PUBLIC SUMMARY DOCUMENT

Product: Crizotinib, 200 mg and 250 mg, capsule, Xalkori®
Sponsor: Pfizer Australia Pty Ltd
Date of PBAC Consideration: November 2013

1. Purpose of Application

The submission requested an Authority Required listing for second-line treatment of a patient with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) who has disease progression following at least one platinum-based chemotherapy. A coordinated application to the Medical Services Advisory Committee (MSAC) for Medicare Benefits Schedule (MBS) listing of ALK gene rearrangement testing was lodged simultaneously.

The PBAC noted that an application for MBS listing would be considered at the MSAC meeting on 28 November 2013.

2. Background

This drug had not been previously considered by the PBAC.

3. Registration Status

Crizotinib was TGA registered on 27 September 2013 for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

4. Listing Requested and PBAC's View

Authority required
Initial PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with a WHO performance status of 2 or less, where:
(1) disease progression has occurred following treatment with at least 1 platinum-based chemotherapy agent; and
(2) there is evidence that the patient has an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.

Authority required
Continuing PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with a WHO performance status of 2 or less, where the patient has previously been issued with an authority prescription for crizotinib and who does not have progressive disease.

The PBAC noted that the proposed requirement to cease crizotinib treatment if disease progression occurs is different from the recommendation in the draft product information,

which states that treatment should continue as long as the patient is deriving clinical benefit. In addition, the PBAC noted that, in the A8081007 trial of crizotinib versus chemotherapy, 69% of patients who had progressed continued on crizotinib beyond disease progression. The pre-subcommittee response (PSCR) indicated the sponsor was willing to work with the Secretariat to develop the final appropriate wording for a PBS listing of crizotinib.

However, in the event of a positive listing recommendation, the PBAC considered the PBS restriction for crizotinib should include the proposed stopping rule, noting that patients with disease progression following crizotinib treatment would be able to receive treatment with pemetrexed.

For more of the PBAC's view on the requested listing see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

ALK rearrangements are found in approximately 3-5% of cases of non-small-cell lung cancer and define a distinct molecular subtype of lung cancer. Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting ALK, MET, and ROS1 tyrosine kinases. Crizotinib has demonstrated antitumor activity in patients with advanced ALK-positive NSCLC (Shaw et al. 2013).

6. Comparator

The submission nominated pemetrexed and docetaxel as comparators for the second-line treatment of advanced ALK-positive NSCLC. The PBAC considered that pemetrexed was the appropriate main comparator for the treatment line and population proposed in the PBS restriction because pemetrexed is the standard of care for patients with adenocarcinomas and more effective than other chemotherapies in patients with ALK-positive NSCLC (Camidge, DR et al J Thoracic Oncol 2011;6(4):774-80 and Lee, JO et al J Thoracic Oncol 2011;6(9):1474-80). As docetaxel is less effective and more toxic than pemetrexed, the effect of rejecting it as the main comparator is to reduce the extent of improvement due to crizotinib in terms of effectiveness, safety and cost offsets. The PBAC also noted that pemetrexed is likely to be displaced rather than replaced by crizotinib, i.e., pemetrexed is likely to be used after progression with crizotinib.

7. Clinical Trials

The pivotal evidence in the submission was study A8081007. This was a Phase III, randomised, open-label study of the efficacy and safety of crizotinib versus chemotherapy (pemetrexed or docetaxel) in patients with advanced ALK-positive NSCLC.

Two single-arm studies of crizotinib were provided as supportive evidence (A8081001 and A8081005). Additionally, the submission presented one randomised trial comparing pemetrexed with docetaxel in patients with NSCLC previously treated with chemotherapy (Hanna et al 2004).

The primary outcome measure in A8081007 was progression-free survival (PFS). Secondary outcome measures were overall survival (OS), objective response rate, duration of response, time to tumour response, disease control rate, adverse events and serious adverse events, and patient-reported outcomes.

The primary outcome measure in Hanna et al 2004 was OS. Secondary outcome measures were toxicities, objective response rate, PFS, time to progressive disease, time to treatment failure, time to response, duration of response and quality of life.

