



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1250.1 – Testing of the anaplastic lymphoma kinase (ALK) gene in patients with non–small cell lung cancer to determine eligibility for treatment with crizotinib

Co-applicants: Abbott Molecular Pty Ltd and Pfizer Australia Pty Ltd

Date of MSAC consideration: MSAC 62nd Meeting, 26 – 28 November 2014
MSAC Meeting, 3 October 2014

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, see at www.msac.gov.au

1. Purpose of application and links to other applications

A resubmission to MSAC from Abbott Molecular and Pfizer Australia was received by the Department of Health in March 2014 requesting reconsideration of Medicare Benefits Schedule (MBS) listing of fluorescent *in situ* hybridisation (FISH) testing in patients with non-small cell lung cancer (NSCLC), for identification of anaplastic lymphoma kinase (*ALK*) gene rearrangement.

2. MSAC's advice to the Minister - November 2014 consideration

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of anaplastic lymphoma kinase (*ALK*) gene rearrangement testing to help select eligible patients with non-small cell lung cancer (NSCLC) for crizotinib treatment, MSAC advised that it supported public funding being achieved by creating a new MBS item with the following item descriptor:

Fluorescence *in situ* hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (*ALK*) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (*EGFR*) gene, requested by, or on behalf of, a specialist or consultant physician to determine if requirements relating to *ALK* gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC advised that an MBS fee of \$400 for this *ALK* gene rearrangement MBS item would be appropriate.

MSAC reaffirmed its October 2014 advice that a separate MBS item would not be required for the associated *ALK* immunohistochemistry test.

MSAC reaffirmed its October 2014 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected from the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (QAP) prospectively for no less than 24 months. This will address anecdotal reports that some patients who are *ALK* IHC negative will respond to *ALK* inhibitors and confirm that the QAP will ensure that community *ALK* IHC testing meets the required standards.

Summary of consideration and rationale for MSAC's advice

MSAC deferred this application at its meeting on 28 November 2013 and its extraordinary meeting on 3 October 2014. MSAC's considerations were coordinated with PBAC consideration of crizotinib on 6-8 November 2013. On 3 October 2014, MSAC indicated support for the proposal to create a new MBS item for *ALK* gene rearrangement testing, but deferred provision of formal advice to the Minister until such time as MSAC advice could be coordinated with a PBAC recommendation to list crizotinib.

MSAC was advised that, at its meeting on 5-7 November 2014, PBAC recommended the listing of crizotinib for use for *ALK*-positive advanced NSCLC.

MSAC's advice to the Minister – October 2014 consideration

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of anaplastic lymphoma kinase (*ALK*) gene rearrangement testing to help select eligible patients with non-small cell lung cancer (NSCLC) for crizotinib treatment, MSAC again deferred the application for the requested MBS item until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) makes a decision regarding the corresponding Pharmaceutical Benefits Schedule (PBS) listing of crizotinib. MSAC advised that, if PBAC subsequently decides to recommend to the Minister that crizotinib be listed on the PBS for the treatment of advanced NSCLC, then MSAC would support an expedited process of reconsideration. This process would be undertaken to ensure MSAC support for public funding of *ALK* testing is aligned with the circumstances recommended by PBAC.

MSAC foreshadowed its support for this public funding being achieved by creating a new MBS item.

MSAC foreshadowed the following item descriptor for the *ALK* gene rearrangement MBS item:

Fluorescence *in situ* hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (*ALK*) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (*EGFR*) gene, requested by, or on behalf of, a specialist or consultant physician to determine if requirements relating to *ALK* gene rearrangement

status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

MSAC foreshadowed an MBS fee of \$400 for this *ALK* gene rearrangement MBS item.

MSAC foreshadowed that a separate MBS item would not be required for the associated *ALK* immunohistochemistry test.

MSAC foreshadowed that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected from the Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (QAP) prospectively for no less than 24 months, with funding of the data collection, analysis and reporting to be obtained from the co-applicants. This will address anecdotal reports that some patients who are *ALK* IHC negative will respond to *ALK* inhibitors and confirm that the QAP will ensure that community *ALK* IHC testing meets the required standards.

Summary of consideration and rationale for MSAC's advice

MSAC noted that extraordinary circumstances had led to cancellation of the July/August 2014 MSAC meeting. Given that consideration of this co-dependent application would need to be realigned with the scheduled November 2014 PBAC consideration of crizotinib to enable preparation of coordinated advice to the Minister, the Department of Health convened an urgent executive MSAC meeting to consider *ALK* testing. The minutes of this meeting and the submission will be tabled at the full MSAC meeting in November 2014.

MSAC noted the uncoordinated approach to resubmissions by the co-applicants following the November 2013 consideration by MSAC and PBAC did not assist either MSAC or PBAC in preparing coordinated advice to the Minister. MSAC noted that the March 2014 PBAC meeting had requested that, if MSAC supported the addition of *ALK* testing to the MBS, associated MSAC advice would need to be incorporated into a major resubmission to PBAC. MSAC considered that the aspects of the resubmission to PBAC that would need to be informed by MSAC advice included:

- (a) the range of sensitivity and specificity estimates of the MSAC-proposed model for overall *ALK* testing to be examined as sensitivity analyses in the economic evaluation of the co-dependent package of *ALK* testing and crizotinib treatment; and
- (b) the costs of the MSAC-proposed model of overall *ALK* testing per patient treated with crizotinib to be included both in this economic evaluation and also the estimated financial implications to the MBS of the MSAC-proposed model for *ALK* testing.

