Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1250 – Testing of the anaplastic lymphoma kinase (ALK) gene in patients with non–small cell lung cancer to determine eligibility for treatment with crizotinib

Sponsor/Applicant/s: **Abbott Molecular Pty Ltd and Pfizer Australia Pty Ltd**

Date of MSAC consideration: **28 November 2013**

1. Purpose of application

A co-dependent application from Abbott Molecular and Pfizer Australia was received by the Department of Health in June 2013 requesting:

- Medicare Benefits Schedule (MBS) listing of fluorescent in situ hybridisation (FISH) testing in patients with advanced or metastatic non-small cell lung cancer (NSCLC), for identification of anaplastic lymphoma kinase (ALK) gene rearrangement; and
- Pharmaceutical Benefits Scheme (PBS) listing for crizotinib for the treatment of advanced and metastatic (stage IIIB and IV) NSCLC patients who test positive for an *ALK* gene rearrangement, where disease progression has occurred following at least one platinum-based chemotherapy.

ALK gene rearrangement is typically a fusion between the anaplastic lymphoma kinase (ALK) and the echinoderm microtubule associated protein-like 4 (EML4) genes. ALK gene rearrangement testing is proposed as a 2-step process with ALK immunohistochemistry (IHC) testing as a triage for ALK fluorescent in situ hybridisation (FISH) testing. ALK gene rearrangement testing will have no direct impact on the health of patients who will receive it. Rather, results of the test will help guide the appropriate choice of chemotherapy. ALK gene rearrangement testing would be an additional test that can be performed on formalin-fixed, paraffin-embedded tumour tissue that is currently routinely biopsied for diagnostic purposes (if sufficient tissue sample is available).

Approximately 3-5% of patients with NSCLC have a translocation of the ALK gene which leads to expression of the ALK protein, and consequently, the activation of signalling pathways that control cell proliferation and survival. While there are multiple treatments for locally advanced or metastatic NSCLC, some of which will be effective in patients with ALK gene rearrangements, there are no treatments, other than crizotinib, that specifically target ALK tyrosine kinase activity.

2. Background

Diagnostic testing for ALK gene rearrangement has not been previously considered by MSAC.

3. Prerequisites to implementation of any funding advice

The clinical evidence informing the use of crizotinib in ALK gene rearrangement positive NSCLC has been derived using the Vysis ALK Break Apart FISH Probe Kit manufactured by Abbott Molecular Diagnostics. This is an in-vitro diagnostic medical device (IVD).

Abbott Australasia Pty Ltd advised that the Vysis Break Apart FISH Probe Kit was granted TGA approval and listed on the ARTG on 3 April 2012 (ARTG identifier 186286).

Seven diagnostic laboratories currently perform ALK FISH testing using the Vysis ALK Break Apart FISH Probe Kit® in Australia: two laboratories in New South Wales, two in Queensland, and one each in Victoria, South Australia and Western Australia.

4. Proposal for public funding

Proposed MBS item descriptor for *ALK* gene rearrangement testing

Category 6 – Pathological Services
Proposed MBS item descriptor in final DAP
MBS item number: *to be advised* Category 6 – Pathological Services An *in situ* hybridisation test of tumour tissue from a patient with locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise specified, to determine if requirements relating to anaplastic lymphoma kinase (ALK) gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $(redacted information) *[A final proposed fee is to be advised by the applicant upon the completion of a cost survey of reference laboratories]*
Proposed item descriptor in submission
MBS item number *to be advised* Fluorescent *in situ* hybridisation (FISH) test of tumour tissue from a patient with non-small cell lung cancer (NSCLC) requested by, or on behalf of, a specialist or consultant physician to determine if requirements relating to anaplastic lymphoma kinase (ALK) gene rearrangement *status* for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $(redacted information)

The submission and the final Decision Analytic Protocol (DAP) proposed that ALK gene rearrangement testing occurs as a 2-step process with ALK immunohistochemistry (IHC) testing as a triage for ALK fluorescent in situ hybridisation (FISH) testing. However, the submission did not include ALK IHC as a triage test in the proposed MBS item descriptor for ALK ISH testing, nor does it suggest a proposed or current MBS item for ALK IHC testing. The final DAP suggested that ALK IHC testing may be funded through the existing MBS item numbers 72846 or 72847.

In situ hybridisation for detecting ALK gene rearrangements is proposed to occur only in EGFR wild type patients, and in patients who have a positive result from immunohistochemistry. However, the proposed MBS item descriptor does not specify ALK FISH testing of only those samples that are EGFR mutation negative and ALK IHC positive (1+, 2+, or 3+). Restricting the testing population to EGFR mutation negative patients would reduce the number of tests performed but would not reduce the number of patients eligible for crizotinib therapy.

The submission did not consider that use of the test should be restricted to the clinical population as outlined in the proposed PBS listing (and as defined in the final DAP). The MBS item descriptor proposed by the submission broadens the eligible population from non-squamous NSCLC or not otherwise specified (as proposed in the DAP) to include patients with squamous NSCLC. However, the submission did not provide any evidence substantiating the inclusion of squamous cell carcinomas or assessed the implications of removing this restriction, as required in the final DAP. The trial evidence, economic model and financial analysis are relevant only to a non-squamous population.

Making the ALK *in situ* hybridisation test a pathology determinable service would permit pathologists to proceed to an ISH test following confirmation of negative squamous histology, a negative EGFR mutation test and a positive IHC test without the delay of receiving another referral from a clinician.

5. Consumer Impact Statement

Feedback was received from two health professionals and two professional bodies, which in general showed support for MBS subsidy of FISH testing for ALK gene for patients with advanced NSCLC.

If funding is approved, one of the professional bodies believes that parallel funding of evidence based treatment options resultant from tests results should be considered in order that additional emotional and financial burden is not born by patients and the family/carers of those with lung cancer.

6. Proposed intervention's place in clinical management

The table below summarises the clinical algorithm proposed in the submission, the base case scenario used in the economic and financial analyses and the scenarios included in the final Decision Analytical Protocol (DAP) 1250 accepted by the Protocol Advisory Sub Committee (PASC) of MSAC.