Details of the trials are presented in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
A8081007	Preliminary Clinical Study Report: Phase 3, Randomized, Open-Label Study of the Efficacy and Safety of PF-02341066 Versus Standard-of-Care Chemotherapy (Pemetrexed or Docetaxel) in Patients With Advanced Non-Small Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Event Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus	30 March 2012 (data cutoff date)
	Shaw et al, Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer	New England Journal of Medicine, 2013; 368(25): 2385-94
A8081001	Preliminary Study Report Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, a c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer	12 September 2011 (Amended Report Signoff Date)
	Camidge et al, Anaplastic Lymphoma Kinase Gene Rearrangements in Non-small Cell Lung Cancer are Associated with Prolonged Progression-Free Survival on Pemetrexed.	Journal of Thoracic Oncology, 2011; 6(4): 774-80
	Shaw et al, Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis.	The Lancet Oncology, 2011; 12(11): 1004-12
A8081005	Second Preliminary Clinical Study Report Phase 2, Open-Label, Single Arm Study of the Efficacy and Safety of PF-02341066 in Patients With Advanced Non-Small-Cell Lung Cancer (NSCLC) Harboring a Translocation or Inversion Involving the Anaplastic Lymphoma Kinase (ALK) Gene Locus	11 February 2013 (administrative update to report)
	Kim et al, Updated results of a global phase II study with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC). Abstract	2012 ESMO Congress Abstract
	Besse et al, Visual disturbances in patients (pts) with anaplastic lymphoma kinase (alk)-positive advanced non-small cell lung cancer (nsclc) treated with crizotinib. Abstract	2012 Annals of Oncology

	Solomon et al, Preliminary characterization of visual events reported by patients receiving crizotinib for the treatment of advanced ALK-positive non-small cell lung cancer. Poster	2011 European Multidisciplinary Cancer Congress
Hanna (2004)	Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.	Journal of Clinical Oncology, 2004; 22(9): 1589-97

8. Results of Trials

With regard to comparative effectiveness, the results for PFS from A8081007 in patients testing positive for ALK gene rearrangement are presented in the table below.

Results of progression-free survival in A8081007 in patients testing positive for ALK gene rearrangement

Randomised treatment groups	Progressed or dead, n/N (%)	Median progression-free survival, months (95% CI)	Difference in median PFS[a], months	Hazard ratio (95% CI) for crizotinib
Crizotinib	100/173 (57.8)	7.7 (6.0, 8.8)	4.7	0.487 (0.371, 0.638)
Chemotherapy	127/174 (73.0)	3.0 (2.6, 4.3)		
Non-randomised treatment groups				
Pemetrexed	72/99 (72.7)	4.2 (2.8, 5.7)	3.5	0.589 (0.431, 0.804)
Docetaxel	54/72 (75.0)	2.6 (1.6, 4.0)	5.1	0.298 (0.207, 0.428)

[a] Absolute difference in median PFS (compared with crizotinib) calculated during the evaluation, confidence intervals are not calculable.

The PBAC considered that the submission's claim of superior effectiveness in terms of PFS was adequately supported by the data in the comparison versus pemetrexed, showing a difference in median PFS of 3.5 months. The PBAC noted that this PFS gain was of similar magnitude to the incremental PFS gains observed for the TKIs (afatinib, erlotinib and gefitinib) proposed for use in EGFR mutation-positive NSCLC as considered at the July 2013 PBAC meeting.

The PBAC noted that the validity of PFS as a surrogate for OS or for quality of life in NSCLC had not been demonstrated in the submission. Nor had the submission addressed whether PFS is of direct patient relevance for quality of life.

The preliminary results for OS in A8081007 in patients testing positive for ALK gene rearrangement are presented in the table below. The PBAC noted that the OS results are from an interim analysis, with 40% of the required events occurring at the time of analysis. The analysis of OS is confounded by the early (median 3.8 months) and extensive (64.4%) crossover of chemotherapy patients to crizotinib.

Preliminary results of overall survival in A8081007 in patients testing positive for ALK gene rearrangement

	Dead, n/N (%)	Median overall survival, months (95% CI)[a]	Hazard ratio (95% CI) for crizotinib
Crizotinib	49/173 (28.3)	20.3 (18.1, NR)	1.021 (0.677, 1.540)
Chemotherapy	47/174 (27.0)	22.8 (18.6, NR)	

[a] The median survival is estimated using the Kaplan-Meier method because fewer than 50% of patients had died in the trial at the time of data cut-off.

The PBAC noted that there was no statistically significant improvement in survival for crizotinib versus chemotherapy in the primary (unadjusted) analysis. The PBAC noted the submission's claim that the intention to treat (ITT) analysis of OS would be unlikely to find any difference in overall survival in patients taking crizotinib compared with those taking pemetrexed or docetaxel because it is confounded by the effects of crossover.