Given the low prevalence of *ALK*-positive patients in the tested population, test performance and test costs have a greater effect on the economic and financial analyses than has been the case for previously considered co-dependent test and medicine packages. MSAC agreed with the views of the March 2014 PBAC meeting, the Pathology Services Advisory Committee (PSAC) and the RCPA that, if optimal testing and oversight of laboratory test standards are not put in place for *ALK* testing as fundamental prerequisites for the use of crizotinib, then patients will be poorly advised, potentially disadvantaged and harmed.

Who to test: MSAC confirmed its previous proposal to confine *ALK* testing to patients with non-squamous or "NOS" NSCLC. MSAC agreed that *ALK*-FISH testing should be confined to tumours which do not harbour an activating mutation in *EGFR* (i.e., *EGFR* wild type cancers).

MSAC noted the lack of available data to identify other markers of resistance or sensitivity to crizotinib for inclusion in any MBS-funded testing related to crizotinib, and agreed that data should be collected prospectively in Australia to improve the future evidence base on these matters.

In relation to using ALK IHC expression as a triage test before testing *ALK* gene rearrangements, MSAC considered that the temporal relationships between faster ALK IHC testing and slower *EGFR* mutation testing, and the need for parsimonious use of the small NSCLC biospecimens, had been adequately resolved and testing with ALK IHC and for *EGFR* mutations can occur in parallel. In its deliberations, MSAC considered the French study by Cabillic et al (2014) indicating 69% sensitivity of ALK IHC testing, and the advice provided by PSAC and the RCPA. MSAC agreed that these considerations did not change its initial view that ALK IHC testing was a suitable triage test for *ALK* gene rearrangement testing. However, MSAC recommended that PBAC take into account that the sensitivity of the ALK IHC could potentially be as low as 69%. MSAC noted the co-applicants' advice regarding the increased fee and considered advice from PSAC and the RCPA that introducing a differential fee for ALK IHC is paradoxically likely to lead to increased usage by inexperienced laboratories: the way the MBS schedule is currently structured tends to discourage performing more than three immunostains. If ALK IHC was associated with a separate item number, it would not "come out" when performed with a panel of other stains (i.e., those used to differentiate between adenocarcinoma and squamous cell carcinoma). On balance, MSAC agreed that ALK IHC should not be acknowledged by a greater than standard fee and the current MBS item for undifferentiated IHC testing would suffice for ALK IHC testing. MSAC also advised that the definition of ALK IHC positive sufficient to progress to *ALK* gene rearrangement testing should be any evidence of immunostaining, i.e. 1+, 2+ or 3+, but not 0.

MSAC advised that *ALK* gene rearrangement testing should be limited to the FISH test, and broadening to include other types of ISH testing would require further evaluation. As a consequence, MSAC advised that a reasonable MBS fee for *ALK* gene rearrangement testing should be \$400. To minimise the rate of false test results, MSAC advised that the PBS restriction for crizotinib should define FISH testing as the basis for confirmatory *ALK* gene rearrangement testing, and also that a test positive result for *ALK* gene rearrangement in a NSCLC tumour should be defined as $\geq 15\%$ positive cells.

When to test: MSAC advised that testing of patients for *ALK* gene rearrangement should be restricted to those with advanced or metastatic NSCLC. MSAC noted that in the future this may need to be broadened to include earlier disease stages if ALK inhibitors are shown to be effective treatments in earlier stage disease. In the meantime, MSAC expected that ALK IHC testing would be performed alongside *EGFR* mutation testing in the initial diagnostic work-up at a local pathology laboratory of a patient presenting at any stage of NSCLC, but that *ALK*-FISH testing would be performed at a specialised pathology laboratory for patients with locally advanced or metastatic NSCLC only.

Other matters: MSAC advised that, on the evidence available, *ALK* gene rearrangement status was not a prognostic factor independent of its ability to predict a better response to crizotinib or pemetrexed.

MSAC noted the true prevalence of *ALK* gene rearrangement in the Australian lung cancer population was uncertain, with published data suggesting a prevalence of 1.2% in resected cases which included about 14% squamous cell carcinomas which are not proposed to be included in the eligible population and only a small proportion of advanced cases (Selinger et

al, 2013). MSAC also noted that the base case of the economic evaluation for the co-dependent package of ALK testing and crizotinib presented in the co-applicants' May 2014 pre-ESC response is that (**redacted**) ALK-FISH tests would be performed (of which (**redacted**) will be false positive IHC results assuming a prevalence of true *ALK* gene rearrangements of (**redacted**)%, and specificity of the IHC test of (**redacted**)%). MSAC further noted that the September 2013 pre-ESC response estimated the prevalence of *ALK* gene rearrangement in Australian locally advanced or metastatic NSCLC patients may be closer to 2.8% based on the suggestion that advanced/metastatic cases have a higher prevalence of mutations. MSAC advised that, in the enriched Australian population proposed for ALK-FISH testing (histology being non-squamous or "NOS", tumour status being *EGFR*-negative, and limited to patients with advanced or metastatic stage of NSCLC), the best estimate of prevalence of *ALK* gene rearrangement was approximately 3%.