Scenarios presented in the submission and final DAP – from the Critique of Contracted Assessment

Scenarios	Biomarkers for testing	Type and stage of NSCLC in testing population	Time of ALK testing	Time of treatment with crizotinib	Analysis presented in submission?
Algorithm and base case scenario presented in the submission					
Submission clinical algorithm (Section A.5)	EGFR mutation testing of all eligible patients ALK gene rearrangement: IHC testing of EGFR M- patients FISH testing of IHC+ patients	EGFR mutation-negative patients with NSCLC	At diagnosis of NSCLC	After first-line treatment failure	Model does not reflect the algorithm proposed in the submission
Submission base case (Sections D and E)	EGFR mutation testing of all eligible patients ALK gene rearrangement: IHC testing of EGFR M- patients FISH testing of IHC+ patients	EGFR mutation-negative patients with locally advanced or metastatic stage IIIB/IV non-squamous NSCLC	At diagnosis of, or at progression to, stage IIIB/IV NSCLC	After first-line treatment failure	Yes
Adequate	Yes	No	No	Yes	NA

data?					
Scenarios requested in the final DAP 1250					
Scenario 1	ALK gene rearrangement: Base case: FISH testing of all eligible patients Scenario analysis: IHC testing of all eligible patients followed by FISH testing of IHC+ patients EGFR mutation testing of all ALK- patients after first-line treatment failure	Patients with locally advanced or metastatic stage IIIB/IV non-squamous NSCLC	At diagnosis of stage IIIB/IV disease	After first-line treatment failure	No
Scenario 2	ALK gene rearrangement: Base case: FISH testing of all eligible patients Scenario analysis: IHC testing of all eligible patients followed by FISH testing of IHC+ patients EGFR mutation testing of all ALK- patients after first-line treatment failure	Patients with locally advanced or metastatic stage IIIB/IV NSCLC	At diagnosis of stage IIIB/IV disease	After first-line treatment failure	No
Scenario 3	ALK gene rearrangement: Base case: FISH testing of all eligible patients Scenario analysis: IHC testing of all eligible patients followed by FISH testing of IHC+ patients EGFR mutation Base case: testing of ALK- patients Scenario analysis: testing of all eligible patients	Patients with locally advanced or metastatic stage IIIB/IV NSCLC	Concurrent with EGFR mutation test, at progression to, stage IIIB/IV disease	After first-line treatment failure	No
Scenario 4	ALK gene rearrangement: Base case: FISH testing of all eligible patients Scenario analysis: IHC testing of all eligible patients at diagnosis followed by FISH testing of IHC+ patients EGFR mutation testing of all ALK- patients after first-line treatment failure	Patients with locally advanced or metastatic stage IIIB/IV non-squamous NSCLC	At diagnosis of, or at progression to, stage IIIB/IV NSCLC	First-line treatment	No

ALK = anaplastic lymphoma kinase; ALK- = ALK gene rearrangement negative; DAP= Decision Analytical Protocol; EGFR = epidermal growth factor receptor; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry; IHC+ = IHC positive; NA = not applicable; NSCLC = non-small cell lung cancer.
Source: Constructed during the evaluation.

The submission's clinical management algorithm included reflex ALK testing at diagnosis of NSCLC. All patients with NSCLC have EGFR mutation testing and those found to be EGFR wild type (M-) would then be eligible for ALK testing. EGFR M- patients would be pre-screened for ALK gene rearrangement using ALK IHC testing. IHC positive samples, regardless of the intensity of the stain, would receive confirmatory ALK FISH testing. As the diagnostic 'gold standard', a positive ALK FISH test result would be required for access to crizotinib treatment.

Although ALK gene rearrangements have been identified in both squamous cell carcinoma and adenocarcinoma, the mutation occurs predominantly in non-squamous NSCLC, with less than 1% of squamous NSCLC patients having ALK gene rearrangements. However, the population in the proposed clinical algorithm does not match that recommended by MSAC for EGFR mutation testing; only patients with non-squamous NSCLC or otherwise not specified would be tested for EGFR mutations, whereas the proposed clinical algorithm includes patients with squamous NSCLC.

The submission's base case, applied in the economic model and financial analysis of the submission, is not consistent with the proposed clinical management algorithm, the scenarios suggested in the final DAP, or the proposed PBS and MBS listings. The submission did not address these differences.

7. Other options for MSAC consideration

ALK gene rearrangement testing

IHC is used to detect the over-expression of specific antigens or proteins. The samples are graded on a scale from 0 to 3+, based on the extent and intensity of staining, with a higher score indicating a greater over-expression of the target antigen or protein. For NSCLC, only an IHC score of 0 may be considered definitively negative for ALK gene rearrangements, in order to avoid any false-negative results. It should be noted that IHC is not likely to be suitable as a stand-alone test for detecting ALK gene rearrangements in NSCLC patients due to problems with false-positive staining and inter-rate variability due to the subjective scoring system.

Other tests capable of ALK gene rearrangement testing include Real-time PCR/real-time polymerase chain reaction (RT-PCR), chromogenic in situ hybridisation (CISH) or silver-enhanced in situ hybridisation (SISH).

As FISH was the testing methodology employed throughout the conduct of clinical trials assessing crizotinib, PASC determined that ALK FISH testing would be considered the evidentiary standard, with other testing strategies to be assessed against this standard for potential eligibility for MBS funding.

In accordance with the DAP, the submission sought to restrict ALK gene rearrangement testing to FISH methodology.

Prevalence

There is uncertainty concerning the true prevalence of ALK gene rearrangements among Australian patients with NSCLC. The submission estimated that ALK gene rearrangements would be present in **(redacted information)**% of Australian patients with non-squamous NSCLC, which is consistent with the prevalence (5.6%) estimated during the evaluation and internationally. However, an Australian study published after the submission dead-line, reported a prevalence of 1.3% among patients with non-squamous NSCLC who had undergone surgical resection.

As 97.2% of that study population had early-stage NSCLC, and the prevalence was estimated to be 2.17-fold higher in patients with advanced disease, the prevalence in advanced or metastatic non-squamous NSCLC is estimated at 2.8%. This is lower than the prevalence predicted in the submission.

The Joint ESCs noted that the prevalence of ALK gene rearrangements varies by histology type, with prevalence increasing to 8.2% in an NSCLC population limited to adenocarcinoma, and that the applicant's Pre-Sub-Committee response referred to the low prevalence of ALK-positivity in patients with squamous histologies. Exclusion of NSCLC with squamous histology will not noticeably reduce the number of patients detected with ALK gene rearrangements.

8. Comparator to the proposed intervention

The comparator proposed in the submission was no ALK gene testing. This was consistent with the nominated comparator in the final DAP.

9. Comparative safety

No safety concerns regarding ALK gene rearrangement testing were reported in the submission. No unexpected serious adverse events occurred during any of the pre-clinical, clinical validation and clinical utility studies.

Safety concerns primarily relate to those patients who will require another biopsy. In Australia, biopsy samples are usually collected at initial diagnosis, using either bronchoscopy or percutaneous fine needle aspiration. If an adequate sample is obtained, no additional procedure will be required for ALK gene rearrangement testing. However, the requirement for histology testing, EGFR testing and two ALK tests could mean the initial tumour sample is of inadequate size. With the addition of ALK IHC and FISH testing, the number of patients with an inadequate tumour sample may increase. Further, ALK FISH testing has an 8.5% failure rate (reported in the submission). These patients would require retesting, increasing the amount of tumour sample required, and further increasing the likelihood of a re-biopsy.