The submission presented analyses to adjust for crossover, as shown in the table below (rank-preserving structural failure time (RPSFT) method and marginal structural modelling (MSM) method). The PBAC noted that the results from these two analyses were not used in the economic model, and the submission's argument that the ratio of PFS to OS demonstrates that the adjustments for crossover using the RPSFT and MSM models do not fully account for the incremental OS effects of crizotinib treatment. Rather, the submission assumed that crizotinib versus chemotherapy would result in a gain of more than 12 months in overall survival, despite a gain of only 4.7 months in PFS from the direct trial.

Results of overall survival in A8081007 in patients testing positive for ALK gene rearrangement, unadjusted and adjusted for cross-over

	Median PFS	Median OS	Hazard ratio (95% CI) for crizotinib	PFS as a proportion of OS
Chemotherapy arms				
A8081007 unadjusted	3.0 months	22.8 months	1.02 (0.68, 1.54)	1 to 7.6
RPSFT method	3.0 months	16.8 months	0.83 (0.36, 1.35)[a]	1 to 5.6
MSM method	3.0 months	13.0 months	0.64 (0.33, 1.24)	1 to 4.3
Hanna pemetrexed	2.9 months	8.3 months	NA	1 to 2.9
Hanna docetaxel	2.9 months	7.9 months	NA	1 to 2.7
Crizotinib arms				
A8081007	7.7 months	20.3 months	NA	1 to 2.6
A8081001	9.7 months	29.6 months	NA	1 to 3.0

[a] Confidence interval calculated using correction for bias of 0.13 (Hall 1992)
RPSFT = Rank-Preserving Structural Failure Time; MSM = Marginal Structural Modelling; NA = not applicable

The submission used an alternative approach in an attempt to fully account for the effects of crizotinib treatment based on the premise that PFS as a proportion of OS should be similar in the crizotinib and chemotherapy arms (if the chemotherapy arm was not confounded by crossover). To support this approach, the submission derived OS associated with pemetrexed or docetaxel, in the absence of crossover to crizotinib, from the docetaxel Kaplan-Meier OS curve from Hanna et al 2004. The median OS for both docetaxel and pemetrexed in this trial was approximately 8 months.

The submission stated that OS in the crizotinib arm of study A8081007 was higher than that of patients treated with either docetaxel or pemetrexed in Hanna et al 2004. The PBAC

rejected the premise that PFS is a constant proportion of OS across treatment options as not being adequately supported by the submission's approach to estimating incremental OS. In particular, the PBAC was concerned that the claim of greater OS in the extrapolated crizotinib arm of A8081007 than in either the pemetrexed or docetaxel arms of Hanna et al 2004 was based on a comparison across arms extracted from two different trials. The PBAC considered that apparent differences in overall survival across the submission's comparison may be the result of differences in the population, medical practice, diagnosis and staging or the use of effective salvage therapies (including crizotinib).

In this regard, the PBAC agreed with the Economics Sub-Committee ESC that, given the need to construct a non-randomised comparison with an unmatched historical control group, a large treatment effect size would be needed in order to confidently exclude the effect of any confounding factors. The PBAC noted that the setting and population in the Hanna trial were different to those of A8081007 and that they were unlikely to be adequately exchangeable to enable a meaningful comparison of outcomes. For example, patients in the Hanna trial were younger, more likely to be non-smokers, and more likely to have squamous histology. In addition, the PBAC agreed with the ESC that advances in clinical practice in the decade since Hanna were also likely to lead to improved OS outcomes. Therefore, the PBAC considered that the 12-month advantage in median OS used in the economic model, based on the comparison of arms extracted from non-exchangeable trials was inappropriate and likely to overestimate the comparative treatment effect of crizotinib.

The PBAC noted the Sponsor's statement in its Pre Sub-Committee Response (PSCR) that OS efficacy relative to current treatment is impossible to prove, but agreed with the ESC that the submission did not provide an estimate of the extent of incremental OS that could be relied upon. The PBAC noted the alternative approaches for estimating the magnitude of incremental OS benefit as identified by the ESC. In particular, the PBAC considered that an analysis based on mature OS data from A8081007 may provide less uncertain results for patients randomised to crizotinib (noting that the date of data cutoff for data presented in the submission was 30 March 2012), and may possibly allow the statistical methods for adjusting for crossover in patients randomised to chemotherapy to be more convincing. The PBAC noted the advice in the Sponsor's PSCR that a final analysis will occur when the target number of events is reached (241 deaths), but that no estimated date of when this was likely to occur was provided.