MSAC advised that the sensitivity analyses of the economic evaluation for the co-dependent package of ALK testing and crizotinib should vary the ALK IHC test performance to include 69% sensitivity and 99% specificity (Cabillic et al, 2014) to examine the consequences of the increased uncertainty of ALK testing performance as expected by MSAC for Australia compared with the laboratory methods adopted for the evidentiary standard used in the trials of crizotinib. In addition, MSAC reiterated its previous advice that the health outcomes in patients with false-positive results should reflect the toxicity of crizotinib, but the progression-free and overall survival outcomes of no treatment because there is no basis to support the co-applicants' claim of a response equivalent to chemotherapy. Similarly, MSAC advised that the estimates of costs in the economic evaluation for the co-dependent package of ALK testing and crizotinib and in the financial implications for the MBS should include the costs of ALK testing as proposed by MSAC for Australia, including by appropriately reflecting the likely average fees charged per test in the economic evaluation and the likely average benefits paid by the MBS per test in the financial analyses. These should include patient initiation fees and fees for specimen referral and retrieval and costs of re-biopsy and re-testing.

MSAC noted that there is an argument for the MBS item for *ALK* gene rearrangement to be made a pathologist determinable service in order to align with *EGFR* mutation testing. However, MSAC agreed with the PSAC advice which noted that, in cases referred on to a specialist laboratory, this could inhibit the ability to get the appropriate referrals, such as confirming that a patient has an advanced or metastatic stage of NSCLC before conducting ALK testing. MSAC therefore foreshadowed that it would advise that any MBS item for ALK-FISH testing would not be made a pathologist determinable service.

3. Background

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

- MBS listing of FISH testing in patients with advanced or metastatic NSCLC, for identification of *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.

MSAC considered this application in November 2013 as Application 1250. The application was deferred pending further information from the co-applicants as well as other

stakeholders, regarding specific clinical, economic and operational aspects of ALK testing options.

The issues to be addressed in the resubmission were as follows:

1. who to test: the appropriate patient population for whom to confine ALK testing
2. when to test: making best use of small volume tumour specimens, minimising unnecessary testing (including integration with *EGFR* mutation testing), and maximising clinical validity and utility of the testing algorithm
3. validity and performance of ALK testing options
4. other issues raised by MSAC.

The March 2014 PBAC meeting deferred a minor resubmission from Pfizer Australia to ascertain Pfizer's input on PBAC's proposed approach to achieve acceptable cost-effectiveness and until such time as MSAC decides to support the corresponding MBS listing of *ALK in situ* hybridisation (ISH) testing (and any other associated molecular testing advised by MSAC) for patients with NSCLC.

Testing for *ALK* gene rearrangement is a new test that is not available to Australian patients outside of participation in clinical trials assessing the pharmaceutical agent crizotinib.

4. 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). As of March 2014, seven diagnostic laboratories 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.

5. Proposal for public funding

The resubmission proposed the MBS item descriptor below for *ALK* gene rearrangement testing.

Table 1: Proposed MBS item descriptor

Category 6 – Pathology Services
Proposed MBS item descriptor
MBS item number to be advised
Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination, with a staining intensity score > 0 , requested by, or on behalf of, a specialist, consultant physician, or pathologist, to determine if requirements relating to ALK gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme are fulfilled.
Fee: \$(redacted)
<i>[Optional Note: Patients are exempt from ALK IHC examination where the available tumour sample is of inadequate quantity or quality for both IHC and ALK FISH testing. Such patients are eligible for ALK FISH testing without documented evidence of ALK immunoreactivity by IHC.]</i>

The proposed fee of \$(redacted) in the resubmission is the same as in the original submission.

The resubmission requested MSAC consider an MBS item for ALK-FISH testing where an ALK IHC triage test is not specifically required in the item descriptor.

The resubmission agreed with the November 2013 proposal by MSAC that ALK testing should be confined to NSCLC patients with a non-squamous histology, or histology not otherwise specified (NOS).

The resubmission noted the exclusion of squamous cell carcinoma from the patient population able to access ALK gene rearrangement testing.

The resubmission proposed to restrict ALK gene rearrangement testing to diagnosis of, or progression to, locally advanced or metastatic NSCLC. However, the resubmission further noted that a future request for expansion of the MBS item to include testing of NSCLC at diagnosis regardless of stage is likely.

In November 2013, MSAC had recommended ALK testing should only be performed in NSCLC patients who are EGFR wild type. The resubmission argued that access to MBS-funded ALK testing should not be conditional on EGFR mutation status so that efficiencies in tissue preservation and time in the pathology laboratories are achieved.

Testing for ALK gene rearrangements in advanced NSCLC patients would be ordered by the treating physician (e.g. medical oncologist or respiratory physician) when treatment with crizotinib is being considered. A pathologist would be responsible for conducting the test and reporting results.

The proposed item description in the resubmission included “a pathologist”, apart from “a specialist or consultant physician,” who may request ALK gene mutation testing or on behalf of whom ALK gene mutation testing may be requested (see table above). The resubmission did not provide any explanation for the addition. It is not clear whether the co-applicants intend the addition as support to a specification that ALK gene rearrangement testing should be a pathologist-determinable service.