The risk of biopsy-related adverse events will vary according to the site of the primary tumour or metastasis and the biopsy method used. This was not addressed in the submission. MSAC advice from the November 2012 Minutes for Application 1161 recommended that economic evaluations and financial analyses should include a re-biopsy complication rate of 14%. The 12% (or an appropriately scaled-up) re-biopsy rate and the resultant complication rate were not addressed in the submission.

10. Comparative effectiveness

Evidence for testing

Prognostic evidence	Retrospective cohort studies that compared outcomes in patients receiving usual care conditioned on the presence or absence of ALK gene rearrangements.	Submission: ☒ k=26 n=8,406
Comparative analytical performance	Studies that compared different testing methodologies from archival specimens or samples to determine analytical validity.	Submission: ☒ k=17 n=2,921 Evaluation: ☒ k=1 n=641

k=number of studies, n=number of patients.

Results of prognostic evidence

Seven studies reported on the overall survival of NSCLC patients with and without ALK gene rearrangement, adjusted for possible confounders. Of these retrospective cohort studies, three reported that there was no difference in the prognosis of patients with ALK gene rearrangement, one reported a worse prognosis, one reported a better prognosis and for two studies, the conclusion was not clear. It remained unclear whether ALK gene rearrangement confers a better or worse outcome, or whether it has no prognostic significance.

Results of comparative analytical performance

The submission proposed that IHC testing would be used to triage FISH testing in a 2-step ALK gene rearrangement testing scenario. However, the accuracy of this 2-step testing strategy relative to FISH testing alone (the evidentiary standard) was not able to be determined from the evidence base. Meta-analysis of the sensitivity and specificity of the IHC and RT-PCR testing alone, relative to the FISH testing alone, were undertaken during evaluation (see tables below) and hierarchical summary receiver operating characteristic (HSROC) graphs were plotted (see below).

Summary of ALK IHC test performance compared with ALK FISH as the evidentiary standard

		Vysis ALK Break Apart FISH test (evidentiary standard)			
		Yes	No		
ALK IHC test (studies using 5A4 or D5F3 antibodies only)	Yes	7	11	PPV[a] = % [95% CI] 38.9% [18.3%, 63.9%]	1-PPV = 61.1%
		25	3	89.3% [70.6%, 97.2%]	10.7%
		28	27	50.9% [37.2%, 64.5%]	49.1%
		9	5	64.3% [35.6%, 86.0%]	35.7%
		13	0	100% [71.7%, 100%]	0%
		22	1	95.6% [76.0%, 99.8%]	4.4%
		19	1	95.0% [73.1%, 99.7%]	5.0%
		5	0	100% [46.3%, 100%]	0%
		14	1	93.3% [66.0%, 99.7%]	6.7%
		9	0	100% [62.9%, 100%]	0%
	No	0	576	NPV[a] = % [95% CI] 100% [99.2%, 100%]	1-NPV = 0%
		0	234	100% [98.0%, 100%]	0%
		0	680	100% [99.3%, 100%]	0%
		0	173	100% [97.3%, 100%]	0%
		1	162	99.4% [96.1%, 100%]	0.6%
		0	130	100% [96.4%, 100%]	0%
		2	59	96.7% [87.6%, 99.4%]	3.3%
		1	73	98.6% [91.7%, 99.9%]	1.4%
		0	30	100% [85.9%, 100%]	0%
		0	25	100% [83.4%, 100%]	0%
Sensitivity and specificity of individual studies		Sensitivity = 100% [56.1, 100]	Specificity = 98.1% [96.6, 99.0]	Size of study: N = 594	
		100% [83.4, 100]	98.7% [96.0, 99.7]	262	
		100% [85.0, 100]	96.2% [94.4, 97.4]	735	
		100% [62.9, 100]	97.2% [93.2, 99.0]	187	
		92.8% [64.1, 99.6]	100% [97.1, 100]	176	
		100% [81.5, 100]	99.2% [95.2, 99.9]	153	
		83.3% [36.5, 99.1]	100% [93.8, 100]	79	
		90.5% [68.2, 98.3]	98.3% [89.9, 99.9]	81	
		100% [73.2, 100]	96.8% [81.5, 99.8]	45	
		100% [62.9, 100]	100% [83.4, 100]	34	
Pooled data[b] % [95% CI]		Sensitivity = 98.4% [90.0%, 99.8%]	Specificity = 98.5% [97.2%, 98.2%]	Positive LR = 66.4 [34.5, 127.7]	
		1-Sensitivity = 1.6%	1-Specificity = 1.5%	Negative LR = 0.02 [0.00, 0.11]	

[a] The PPV and NPV values for studies with prevalences below 10% are in boldface as they are more applicable to the Australian population.

[b] Using the STATA metandi command.

CI = confidence interval; FISH = fluorescent in situ hybridisation; IHC = immunohistochemistry; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

The table above indicates that a negative ALK IHC test is highly predictive of a negative ALK gene rearrangement using FISH. The high level of agreement between IHC-negative and FISH-negative test results is important as both the final DAP and the submission

proposed that ALK IHC testing be used as a triage test to rule out ALK gene rearrangements in patients who would then need no further testing. These data show that very few patients would miss out on potentially beneficial treatment with crizotinib due to an inaccurate IHC test result.

The median positive predictive values for studies with a prevalence below 10% (according to the FISH test; k = 6) indicate that a substantial number of ALK IHC positive NSCLC tumours would not have an ALK gene rearrangement when FISH tested. Approximately 2 (ranging from 0-6) Australian patients out of every 10 that receive a positive IHC test result will not actually have an ALK gene rearrangement detectable by FISH testing and so would not be suitable for crizotinib treatment (1 – PPV). Thus, ALK IHC testing is not useful as a stand-alone test, but would be useful as a less specific triage test to reduce the number of patients requiring ALK FISH testing.