The PBAC noted that, from the prediction bands reported by Johnson et al (Johnson KR, Ringland C, Stokes BJ et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006; 7(9):741-6) for chemotherapies (rather than targeted therapies) in lung cancer, the threshold incremental PFS gain needed to predict an incremental OS gain from a new trial with 250 participants was a median of 3.3 months, which was exceeded by the observed median of 3.5 months for crizotinib over pemetrexed in A8081007. This provides support for the claim of an improvement in OS. However, applying the meta-regression to the A8081007 differences in median PFS predicts a difference in median OS of 3.1 months over the chemotherapy arm and 2.3 months over pemetrexed alone, which suggests that the submission's claim of a 12-month improvement in OS is an over-estimate.

The PBAC agreed with the ESC that there may be a potential role for (and potential cost-effectiveness of) crizotinib in the third-line treatment setting, rather than the second-line

setting, given that patients enrolled in the chemotherapy arm of A8081007 had a median OS of 22.8 months (compared to 20.3 months in the crizotinib arm; HR 1.021 (0.667, 1.540)), and a high rate of crossover to crizotinib.

The PBAC noted that EQ-5D results from A8081007 were used to model a 0.112 – 0.045 = 0.067 difference in utility across the two arms of the model in the progression-free on treatment health state and agreed that a claim for a quality of life advantage for crizotinib was reasonable.

With regard to comparative harms, the PBAC noted that crizotinib was associated with a greater rate of diarrhoea, vision disorder, nausea, vomiting, constipation, elevated transaminases, oedema and upper respiratory tract infection than either pemetrexed or docetaxel. Both neuropathy and neutropenia were most common in patients receiving docetaxel, followed by crizotinib and then pemetrexed. The PBAC also noted that most men on crizotinib get rapid onset hypogonadism, and that cases of fatal pneumonitis, interstitial lung disease, QT prolongation and profound bradycardia have been reported.

The PBAC noted that visual disorder appeared to be an adverse effect that is unique to crizotinib, occurring in greater than 50% of patients, although it is reported to be mild in more than 98% of cases. The exact mechanism of vision changes in patients taking crizotinib is not known, but is likely to be related to the fundamental role of ALK in the physiology of the visual system. The PBAC noted that the visual changes manifest as light-dark accommodation problems without objective ophthalmological abnormalities in about 60% of crizotinib-treated patients and the likelihood of resolution over the short term is low.

The PBAC considered that the risk of visual disorders might be considered acceptable given the end stage of the disease and the lack of early signals of more severe manifestations suggesting that it might take some time for any worsening of these symptoms to emerge. However, the PBAC considered that the sponsor should put in place a process for monitoring of side effects associated with crizotinib, particularly the visual changes.

9. Clinical Claim

The submission described crizotinib treatment of patients identified with ALK gene rearrangement as superior in comparative effectiveness and non-inferior in terms of comparative safety to single agent chemotherapy (pemetrexed or docetaxel).

The PBAC considered the claim of superior effectiveness in terms of improvement in PFS versus pemetrexed was supported. However, the PBAC did not consider PFS alone to be an adequately informative outcome for patients with advanced NSCLC. The PBAC did not consider the claim of superior effectiveness in terms of OS, the more informative outcome for patients with advanced NSCLC, was adequately supported by the approach taken in the submission. The Committee considered that the method preferred for estimating incremental OS in the submission was inappropriate.

The PBAC considered that the submission's claim of non-inferior comparative safety was adequately supported by the trial evidence. However, the PBAC was concerned by the high

incidence of visual disturbances, male hypogonadism and gastrointestinal disturbance and considered that visual disturbances in particular warranted further investigation.

10. Economic Analysis

The submission presented a cost-utility analysis, based on a claim of improved PFS presented in the clinical evidence, as well as an improvement in quality of life and overall survival. The PBAC considered that, while the comparative evidence from A8081007 supported the superiority claim for PFS (which was modelled accordingly), it did not support a superiority claim for OS. OS data from Hanna et al 2004 was used for the comparator arm in the economic model, rather than any OS results from A8081007.