The proposed inclusion of ‘a pathologist’ would not match the item descriptors of any of the currently MBS-funded pathology tests necessary to determine eligibility for access to drugs on the PBS. In its consideration of Application 1161 (*EGFR* mutation testing for first-line gefitinib treatment), MSAC advised that the proposed *EGFR* mutation testing “should be made a pathology determinable service so that the pathologist can perform *EGFR* mutation testing on samples which meet the requisite histological criteria” as this would ensure that “the diagnostic process is not interrupted by the need to get a referral from a clinician for mutation testing” (p1, [Public Summary Document, MSAC, August 2013](#)).

6. Summary of Public Consultation Feedback/Consumer Issues

Public consultation feedback noted the likely limited access to *ALK* gene rearrangement testing, which will have an impact on rural patients and others who have difficulty accessing the limited sites where this could be provided.

If *ALK* gene rearrangement testing is likely to increase the possibility of a patient having to return to provide an extra sample of tumour tissue, this creates time and travel cost impact in addition to any risks directly related to the procedure.

Public comment reflected a preference for a coordinated approach to the assessment of *ALK* gene rearrangement testing and to minimise the suboptimal use of crizotinib.

Consumers noted the complex terminology involved, which is a source of confusion when patients try to understand the impact of testing on their prognosis by improving the management of their disease. Consumers noted that the SBA considered the impact on patients only in terms of treatment retention, not therapy preferences nor reasons for declining to participate or continue treatment.

Consumers must be supported and enabled to provide genuine informed consent to this (and any other) procedures with due consideration for additional financial and quality of life costs that offer no substantial benefit, from their informed perspective.

7. Proposed intervention’s place in clinical management

Testing for *ALK* gene rearrangements is expected to be added to current testing of patients with NSCLC.

ALK gene rearrangement testing is proposed to be conducted as 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.

Options to enrich the NSCLC population for *ALK*-FISH testing were proposed, including a 2-step process with *ALK* immunohistochemistry (IHC) testing as a triage.

8. Comparator

The comparator originally proposed was no *ALK* gene rearrangement testing. This is consistent with the nominated comparator in the final DAP, and no change was made in the resubmission.

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 would require another biopsy. In Australia, biopsy samples are usually collected at initial diagnosis of NSCLC (regardless of cancer stage), using either bronchoscopy or percutaneous fine needle aspiration. If an adequate sample is obtained, no additional procedure or sample retrieval would be required for *ALK* gene rearrangement testing (if the limitation to advanced or metastatic stages of the cancer were removed from the proposed MBS item descriptor as was proposed in the original submission and previously supported by MSAC). However, the requirement for histology testing, *EGFR* mutation testing and two *ALK* tests could mean the initial tumour sample is of inadequate size. With the addition of *ALK* IHC and *ALK*-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 varies according to the site of the primary tumour or metastasis and the biopsy method used. This was not addressed in the resubmission. MSAC advice from the November 2012 Minutes for *EGFR* mutation testing in NSCLC (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 resubmission.

MSAC noted that additional training in *ALK* gene rearrangement testing would be required via a quality assurance program (QAP) module to ensure competency in reporting results. In response, the co-applicants agreed that a dedicated QAP module would be critical to determining eligibility for crizotinib, and indicated that it is their understanding that such a module will be developed by the RCPA. In its parallel correspondence to MSAC, the RCPA confirmed that IHC could feasibly be added to an existing module being developed on *ALK*-FISH. In its parallel correspondence to MSAC, Roche Diagnostics included costs of training and QAP activities in its cost estimate for VENTANA[®] *ALK* IHC.

10. Comparative effectiveness

Prognostic evidence

No new studies on prognosis were provided in response to MSAC's November 2013 request for Australian studies.

However, the September 2013 pre-ESC response attached to the resubmission cites a recent meta-analysis by Dearden et al (2013), which observed that *ALK* prevalence in Western populations was broadly consistent with that in Asian populations. Furthermore, given the *ALK* mutation is itself a driver of oncogenic activity, the September 2013 pre-ESC response argued that differences in the demographic characteristics of East-Asian populations, such as smoking status, are unlikely to affect the generalisability of these studies.

Comparative analytical performance

No new studies on comparative analytical performance were provided in response to MSAC’s November 2013 request for Australian studies. This includes no new studies comparing FISH with other bright field ISH as highlighted by MSAC.

The critique of the resubmission summarised a recently published large French study (Cabillic 2014) comparing parallel FISH and *ALK* IHC testing (using a primary monoclonal *ALK* antibody clone 5A4 as was advised in the final DAP) in 3,244 consecutive NSCLC cases at two independent centres. Of these 3,244 cases, 481 (15%) FISH tests were non-contributory and 80 (2%) IHC tests were non-contributory, due to inadequate samples or problems with the test (thirty-one or 1% were non-contributory for both tests). Of the 150 specimens that tested positive with either test, 80 specimens were tested FISH-positive/IHC-positive, 36 FISH-positive/IHC-negative, 19 FISH-negative/IHC-positive and 15 FISH-non-contributory/IHC-positive. The authors believed that this was the largest known published series to date and concluded that, while many pre-analytical factors might account for the apparent discrepancies, the study highlighted “the need of combined testing to optimize the detection of *ALK* inhibitor-eligible patients given that some patients with discordant testing were found to respond to crizotinib”.