Summary of ALK RT-PCR test performance compared with ALK FISH as the evidentiary standard

		Vysis ALK Break Apart FISH test (evidentiary standard)			
		Yes	No		
ALK RT-PCR test	Yes	5 3 10 4	0 1 2 0	PPV[a] = % [95% CI] 100%[46.3%, 100%] 75.0%[21.9%, 98.7%] 83.3%[50.9%, 97.1] 100%[39.6%, 100%]	1-PPV = 0% 25% 16.7% 0%
	No	0 0 1 3	82 19 7 126	NPV[a] = 100% [94.4%, 100%] 100% [79.1%, 100%] 87.5% [46.7%, 99.3%] 97.7% [92.8%, 99.4%]	1-NPV = 0% 0% 12.5% 2.3%
Sensitivity and specificity of individual studies		Sensitivity = 100% [46.3, 100] 100% [31.0, 100] 90.9% [57.1, 99.5] 57.1% [20.2, 88.2]	Specificity = 100% [94.4, 100] 95.0% [73.1, 99.7] 77.7% [40.2, 96.1] 100% [96.3, 100]	Size of study: N = 87 23 20 133	
Pooled data[b] % [95% CI]		Sensitivity = 86.0% [59.7%, 96.2%]	Specificity = 99.2% [78.4%, 100%]	Positive LR = 104.3 [3.5, 3,150.1]	
		1-Sensitivity = 14%	1-Specificity = 1.9%	Negative LR = 0.14 [0.04, 0.48]	

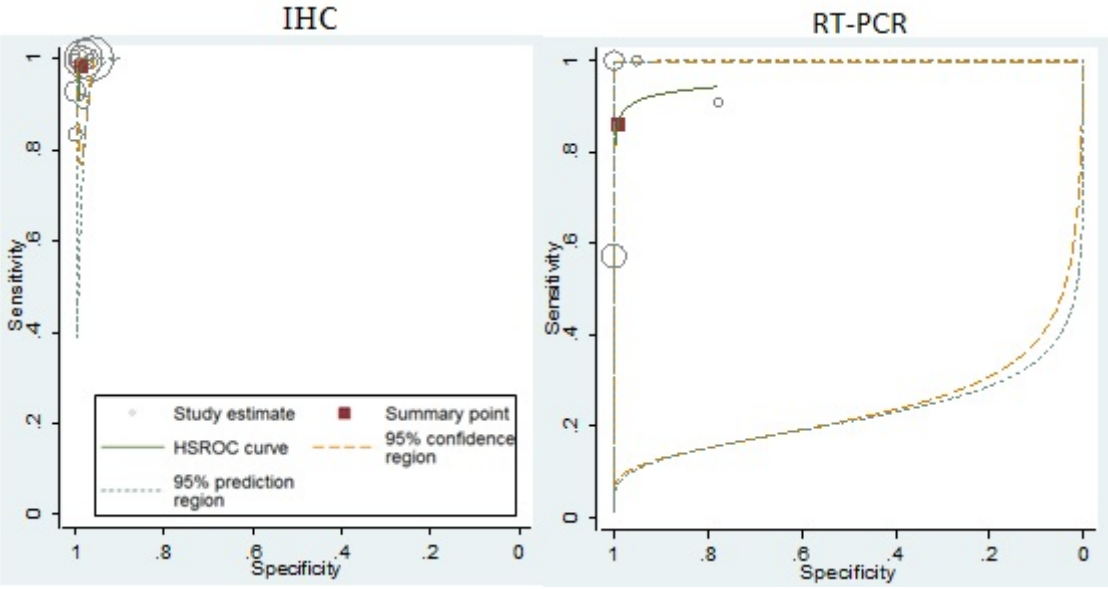
[a] The PPV and NPV values for studies with prevalences below 10% are in boldface as they are more applicable to the Australian population.

[b] Using the STATA metandi command.

CI = confidence interval; FISH = fluorescent in situ hybridisation; IHC = immunohistochemistry; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

The pooled results of the ALK RT-PCR test compared to the FISH test have wider confidence intervals than the IHC comparison because, as can be seen in the graphs below, the ALK RT-PCR meta-analysis is reliant on only a few studies and so the precision of the estimates is poor. The submission concluded that the ALK RT-PCR test would be less reliable than the FISH test to determine eligibility for crizotinib treatment. The HSROC graph for IHC testing indicates that diagnostic accuracy is uniformly high (close to 1) with a reasonably precise 95% confidence region going no lower than approximately 0.8. However, the evidence base is not yet substantial enough to rule out that additional future evidence might report lower test sensitivity, even though specificity is likely to remain reasonably consistent with the current evidence base.

HSROC graph of comparative sensitivity and specificity for ALK IHC and RT-PCR testing versus ALK FISH testing



The agreement between the methodologically similar CISH and FISH tests was high in the two studies that compared these methods. Thus, it is possible that these two testing methods could be used interchangeably. There were no studies comparing SISH with FISH. The submission noted that there are currently no commercial ALK CISH or SISH kits available in Australia.

The submission provided evidence that ALK gene rearrangement is the biomarker upon which crizotinib acts. It remains unclear whether the presence of ALK gene rearrangement is associated with a different prognosis to those patients without ALK gene rearrangement. However, given the direct comparison of crizotinib with an appropriate comparator in patients with ALK gene rearrangement, it is unlikely that a prognostic effect associated with the biomarker would explain observed differences in treatment effect.

11. Economic evaluation

The submission presented a cost-utility analysis with a two-stage modelled economic evaluation for testing and then treating patients with Stage IIIb/IV EGFR negative NSCLC following disease progression after at least one platinum-based chemotherapy regimen.

The model presented in the submission was generally consistent with the assessment of advanced non-squamous NSCLC patients as proposed in the DAP, although it did not include those with not otherwise specified NSCLC. It allows for the implications of false positive and false negative ALK test results to be explored quantitatively. However, the structure of the model did not consider third-line crizotinib treatment following second-line pemetrexed or docetaxel; use in the third-line setting has been assumed in the financial analyses.

The treatment duration in the economic model was not consistent with the assumed treatment duration. The Joint ESCs noted that the economic model was sensitive to changes in crizotinib treatment duration.

The economic model did not consider a number of variables in the base case analysis, including test-related costs (such as appropriate patient episode initiation (PEI) and specimen referral or sample retrieval fees), rates of re-testing, re-biopsy and adverse events related to re-biopsy. A 4.8-8.5% re-testing rate should have been included. Given that the ALK testing

algorithm requires samples sufficient for an additional two tests, the rate of re-biopsy may be higher than previous recommendations by MSAC (12%, Application 1161 Minutes November 2012).

Where some variables were considered in the base case, uncertainty around many estimates had not been investigated, including prevalence and utility. While varied sensitivity and specificity values may be tested, the submission assumed that crizotinib treatment in ALK- patients (i.e. false positives) confers neither benefit nor harm when compared to treatment with chemotherapy. This was an unreasonable assumption and the true effect of false positives remained inadequately assessed.

The base case economic evaluation estimated an incremental cost per extra QALY gained of between $45,000 – $75,000.

Key univariate sensitivity analyses were presented by the submission and additional analyses were conducted during the evaluation. The sensitivity analyses conducted around the sensitivity and specificity did not adequately address the uncertainty around the implications of false positive and false negative patients, as false positives are assumed to respond to crizotinib treatment as for chemotherapy.