The PBAC considered that the use of single arms from two different trials, unadjusted for a common reference, in the economic model to represent OS with crizotinib and chemotherapy (A8081007 and Hanna, respectively) was not a reasonable comparison and was biased in favour of crizotinib.

The submission presented a two-stage modelled economic evaluation for testing then treating patients with Stage IIIB/IV EGFR negative NSCLC following disease progression after at least one platinum-based chemotherapy regimen. The results of the economic evaluation produced an incremental cost per quality adjusted life year (QALY) in the range of $45,000-$75,000.

From the results of sensitivity analyses presented in the submission and conducted during the evaluation, the PBAC noted that the model was most sensitive to changes in OS and treatment duration. The PBAC considered the base case ICER in the range of $45,000-$75,000/QALY to be an unreliable estimate of the cost-effectiveness of crizotinib treatment because the incremental OS gain was generated by extrapolation of immature OS data from A8081007 for crizotinib, and the modelling of OS data from an inappropriate source for chemotherapy. The PBAC considered this base case ICER to be biased in favour of crizotinib and that the likely true ICER would mean that crizotinib is not acceptably cost-effective at the requested price.

The PBAC noted that use of OS increments of 3.5 months (using the RPSFT method of accounting for cross-over) and 7.3 months (using the MSM method of accounting for cross-over) resulted in ICERs in the range of $105,000 – 200,000 .

11. Estimated PBS Usage and Financial Implications

The submission estimated the net cost to the PBS and MBS of ALK testing and crizotinib to be less than 10 million per year in Year 5. The PBAC noted that more than 3000 patients would need to be tested each year to result in 70-80 patients being treated.

12. Recommendation and Reasons

The PBAC considered that the cost-effectiveness of crizotinib was not supported by approach used in the submission.

Although proposing to support the application on the basis of acceptable comparative effectiveness, the PBAC deferred the application for crizotinib to ascertain the applicant's input on its proposed approach to achieve acceptable cost-effectiveness and until such time as MSAC decides to support the corresponding MBS listing of ALK ISH testing (and any other associated molecular testing advised by MSAC) for patients with NSCLC. The PBAC advised that, if MSAC provides supportive advice regarding ALK-ISH testing then the PBAC would support an expedited process for reconsideration. This would ensure alignment of a PBAC recommendation for crizotinib with the circumstances advised by MSAC. The PBAC considered that a minor re-submission would be suitable to convey the applicants' inputs on an aligned PBS restriction for crizotinib and on a revised basis to consider the incremental cost-effectiveness of crizotinib.

The PBAC considered pemetrexed to be the appropriate main comparator.

The PBAC considered that it would be informative to re-run the model as presented in the submission, with inputs adjusted to include:

- a 3.1 month incremental OS gain over the chemotherapy arm (in line with the projection based on the meta-regression by Johnson et al 2006) or a 3.5 month incremental OS gain over the chemotherapy arm (in line with the more conservative results of the two methods of adjusting for crossover);
- costs for broader mutation testing as might be advised by MSAC; and
- costs for management of adverse events (e.g., routine ophthalmological monitoring);
- with an adjustment to the price of crizotinib to achieve an ICER of the order of $50,000-60,000 per QALY in line with other PBAC-recommended oral medicines to treat advanced NSCLC.

In the event of a positive listing recommendation, the PBAC considered the PBS restriction for crizotinib should include the proposed stopping rule, noting that patients with disease progression following crizotinib would be able to receive treatment with pemetrexed.

The PBAC also foreshadowed that the restriction for crizotinib should:

- include reference to disease stage (locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC);
- limit PBS-subsidised use to patients with adenocarcinoma histology, noting that 93% of patients in the key study presented in the submission had adenocarcinoma;
- exclude patients with coexistent mutations which confer resistance to crizotinib (EGFR mutations, KRAS mutations, KIT amplification, BRAF mutations or MET mutations); and
- exclude heavily pre-treated patients (i.e., limit the restriction to those who have failed platinum doublet therapy in the first-line setting.)

The PBAC also considered that the definition of the appropriate patient population for treatment with crizotinib would be dependent on the findings of MSAC in relation to mutation testing.

To this end, the PBAC sought MSAC advice over whether MSAC would support ALK ISH testing (and any other molecular testing considered necessary) to identify the patient population for whom the net benefit to harm ratio of crizotinib is favourable. Specifically, the PBAC sought MSAC advice on the following aspects of the co-dependent testing of ALK gene rearrangements.