In the Cabillic (2014) study, the number of IHC false negatives (36 FISH-positive/IHC-negative) was nearly double that of the IHC false positives (19 FISH-negative/IHC-positive). The table below shows the diagnostic accuracy data from Cabillic (2014) for *ALK* IHC compared to *ALK*-FISH, with *ALK*-FISH used as the reference standard. This table excludes the 530 cases where either the IHC result or the FISH result was non-contributory. From this table, the sensitivity of *ALK* IHC in these 2,714 patients was 69.0% and the specificity was 99.3%. The value for sensitivity in the Cabillic (2014) study is considerably lower than those from studies identified in the literature search included in the original submission.

Diagnostic accuracy data from Cabillic (2014)

		FISH		
		Positive	Negative	Total
IHC	Positive	80	19	99
	Negative	36	2579	2615
	Total	116	2598	2714

Source: Table 3, page 303, Cabillic (2014)

The critique of the resubmission summarised another recent Canadian study by Conklin (2013) which compared five different *ALK* IHC detection systems (two using clone 5A4 and one using clone D5F3, both of which were advised to be suitable in the final DAP, and two using clone *ALK1*, which was not advised to be suitable in the final DAP) to *ALK*-FISH, with all tests conducted in parallel. Of the 377 cases, FISH could not be performed on 104 (28%), mostly due to high fluorescent background, which was mostly attributed to a prolonged fixation time before embedding. Eleven specimens of the remaining 273 cases tested positive with any of the six tests. Three were confirmed as FISH positive based on whole section tissue. *ALK* IHC reported sensitivity values ranging between 66% (for clone *ALK1*) and 100% (for clones 5A4 and D5F3).

Sensitivity is the key diagnostic measure for ALK IHC when it is proposed to be used as a triage test for *ALK*-FISH, as patients who receive a false negative result from IHC testing would not proceed to FISH testing and will not be able to access crizotinib.

Both the original submission and the resubmission used a sensitivity of 100% for ALK IHC testing in their base case analyses and the original submission included a value of 95% in sensitivity analyses (Table D.6-1, original submission). Given the results described above, an exploration of a broader range of sensitivity values, and a more thorough consideration of the consequences of false negative ALK IHC results is warranted.

In response to MSAC's November 2013 request for a definition of ALK IHC positive test results, the resubmission advised that these are interpreted as two alternative outcomes: negative, when there is no staining; or positive, when there is any staining. This advice is consistent with that of the RCPA and Roche Diagnostics in their correspondence, and also with the definitions used by the Cabillic (2014) and Conklin (2013) studies, above.

Similarly, in response to MSAC's November 2013 request for a justification of *ALK*-FISH positive test results, the resubmission reaffirms the proposed use of $\geq 15\%$ positive cells to define a NSCLC as positive for *ALK* gene rearrangement as being widely accepted and the definition used for the evidentiary standard in the crizotinib trials. The resubmission provided no additional justification for the ≥ 4 areas with ≥ 15 nuclei/area by Camidge (2010) relied on by MSAC in November 2013. However, the resubmission did report that there is currently no evidence of a proportional relationship between percentage of *ALK*-positive cells and response to ALK inhibitors.

Data on prevalence of *ALK*-positivity

No new studies on prognosis were provided in response to MSAC's November 2013 request for Australian studies.

However, the September 2013 pre-ESC response attached to the resubmission summarised a recent study in Australian NSCLC patients, which identified 7 cases of *ALK* gene rearrangement in 594 resected NSCLC samples (including squamous carcinoma), corresponding to a prevalence of 1.2% (Selinger et al 2013). Adjusted for disease stage (based on a comparison of *ALK* gene rearrangement rates in early and advanced stage NSCLC patients which found a 2.17-fold increase in prevalence associated with advanced disease), the September 2013 pre-ESC response estimated the prevalence of *ALK* gene rearrangement in Australian locally advanced or metastatic NSCLC patients may be closer to 2.8%. Based on the meta-analysis by Dearden et al (2013), the September 2013 pre-ESC response noted that *ALK* prevalence in Western patients was similar to that of Asian patients (6.4% and 5.4%, respectively). The September 2013 pre-ESC response also reported, without any citation details, that four centres in Australia reported an *ALK* prevalence of 3.3% (6 of 183 patients).

11. Economic evaluation

The economic evaluation was not re-presented in the resubmission. Variables that may need to be adjusted in the economic evaluation included in the original submission following the October 2014 MSAC reconsideration include:

- whether *EGFR* mutation testing is used to enrich the population for ALK testing (this will affect the prevalence of *ALK* gene rearrangements in this ALK-tested population);

- whether ALK IHC testing is used as a triage test before *ALK*-ISH testing and, if so, at what unit cost, disaggregated to the MBS and to patients and then aggregated overall;
- the rate of re-testing and re-biopsy for any particular MSAC-supported test strategy (including costs of adverse events following re-biopsy);
- when ALK testing should occur (at initial diagnosis of any non-squamous or not otherwise specified NSCLC, or at initial diagnosis of advanced or metastatic NSCLC);
- the patient episode initiation fee(s) for any particular MSAC-supported test strategy;
- fees for specimen referral and retrieval for any particular MSAC-supported test strategy;
- the unit cost for *ALK*-ISH testing, disaggregated to the MBS and to patients and then aggregated overall;
- wider sensitivity analyses for prevalence and for overall sensitivity and specificity of ALK IHC testing; and
- reduced crizotinib treatment effect for false-positive patients.