12. Financial/budgetary impacts

The populations estimated in the financial analysis do not reflect the populations proposed in the MBS and PBS restrictions or the proposed clinical management algorithm. Broadening the tested population is likely to result in a large incremental number of tests performed (over the submission's estimates), for a small incremental increase in the number of ALK+ patients eligible for crizotinib treatment.

Test cost/patient

The test cost per IHC test is $59.60 (using current MBS item 72846). For each patient with a positive IHC test, a FISH test would be required to confirm the presence of an ALK rearrangement. The proposed fee per FISH test was $**(redacted information).**

The submission had not considered other costs associated with ALK testing, including appropriate Patient episode initiation (PEI), specimen referral and sample retrieval fees.

Costs of testing in the base case funding scenario for 2014

Annual estimates	Submission base case
Number of patients tested	(redacted information)EGFR wild type Stage IIIb/IV non-squamous NSCLC patients
Prevalence	(redacted information)% (range tested: 3.5-6.0%)
Number of test positive patients	(redacted information) patients
Number of patients treated	(redacted information) patients
Number of tests per patient tested (assuming no re-testing)	(redacted information) *(1 IHC at $59.60 per test and (*(redacted information)*FISH at $*(redacted information) *per test)*
Test cost per patient tested	*$*(redacted information) *($59.60*(redacted information)*)*
Test cost per patient treated	*$*(redacted information)

Source: Constructed from Table E.2.1, Table E.2.2 and TableE.4.1 in Section E of the evaluation. *(This does not take into consideration testing at diagnosis.)*

Number of patients likely to be tested

The likely number of patients to be tested was estimated to be less than 5,000 patients in 2014 and in 2018 for IHC testing and less than 1,000 in 2014 and in 2018 for FISH testing.

The total number of patients with Stage IIIb/IV non-squamous NSCLC is likely to be underestimated, due to underestimated projections of incident lung cancer cases, underestimated progression in patients diagnosed with early stage disease and the exclusion of not otherwise specified carcinomas from the non-squamous population as per the proposed MBS item descriptor in the DAP.

Cost to the MBS
The estimated net cost to the MBS was less than $500,000 in 2014 and in 2018.

The submission considered only the cost of IHC and FISH testing in the costs to the MBS and did not exclude patient co-payments nor consider safety net consequences. Rates of re-biopsy (>12%) and re-testing (8.5%) were not considered in the base case financial analyses (which might increase if a new biopsy is requested when a patient with an earlier stage NSCLC progresses to Stage IIIb or IV even though ALK mutation status is not considered likely to change during the course of the disease), nor appropriate PEI, specimen referral or sample retrieval fees. The technical efficacy of FISH ranged between 91.5-95.2% in the submission, but only the lower re-testing rate (4.8%) was considered in sensitivity analysis.

Cost to the Government
The estimated net cost to the Government was less than $10 million in 2014 and in 2018.

The submission had not considered the cost impact of reduced chemotherapy administrations, and increased re-biopsy or adverse events related to re-biopsy to state hospital budgets. Given the high cost of re-biopsy (Bronchoscopy AR-DRG E42C, $1,793) and treatment of associated adverse events (AR-DRG E42B, $10,657, or E42A, $23,371), the inclusion of these costs is likely to result in net costs to state hospital budgets.

There is potential for the net cost/year to the MBS to be greater than estimated in the submission given that the population eligible for testing may be underestimated. Sensitivity analyses indicated that the financial analyses are sensitive to the proportion of lung cancers that are non-squamous or not otherwise specified, as well as the prevalence of ALK rearrangements.

There may be potential usage within the requested listing that has not been accounted for in the financial analysis. The population estimated in the financial analysis does not reflect the population proposed in the MBS and PBS restrictions. The proposed FISH MBS descriptor does not restrict by disease stage or histology, and the current IHC descriptor contains no restrictions.

There may be potential usage outside of the requested MBS listing, as the proposed MBS item descriptor for FISH does not specify that patients require a positive IHC test. In addition, the MBS item descriptor does not restrict testing to EGFR wild type, so there may be leakage of testing to patients with EGFR mutations.

13. Key issues for MSAC from ESC

Clinical Issues
The MBS item descriptor proposed by the submission broadens the eligible population from non-squamous NSCLC or not otherwise specified (as proposed in the DAP) to include patients with squamous NSCLC. The MBS item descriptor does not specify ALK FISH testing of only those samples that are EGFR mutation negative and ALK IHC positive (1+, 2+, or 3+), as in the proposed clinical pathway and as modelled.

There were concerns about the timing of the ALK test:

- EGFR mutation testing of patients with advanced or metastatic non-squamous NSCLC at the time of initial diagnosis, followed by reflex ALK testing of those patients found to be EGFR mutation negative would be appropriate, enabling physicians to make the treatment decisions for these patients as soon as possible;
- For patients who are diagnosed with early disease, the prevalence of ALK gene rearrangement may be lower. If this is a consequence of the development of an ALK gene mutation as the disease progresses, MSAC may wish to consider the appropriateness of ALK testing at diagnosis regardless of stage. Alternatively, a re-biopsy at diagnosis of or progression to advanced disease may be required to ensure all patients with the ALK gene rearrangement are identified for second line treatment with crizotinib.

Analysis of the diagnostic accuracy data showed that there is a high level of agreement between IHC-negative and FISH-negative test results, and that very few (if any) patients would miss out on potentially beneficial treatment with crizotinib due to an inaccurate IHC test result, justifying the use of the ALK IHC test as a triage test.

Due to the subjective nature of determining positivity with IHC testing, and the potential for technical problems leading to false positive (or negative) test results, the Joint ESCs agreed with the submission that all testing should be performed in diagnostic laboratories that are subject to a rigorous quality assurance program so that patient outcomes are not jeopardised by sub-standard or inadequate testing protocols.

Economic and Financial Issues

The MBS item descriptor was not consistent with the modelled population: the population tested in the model comprises patients with advanced, EGFR wild-type, non-squamous NSCLC, whereas the item descriptor (for FISH) does not restrict by disease stage, EGFR status, ALK IHC status, or NSCLC histology.

The population assumed in the financial analyses was narrower than the proposed FISH MBS restriction-where testing is costed only for patients with advanced non-squamous NSCLC.

The tested population assumed in the submission (advanced non-squamous NSCLC) is likely to be underestimated, based on the assumptions used to estimate those eligible; the financial analyses are particularly sensitive to the proportion of the population with eligible NSCLC histology.

There is potential for leakage; the proposed FISH item descriptor is not restricted to patients with a positive ALK IHC test nor to patients with EGFR wild type status, and the current descriptor for IHC contains no restrictions.

The submission had not considered costs to state government health budgets; given the high cost of re-biopsy and treatment of associated adverse events, the inclusion of these costs is likely to result in increased net costs.