Who to test:

a) Should ALK gene rearrangement testing (and therefore crizotinib treatment) of patients with NSCLC be restricted to particular histology subtypes? Although the submission does not propose any restriction by histology subtype, restricting to patients with the adenocarcinoma subtype would reflect the key trial in which 93% patients had adenocarcinoma, and might enrich the population for testing by reducing other histology subtypes with negligible prevalences of ALK gene rearrangements.
b) Should patients with evidence of mutations which confer likely primary resistance to crizotinib be excluded from testing for ALK gene rearrangements? Examples of these mutations include EGFR mutations, KRAS mutations KIT amplification, BRAF mutations or MET mutations. The pre-crizotinib sample (REF Kris, MG et al. *Identification of driver mutations in tumor specimens from 1,000 patients with lung adenocarcinoma: The NCI's Lung Cancer Mutation Consortium (LCMC) [abstract]*. J Clin Oncol 29 (Suppl.), CRA7506 (2011); also Camidge and Doebele. *Treating ALK-positive lung cancer – early successes and future challenges.* Nature Reviews clinical oncology 2012;9:268-277) of patients with ALK gene fusions demonstrates that 13% also had EGFR, KRAS, BRAF or MET mutations. Although these mutations were initially thought to be mutually exclusive with ALK gene rearrangements Ou, S-HI et al (*Crizotinib for the treatment of ALK-rearranged non-small cell lung cancer: a success story to usher in the second decade of molecular targeted therapy in oncology.* The Oncologist 2012;17(11):1351-75) reported that, of ALK-positive patients with NSCLC, 2.6-9.5% had a concurrent EGFR mutation and from Attachment 1, Table A. 1.3 of the submission, 2.6-9.1% had a concurrent KRAS mutation.

Should testing in the context of ALK gene rearrangement also incorporate other rare targets for crizotinib such as ROS1 rearrangements?

When to test:

a) What is the place of testing for ALK expression? Is it useful for triaging patients for ALK gene amplification testing? Do varying extents of ALK expression modify the prediction of variation in the effect of crizotinib based on ALK gene amplification?
b) Should testing of patients with NSCLC be restricted or allowed to be conducted anytime from (and including) initial diagnosis? If restricted, should this be when patients present with advanced (Stage IIIB and Stage IV) disease or after patients with advanced disease fail first-line platinum-based therapy?

How to test:

Are there any aspects of an MBS item descriptor which would facilitate practical implementation in diagnostic pathology practice? This is relevant, because ALK gene

rearrangements are rare and so the costs of identifying these patients, e.g., in terms of pathology laboratory practice changes and workflow, are underestimated by the submission's use of the unit cost of FISH testing.

How to test:
Are ALK gene rearrangements a positive prognostic factor?

The PBAC also sought from the applying sponsors (Pfizer and Abbott Molecular) any molecular data which impacts on the net benefit to harm ratio of crizotinib and thus informs an analysis which takes into account the consequences for patients of missing out on effective standard therapies because they have inappropriately received treatment with crizotinib because of poor molecular targeting.

In the event of a positive recommendation to list crizotinib, the PBAC considered that:
- crizotinib is not suitable for prescribing by nurse practitioners;
- the Safety Net 20 Day Rule should apply; and
- in accordance with subsection 101 (3BA) of the *National Health Act* 1953, on the basis of the evidence available to it at its November 2013 meeting, the Minister should be advised that crizotinib should not be treated as interchangeable on an individual patient basis with any other drug(s) or medicinal preparation(s).

In the event of a positive recommendation to list crizotinib, the PBAC foreshadowed that it intended to review:
- the conditions of the PBS listing of crizotinib as soon as first-line data is available to be provided by the applicants
- any new molecular data which becomes available to be provided by the applicants which might have consequences for the PBAC's analysis of the benefit to harm ratio of crizotinib compared to pemetrexed (the updated analysis should take into account the consequences for patients of missing out on effective standard therapies because they have inappropriately received crizotinib due to poor molecular targeting).

Outcome:
Deferred

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Provision of overall survival evidence is an ongoing challenge in oncology necessitating alternative approaches to address reimbursement requirements in the context of the data deficiencies from clinical trials involving cancer patients. The Sponsor will work with the Committee to enable a

pragmatic assessment of the cost-effectiveness of crizotinib in ALK-positive non-small cell lung cancer.