The resubmission did not provide additional data on the re-test rate in response to MSAC's November 2013 request. Re-test data is considered significant, given the need for extra slide(s), and that there may be insufficient tumour tissue remaining. However, the RCPA advised that the re-test rate is likely to be lower than the 8.5% suggested by MSAC.

The proposed fee for this item in the resubmission is \$(**redacted**), which is unchanged from the original submission. The resubmission provided a "micro-costing" summary to justify the proposed fee, however no details of the calculations or additional data sources were provided. The resubmission reports that the most common batch size for testing is 8, which results in a total cost of \$(**redacted**) for that batch. Costs are reduced for larger batches. Therefore, if the batch size is a determinant of the fee, it would be useful to obtain a true average batch size.

12. Financial/budgetary impacts

The original submission restricted the patient population used in the financial calculations to those with advanced non-squamous only NSCLC, and was estimated to be less than 5,000 in Year 1. The resubmission expands the patient population to add those with advanced not otherwise specified (NOS) NSCLC, which increases the patient population to less than 10,000 in Year 1.

The submission underestimated the total number of advanced NSCLC patients, according to Australian Institute of Health and Welfare (AIHW) projections. This will increase the MBS costs of ALK testing by about \$(**redacted**) to \$(**redacted**) a year.

If there is no restriction of ALK testing to *EGFR* wild type tumours, this would increase costs (estimated by the resubmission to be about \$(**redacted**) per year). The resubmission argued that access should not be restricted based on *EGFR* mutation status, whilst the RCPA agreed that it should be restricted.

However, the resubmission's comparison of the costs of different testing scenarios for parallel or sequential *EGFR* and ALK testing is oversimplified, with some potential savings or costs omitted (such as patient episode initiation, sample retrieval fees, retesting, adverse events related to re-biopsy).

In the table below, the critique re-calculated costs for all advanced non-squamous or NOS NSCLC, and an error made in the submission was corrected relating to numbers of IHC false

positives as the prevalence of *ALK* positives was for all NSCLC and will be higher in *EGFR* wild type tumours (now slight overestimate), but otherwise adopting the resubmission's assumptions, such as excluding costs for patient episode initiation, re-testing, re-biopsy and associated adverse events, specimen referral and retrieval fees. 100% of the fee was used rather than the appropriate benefit, and the safety net was not taken into consideration.

The critique also extended the resubmission's financial analysis to examine a range of testing scenarios; i.e., as well as examining the budgetary implications of restricting *ALK* testing to *EGFR* wild type tumours or not, also examining the budgetary implications of *ALK* testing with or without triaging with *ALK* IHC, and of revising the unit cost of *ALK* IHC.

If *ALK* IHC testing is used to triage, then less *ALK*-ISH testing will be carried out. However if *ALK* IHC test results are not sensitive enough, the number of false negative IHC results may be unacceptably high because they would result in a greater proportion of eligible patients being denied effective crizotinib due to errors arising from the testing strategy. Not including *ALK* IHC testing is projected to increase the projected net costs from around less than \$1 million in Year 5, to less than \$2 million in Year 5.

Estimation of costs of *ALK* testing using same assumptions as in the resubmission

(Table redacted)

13. Key issues from ESC for MSAC

ESC noted that different options remained across several aspects of the definition of the patient population proposed to be eligible for *ALK* gene rearrangement testing in the proposed MBS item descriptor.

- Type of *ALK* gene rearrangement test: the resubmission reiterated the nomination of a FISH test of tumour tissue, rather than an ISH test, but did not update the comparative analytical validity data supplied in the original integrated submission. The pre-ESC response (p2) noted that agreement between these assay techniques is high due to their methodologically similar nature, but that currently there are no other *ALK*-ISH kits commercially available in Australia. It proposed that any MBS item descriptor should specify *ALK*-FISH testing until clinical utility data involving other test modalities become available. ESC advised that, given the precedent with ISH testing for *HER2* (which was based on comparative analytical validity data rather than clinical utility data), the supportive comparative analytical validity data available to date and to anticipate bright field ISH becoming available in the near future, MSAC should expand any MBS item descriptor beyond FISH testing to include any type of ISH testing." ESC further advised that no comparative analytical validity data had been provided by the co-applicants which would provide a basis to argue against this advice.
- Staging of NSCLC: the resubmission proposed limiting testing to patients with locally advanced or metastatic NSCLC. However it indicated that MSAC advice would be accepted on this matter, and also proposed linking *ALK* testing with *EGFR* mutation testing, which MSAC previously advised not to be limited to later stages of NSCLC to facilitate good pathology laboratory practice in managing small tumour samples. ESC advised that, given the precedent with *EGFR* mutation testing (which similarly allows earlier testing than the stage of NSCLC in the PBS restrictions which apply to the co-dependent tyrosine kinase inhibitors), MSAC should not limit any MBS item descriptor to any particular staging of NSCLC.
- Histology of NSCLC: given the precedent with *EGFR* mutation testing, ESC agreed with the resubmission that any MBS item descriptor should be limited to patients with

NSCLC which is “shown to have non-squamous histology or histology not otherwise specified”.