The costs of re-biopsy, re-testing and adverse events related to re-biopsy had not been considered in the submission; the ICER is sensitive to the inclusion of these costs in the economic model.

The submission had not considered the patient episode initiation fee (which might only be

excluded in the context of reflex testing), or fees for specimen referral or sample retrieval.

The estimate of prevalence had not been based on Australian studies; the true prevalence of the biomarker in the proposed testing population is unknown, however may be overestimated in the submission.

In the economic model of the submission, false positives (i.e. ALK- treated with crizotinib) were assumed to respond to crizotinib as they would for chemotherapy. This is an inconsistent application of the proposed mechanism of action of crizotinib. It was also not consistent with the argument of biological plausibility if treatment effect variation, due to ALK status, is assumed. Rather, the assumption would have to be that ALK testing is simply a prognostic marker, so pairing with crizotinib may not be required as other drugs may work equally as well in this ALK+ population subgroup. Effectively, the submission assumed that targeted treatment (against ALK which is not expressed in adults normally) will have similar efficacy as a systemic chemotherapy. The Joint ESCs did not consider this assumption to be reasonable.

14. Other significant factors

Nil.

15. Summary of consideration and rationale for MSAC's advice

Anaplastic lymphoma kinase (ALK) is a validated new target for non-small cell lung cancer (NSCLC) therapy. Crizotinib is an oral small-molecule tyrosine kinase inhibitor targeting ALK, MET and ROS1 tyrosine kinases. Crizotinib has demonstrated antitumour activity in patients with advanced ALK-positive NSCLC (Shaw et al. 2013; NEJM 368: 2385-94). The applicant proposes an MBS item number for ALK gene rearrangement testing to help select eligible patients with NSCLC for crizotinib treatment. MSAC considered this testing in the context of an integrated co-dependent application which also enabled consideration of the co-dependent crizotinib treatment by the Pharmaceutical Benefits Advisory Committee (PBAC).

MSAC noted that the 6-8 November 2013 PBAC meeting had deferred the co-dependent application for crizotinib and had referred several matters for MSAC consideration.

The final Decision Analytical Protocol (DAP) proposed that ALK gene rearrangement testing could occur as a two-step process, with ALK immunohistochemistry (IHC) testing as a triage for ALK fluorescent in situ hybridisation (FISH) testing to identify translocation or inversion events involving the ALK gene locus (e.g., resulting in EML4-ALK fusion). The submission agreed with this, but did not refer to ALK IHC testing in the proposed MBS item descriptor and did not nominate a threshold ALK IHC result which would trigger ALK gene rearrangement testing on a reflex basis.

Proposed MBS item descriptor for *ALK* gene rearrangement testing

Category 6 – Pathological Services
Proposed MBS item descriptor in final DAP
MBS item number: to be advised An in situ hybridisation test of tumour tissue from a patient with locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise specified, to determine if requirements relating to anaplastic lymphoma kinase (ALK) gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $**(redacted information)** [A final proposed fee is to be advised by the applicant upon the completion of a cost survey of reference laboratories]

Proposed item descriptor in submission
MBS item number to be advised Fluorescent in situ hybridisation (FISH) test of tumour tissue from a patient with non-small cell lung cancer (NSCLC) requested by, or on behalf of, a specialist or consultant physician to determine if requirements relating to anaplastic lymphoma kinase (ALK) gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: **(redacted information)**

Who to test: The applicant proposes that the eligible population for ALK testing be extended beyond the clinical population defined in the primary question of the final DAP: "non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise specified" by also including the testing of patients with squamous NSCLC. MSAC noted that the proposed eligible population does not match that recommended by MSAC for epidermal growth factor receptor (EGFR) mutation testing where only patients with non-squamous NSCLC or otherwise not specified would be tested for EGFR mutations.

MSAC considered the following three options regarding confining ALK testing to various histopathological subtypes of NSCLC: a) adenocarcinoma – on the basis that this reflected the histology of 93% of patients in the key study of crizotinib (Shaw et al., 2013); b) non-squamous or not otherwise specified ("NOS") – reflecting the negligible prevalence of ALK gene rearrangements in squamous NSCLC; and c) all NSCLC subtypes as requested by the sponsor. It was considered that confining testing to adenocarcinomas was too restrictive and would result in ALK-positive tumours being missed. This is because the diagnosis of lung cancer is often based on small biopsies and some tumours have a mixed morphology of which adenocarcinoma may only be a small component or a morphology where the precise subtype cannot be determined (so called "NOS"). MSAC did not consider testing of squamous cell cancers was justified given the negligible prevalence (<1%, Paik et al. 2011; J Thorac Oncol 6:466-72 and Boland et al. 2009; Hum Pathol 40: 1152-8) of ALK gene rearrangements in this patient group. Also MSAC recognised the importance of aligning EGFR mutation testing and ALK testing in the diagnostic workflow of processing a lung cancer. Furthermore, the submission did not provide data on the health outcomes of treating ALK-positive squamous NSCLC and did not estimate the increase in the number and costs of ALK testing for all NSCLC. In summary, and similar to MSAC's previous advice in relation to EGFR mutation testing, MSAC recommended confining ALK testing to patients with non-squamous or "NOS" NSCLC.

MSAC also noted that further information was needed from the applicant in order to address the questions referred from PBAC regarding whether patients with evidence of mutations which confer likely primary resistance to crizotinib should be excluded from testing for ALK gene rearrangements or whether testing in the context of ALK gene rearrangements should also include other rare targets for crizotinib. If so, MSAC foreshadowed that such exclusions may need to be included in the MBS item descriptor to inform reflex testing for ALK gene rearrangements. The current data indicated that EGFR activating mutations and ALK gene rearrangements are mutually exclusive. Further, patients with EGFR activating mutations would be offered treatment with one of the PBS-listed tyrosine kinase inhibitors. For these reasons, testing ALK gene rearrangements should be confined to tumours which do not harbour an activating mutation in EGFR (i.e., EGFR wild type cancers). MSAC was not provided with data on the need for molecular testing for other mutations which may confer resistance or sensitivity to crizotinib. MSAC requested that the applicant provide relevant new data regarding these other mutations to the committee as it emerges.

When to test: The applicant proposes that the eligible population for ALK testing be extended beyond the clinical population outlined in the proposed crizotinib PBS listing and as defined in the primary question of the final DAP: "locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC)" by also including the testing of patients at initial diagnosis of NSCLC regardless of staging because:

- a submission to extend the proposed listing of crizotinib for use in all lines of therapy is likely, and including FISH testing at initial diagnosis in the descriptor would save additional MSAC evaluations in the near future
- knowledge of the *ALK* gene rearrangement status from diagnosis of Stage IIIB/IV disease would eliminate the delay (likely to be 2–4 weeks) between first-line treatment failure and initiation of second-line treatment with crizotinib
- *EGFR* mutation testing may also occur at diagnosis of NSCLC, and reflex testing for an *ALK* gene rearrangement need only occur if the *EGFR* test is negative for an activating *EGFR* mutation.

