regarding the type of visual disturbances reported but based on anecodotal evidence these relate to colour perception and not acuity of vision and are usually manageable.

General comments

2.27 The Subcommittee considered that the evidence for crizotinib for the treatment of ALK positive advanced and metastatic NSCLC was of good strength and quality but noted that the short follow-up and confounding by crossover. Members considered that there was likely an incremental benefit from crizotinib treatment compared with platinum based chemotherapy in this population as the survival figures are very good for a patient population with such a poor prognosis; however, more mature PFS and OS data were needed.

2.28 The Subcommittee considered that the toxicity profile of crizotinib appeared manageable.