- ALK IHC triage testing: the resubmission proposed that *ALK* gene rearrangement testing be limited to tumour tissue with documented evidence of ALK reactivity by IHC examination, with a staining intensity score >0. The resubmission indicated that MSAC advice would be accepted on this matter. It noted that current standard laboratory practice is to use ALK IHC as a triage test, and so indicated that this restriction may be unnecessary because it is unlikely to affect practice. To avoid disadvantaging some patients, the resubmission also proposed an optional note in the event that ALK IHC examination is retained in the MBS item descriptor, which is intended to exempt patients from this triage test if the sample is inadequate to support both it and definitive *ALK* gene rearrangement testing. However, neither the resubmission nor the pre-ESC response estimated the financial implications of not using ALK IHC as a triage test. ESC considered these issues further below.
- Pathologist: given the precedent with *EGFR* mutation testing, ESC agreed with the commentary and the pre-ESC response (p3) that any MBS item descriptor should not include a pathologist as an alternative to a specialist or a consultant physician as proposed in the resubmission. Rather, any MBS item for *ALK* gene rearrangement testing should be made a “pathologist determinable service.”
- *EGFR* mutation testing: although the resubmission proposed linking ALK testing with *EGFR* mutation testing, it did not include any text referring to *EGFR* mutation testing in its proposed MBS item descriptor. The resubmission and pre-ESC response (p1) discussed the advantages in terms of time, efficiency and optimisation of scarce tumour tissue by minimising the wastage associated with refacing and recutting a cell block for molecular analysis. The financial implications calculations in the resubmission and the pre-ESC response both limited ALK testing to tumours which were not *EGFR* mutation positive in the base case, but included a sensitivity analysis around this assumption. ESC considered these issues further below.
- Other mutation testing: the resubmission did not propose any reference to any other mutation testing. ESC agreed that there was no evidentiary basis to do so.
- Source of tumour tissue: the resubmission did not propose to identify any particular source of tumour tissue. Recalling MSAC’s considerations of this issue in the context of *EGFR* mutation testing, ESC agreed that there was no evidentiary basis to do so.
- ALK IHC MBS item: if MSAC considers that ALK IHC is an appropriate test, and that a greater than standard MBS fee is justified, then MSAC will need to advise on the creation of a new MBS item and its corresponding item descriptor or to amend the MBS item descriptor for IHC testing where a greater fee has already been accepted.

ESC noted that adding ALK testing (*ALK*-ISH testing with or without ALK IHC triage) would increase the risk that a patient would need to return to provide a further biopsy sample in order to complete testing. This would be associated with the increased risk of harm, inconvenience and associated costs.

In terms of test performance, ESC noted that the resubmission reiterated the basis for determining *ALK*-positive status with respect to FISH testing, but provided no further explanation on the derivation of this basis and did not propose to include any definition in any MBS item descriptor or PBS restriction. No new data were provided to apply the results to the Australian population; the previous basis for arguing applicability were reiterated, including the estimate of *ALK*-positive prevalence as being 4.86%. Despite the November 2013 PBAC and MSAC doubts about attributing a crizotinib effect equal to standard care in *ALK*-negative patients, and the resubmission acknowledging that FISH test performance is

not perfect in regular practice, no revised sensitivity analysis is presented to show the consequences of false positive results on overall cost-effectiveness.

Similarly, ESC noted that the resubmission advised, with support from the other sources consulted by the November 2013 MSAC meeting (Roche Diagnostics and the RCPA), that *ALK*-positive status with respect to IHC testing with the appropriate clones is determined simply as being immunostaining present rather than absent. This definition was proposed for inclusion in the MBS item descriptor. ESC discussed the large new comparative analytic validity study comparing FISH with IHC by Cabillic (2014). In contrast with other studies presented in the original submission which reported reduced sensitivity, this study reported a sensitivity result as low as 69% in the context of an antibody clone (5A4) widely recommended as appropriate. In addition, the study used the lowest extent of immunostaining in its definition for *ALK* IHC positivity. The false negative rate associated with this sensitivity raises concerns about the appropriateness of using this *ALK* IHC test as a triage before more definitive *ALK*-ISH testing. The pre-ESC response (p3) suggests that this study may represent an outlier. However, ESC was concerned that the reasons for this suggestion (that the results were possibly affected by extra-tumour factors such as tissue preparation or testing protocol) may not be sufficiently reduced by the standardization of *ALK* immunostaining procedures or incorporating *ALK* IHC into the *ALK*-FISH slide program emphasised by the RCPA. Overall, ESC advised that the performance of *ALK* IHC triage testing was a key issue for MSAC consideration.