MSAC noted that the final DAP raised this option as a secondary question, but that the submission did not did not estimate the increase in the number and costs of ALK testing of this option, nor did it justify this option in terms of incremental health outcome benefits. MSAC requested further information from the applicant to assess whether to allow testing of all patients at first diagnosis of NSCLC, irrespective of disease stage at presentation. MSAC noted the applicant's response to the ESC report which indicated that ALK gene rearrangement should not change over the course of the disease and so testing at an early disease stage would not need to be followed by a re-biopsy on progression to advanced disease.

MSAC further commented that, while some of the issues regarding timing of ALK testing in NSCLC were similar to those recently addressed in considering EGFR testing, there were a number of key differences. Firstly, the prevalence of ALK gene rearrangements is significantly lower than the prevalence of EGFR activating mutations. Secondly, ALK gene rearrangement testing requires more specialised pathologist expertise than EGFR mutation testing, for both IHC and then FISH testing. Thirdly, FISH testing availability is more limited. The main similarities with EGFR testing were that allowing ALK (IHC then FISH, or just IHC) testing to occur immediately following a diagnosis of NSCLC may help ensure sufficient time for triaging in local pathology laboratories and on-referral of the ALK gene rearrangement FISH testing (ALK-FISH testing) to a central super-specialised pathology laboratory with appropriate accreditation.

MSAC considered that the data in the submission supported the proposition that ALK-FISH testing should be centralised in specialised accredited laboratories. MSAC considered ALK-FISH testing was more complex than other cancer ISH tests on the MBS such as ISH testing for HER2 gene amplification. The interpretation of ALK-FISH testing required the identification and quantification of split apart signals in cancer cells against a background of contaminating normal cells some of which may also be ALK positive. Also, in contrast to breast cancer, the amount of lung cancer tissue is often limiting and for this reason a high priority needed to be given to the judicious sequencing of immunostaining and molecular testing. It was considered important that finite amounts of lung cancer tissue were not wasted by inappropriate molecular or other testing.

MSAC noted that optimal interpretation of ALK-FISH testing may well require ALK immunostaining to be performed in the same laboratory. MSAC noted, however, that most ALK immunostaining tests were likely to be negative and thus it may not be practical for

ALK immunostaining and ALK-FISH testing to be performed in a central laboratory. MSAC also noted that, if all ALK testing were to be centralised to only a small number of ALK-accredited laboratories, there would be a potential for these providers to become overwhelmed with lung cancer specimens and this would delay the turnaround time for test results. For these reasons, testing all people with NSCLC at diagnosis might also inadvertently have undesirable consequences for patients, as well as increasing costs and potentially creating workflow difficulties for the central laboratories. A more practical model of testing could involve screening for ALK-positive tumours by immunostaining in the initial diagnostic laboratory and referring only positive tumours to the central laboratory for ALK-FISH testing. The latter scenario may require repeating the immunostaining in the central laboratory. Accordingly, MSAC requested further data from the applicant on the re-test rate, and the potential rate of insufficient tissue given an additional slide(s) will be required for repeat immunostaining. Irrespective of which testing scenario was used, the expert pathologists in the central laboratory would require additional training in conducting the ALK-FISH testing. MSAC noted the importance of a dedicated quality analysis protocol module with appropriate accreditation to ensure competency in reporting results which are critical to determining eligibility for crizotinib.

MSAC agreed that the ALK IHC test is a useful triage test, and analysis of the diagnostic accuracy data showed that there is a high level of agreement between IHC-negative and FISH-negative test results (100% specificity) where IHC testing used anti-ALK antibody clones 5A4 or D5F3 as defined in the Final DAP. MSAC noted that the performance of ALK testing with IHC may be very dependent on the antibody clone used for testing. Immunostaining is a qualitative assay and the quality of the test results varies according to the antibody used and associated equipment. Given the importance of the triage immunostaining step for detecting ALK gene rearrangements by FISH, MSAC considered that further data was needed on how standardization of the immunostaining would be implemented in clinical practice. MSAC also noted that the turn-around time for ALK IHC testing is likely to be quicker than for EGFR mutation testing, which needs to be considered when optimising the temporal sequence of reflex testing of the biopsy specimen in the initial and central laboratories. Moreover, IHC potentially only requires a single formalin-fixed paraffin-embedded section, compared to possibly multiple sections need to ensure sufficient tumour cells for EGFR mutation testing.

MSAC questioned how best to define a positive IHC result for the purposes of determining eligibility to proceed to ALK gene rearrangement testing, particularly given the subjective nature of the IHC assessment. The numbers and costs of ALK gene rearrangement testing would increase if the extent of overexpression moves to include 2+ and possibly 1+ as well as 3+. MSAC requested further information from the applicant to assess these issues and also whether varying extents of ALK expression might also modify the prediction of variation in the effect of crizotinib based on ALK gene amplification.

MSAC considered whether ALK IHC testing involving recently developed antibody clones should be differentiated from the standard IHC MBS items for the purposes of defining an MBS item and for setting its fee. MSAC noted that IHC assays currently recognised as being of greater complexity and difficulty to score are the breast cancer prognostic biomarkers for oestrogen receptors, progesterone receptors and HER2. ALK IHC testing would involve higher material costs with built-in controls (the antibodies and analysers are often co-dependent). MSAC also noted that a separate MBS item for ALK IHC testing would require its own quality assurance and accreditation standards and would help monitor the association with ALK gene rearrangement testing. MSAC further noted that a larger ALK IHC fee would increase overall costs of ALK testing beyond those estimated in the submission. MSAC

requested that the Department seek input from the suppliers of these antibody clones and the Royal College of Pathologists of Australasia to further inform these considerations of ALK IHC testing.

MSAC sought further input on all these issues from the applicant, preferably in consultation with the pathology community, in order to inform its advice in response to PBAC's overall question about aspects of an MBS item descriptor which would facilitate practical implementation in diagnostic pathology practice, including whether to specify prior tests for other biomarkers, whether to specify triage testing using ALK IHC, and whether to specify ALK gene rearrangement testing as a pathology determinable service based on threshold results from prior tests.

Test performance: Before advising on any prognostic effect of ALK gene rearrangement, MSAC would prefer to review Australian data if available. Most studies presented were undertaken in Asian populations and it is unclear whether these results are generalisable to the Australian population. Similarly, MSAC also required more data about the prevalence of ALK gene rearrangements among Australian patients with NSCLC. Reported prevalence varies across histology type and whether it assessed in patients with any stage of NSCLC or only in patients with advanced NSCLC, so the estimate relied upon should reflect these characteristics of the population defined as eligible for testing in the MBS item descriptor. The submission's nominated ALK prevalence estimate is **(redacted information)**%, based on pooling of studies reporting prevalence across all stages of the adenocarcinoma histology subtype of NSCLC.

The comparator proposed in the submission is no ALK gene testing. Other test methodologies, such as IHC, chromogenic and silver-enhanced in situ hybridisation (CISH and SISH) and reverse transcriptase–polymerase chain reaction (RT-PCR) were also compared against the FISH test in the submission. MSAC noted that ALK-FISH is the only clinically validated ALK test and represents the "evidentiary standard" as a result of its use to select participants for the randomised trial of crizotinib. MSAC noted that there was ongoing research to develop bright field ISH testing in for ALK gene rearrangements and expected more analytical evidence comparing these with FISH to emerge in the near future. RT-PCR testing is limited in that it can only identify known ALK fusion variants.

MSAC noted that FISH testing is the 'gold standard' method and, in ideal circumstances, has 100% sensitivity and specificity. Test accuracy is likely to be reduced in less ideal circumstances because there is some subjectivity of assessment and thus likely variation across experts in determining what constitutes a FISH-positive result from a tumour specimen. Apart from observer error, there are many factors associated with errors in FISH tests including nuclear truncation, aberrant probe hybridisation and background noise. All these factors may contribute to false-positive and false-negative FISH results. Camidge et al. 2010 Clin Cancer Res 16:5581-90 reported an analysis to advise that a way of minimising false results was to optimise the number of tumour areas examined in a specimen and specifically proposing examination of four or more areas with fifteen or more nuclei in each area, meaning that sixty or more nuclei should be examined per tumour specimen.

In terms of setting the cut-off point of 15% tumour cells to be positive for determining overall positivity of the tumour specimen (i.e., for ≥15% positive tumour cells to be classified as a positive tumour specimen), MSAC noted that Abbott had calculated this for its Vysis ALK-FISH assay based on 30 tumour specimens designated as negative for ALK rearrangement and then verified its calculation with a further 25 tumour specimens. Camidge et al., 2010 evaluated the signal patterns generated by the Vysis ALK-FISH assay in non-tumour and

tumour samples from both ALK-positive and ALK-negative patients. Positivity occurred in 22.3% to 86.6% of the enumerated cells in the ALK-positive tumour samples, compared to a background positivity in 11% of cells in both non-tumour and ALK-negative tumour samples. The cut-off point of 15% thus falls within the non-overlapping area of cell positivity between the background and ALK-positive tumour samples (i.e., >12% and <21%), suggesting this value can accurately differentiate between biological and assay-related variability. MSAC requested that the applicant provide both further justification of the precise basis for the current threshold of 15% positive cells and also data on the relationship between percentage of ALK positive cells and response to crizotinib.

MSAC commented that the sensitivity analyses conducted for the economic evaluation in relation to test sensitivity and specificity did not adequately address the uncertainty around the implications of false-positive and false-negative patients, as false positives are assumed to respond to crizotinib treatment to the same extent as the comparator chemotherapy. MSAC did not agree with the applicant's assumption that false-positive (i.e., truly ALK-negative) patients would respond to crizotinib as they would for chemotherapy.

No safety concerns regarding ALK gene rearrangement testing were reported in the submission and no unexpected serious adverse events occurred during any of the studies. MSAC noted some safety concerns remain for those patients requiring a second biopsy, as a tumour sample can be used only a limited number of times.

MSAC noted that the costs of re-biopsy, re-testing (of both ALK IHC across laboratories and also ALK-FISH given 8.5% of these tests are uninformative due to failed hybridisation), adverse events, patient episode initiation fee (unless reflex testing), fees for specimen referral and retrieval were not included in the economic analysis. MSAC decided the sponsor's proposed MBS fee of (redacted information) for ALK-FISH testing was not adequately justified considering the current cost is (redacted information) in at least one Australian laboratory.

MSAC noted that the population included in the financial analyses is narrower than that covered by the proposed ALK-FISH MBS item descriptor (costed only for advanced non-squamous NSCLC); costs are therefore underestimated. MSAC also noted the potential for ALK re-testing was not considered in these analyses.

MSAC discussed the number of patients likely to be tested and treated. The submission's base case estimated that, of a total population of less than 5,000 tested with ALK IHC in the first year of listing, approximately less than 1,000 ALK-FISH tests would need to be carried out for **(redacted information)** patients to be treated; of those treated, not all will benefit.

Lay Summary

Less than 5% of patients with NSCLC have a rearrangement in the *ALK* gene, and will potentially benefit from crizotinib treatment. Testing patients with FISH for this rearrangement will help to guide whether crizotinib is an appropriate treatment. The applicant proposes that the test be added to current tests performed on NSCLC samples. The applicant has not provided sufficient evidence to support practical implementation of its proposal. *ALK* gene rearrangement testing is a complex procedure and can only be undertaken by expert pathologists in specialised laboratories.

At this time, MSAC deferred approval of public funding for this test until further information is provided.

16. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of *ALK* gene rearrangement testing to select eligible patients with NSCLC for crizotinib treatment, MSAC deferred finalising its advice to the Minister on public funding until PBAC makes a positive recommendation regarding crizotinib and the issues raised by MSAC above regarding the testing have been addressed. These include: further information on how ALK testing (both IHC and FISH) should be incorporated into the overall test strategy in NSCLC to:

- make best use of small volume tumour specimens
- optimise high-level pathology expertise required
- minimise unnecessary testing
- optimally integrate with EGFR mutation testing
- maximise the clinical validity and utility of the testing algorithm.

MSAC foreshadowed that the MBS item descriptor should then align with the PBS restriction.

17. Applicant's comments on MSAC's Public Summary Document

Abbott Molecular and Pfizer Australia are disappointed by the decision of MSAC to defer finalising its advice to the Minister. The Vysis ALK break apart FISH probe kit was used throughout the three crizotinib registration clinical trials, thereby establishing its diagnostic and clinical value. The Vysis break apart ALK FISH probe kit is the global evidentiary standard and is currently used by a number of Australian pathology laboratories to clinically diagnose ALK positivity in NSCLC patients. Abbott Molecular and Pfizer Australia are committed to working with MSAC to enable a pragmatic assessment that allows patients timely access to ALK testing and, where identified, to crizotinib treatment. The Applicants believe they have addressed the key issues raised by MSAC since this initial evaluation, and await the delayed July/August MSAC meeting for consideration of their 12th March 2014 reapplication.

18. Context for decision

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;
- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

19. Linkages to other documents

MSAC's processes are detailed on the MSAC Website at: www.msac.gov.au.