Few details were provided to support the proposed fee for *ALK*-FISH testing of \$(redacted), beyond noting that costs vary most according to batch sizes (the most common batch size of 8 resulting in \$(redacted)/test, dropping to \$(redacted)/test for a batch of 16), and also on different costs for different FISH assays. ESC noted that a higher MBS fee for a determinative *ALK*-ISH test may generate a financial incentive for pathology laboratories to test all NSCLC samples without reference to any prior *EGFR* mutation test or *ALK* IHC test. If so, the incremental cost per extra QALY gained for the overall co-dependent package of *ALK* testing and crizotinib and also the corresponding financial analyses may both be underestimated.

Similarly, few details were provided to support the proposed fee for *ALK* IHC testing being \$75.49 to reflect the current MBS fee for HER2 IHC testing. ESC noted that both Roche Diagnostics and the RCPA argued that the unit costs of the reagents are greater due to the need to use more recently developed clones. An *ALK* IHC test with a greater fee may also increase use of this test at initial diagnosis of NSCLC.

The overall cost-utility analysis was not revised to reflect changes in the proposed population for testing, such as including the not otherwise specified NSCLC population and examining the consequences of different test strategies (including the reduced sensitivity of *ALK* IHC triage from the Cabillic 2014 study) on overall cost-effectiveness. These different strategies require updated costs to reflect different consequences for patient episode initiation (PEI) fees, specimen referral and retrieval fees, an 8.5% failure rate of FISH and >12% rate of re-biopsies with their associated adverse effects and costs. If MSAC was sufficiently confident from the information available to nominate a preferred *ALK* testing strategy, these variables could be more accurately estimated for both the cost-utility analysis and the financial analyses.

ESC noted the following additional issues with the financial analyses.

- The critique appropriately adjusted these estimates to reflect costs for all advanced non-squamous and not otherwise specified NSCLC (increasing numbers tested from about **(redacted)** per year to more than **(redacted)** per year).
- The estimates are based on MBS fees, not benefits paid by the MBS.
- As in the original submission, the resubmission's epidemiological approach projected patient numbers from age-standardised incidence rates of cancer. This approach fails to account for changes in the age-sex composition of the overall population. The results are underestimates compared with projections based on projecting age-sex specific incidence rates as reported by AIHW. The consequences of this on the financial implications are illustrated below as increasing the MBS costs by about **\$(redacted)** to **\$(redacted)** per year.

Revised estimate of costs of ALK testing to reflect AIHW projections while keeping other assumptions as in the resubmission

(Table redacted)

- The estimates do not make any adjustments for variations in ALK IHC sensitivity and specificity.
- The ALK IHC unit costs are underestimated to the extent that a higher fee is required. From the table in Section 12, if the fee is increased from **\$(redacted)** to **\$(redacted)**, MBS costs increase by about **\$(redacted)** to **\$(redacted)** per year ([N] minus [M]).
- Whether *EGFR* mutation testing is used as a triage test has an impact on the financial estimates. From the table in Section 12, if *EGFR* mutation testing is excluded, and ALK IHC testing is retained, MBS costs increase by about **\$(redacted)** to **\$(redacted)** per year ([O] minus [M]), or by **\$(redacted)** to **\$(redacted)** per year if the ALK IHC fee is increased from **\$(redacted)** to **\$(redacted)** ([Q] minus [M]).
- Whether ALK IHC testing is used as a triage test has a larger impact on the financial estimates. This is not examined in the pre-ESC response. From the table in Section 12, if ALK IHC testing is excluded, and *EGFR* mutation testing is retained, MBS costs increase by about **\$(redacted)** to **\$(redacted)** per year ([P] minus [M]). If it is excluded as well as *EGFR* mutation testing, the lack of ALK IHC testing contributes about **\$(redacted)** to **\$(redacted)** per year to the increase in MBS costs ([R] minus [P]).
- If neither *EGFR* mutation testing nor ALK IHC testing is used, MBS costs increase by about **\$(redacted)** to **\$(redacted)** per year ([R] minus [M]).
- By way of context, the annual costs of ALK testing to the MBS of between **\$(redacted)** and **\$(redacted)** per year (without increasing the estimated patient numbers) compares to the annual net costs to the PBS of the co-dependent crizotinib of between **\$(redacted)** and **\$(redacted)** per year.

In relation to *EGFR* mutation testing, ESC advised MSAC that, because it is already MBS funded for use in the same population proposed for ALK testing and the incidence of being both *ALK*-positive and *EGFR*-positive is so rare, that it makes good sense to:

- exclude any reference to NSCLC staging in any MBS item descriptor of *ALK*-ISH testing
- refer to *EGFR* mutation testing in any MBS item descriptor of *ALK*-ISH testing
- continue to include the consequences of *EGFR* mutation testing in calculating the cost-utility analysis and financial analysis involving *ALK*-ISH testing.

In relation to ALK IHC testing, ESC advised MSAC that the issues were more complex due to recent doubts about the sensitivity of this test, which is the most important test characteristic for a triage test given that this would mean more patients are denied access to more effective therapy. However, the cost consequences of its exclusion from the overall

ALK testing strategy would both affect the overall cost-utility analysis, and also be greater than the consequences of excluding *EGFR* mutation testing on the financial analyses.

14. Other significant factors

The table below summarises the options for MSAC consideration.

Descriptor component	Resubmission's nominated option	MSAC's alternative options
Who to test		
NSCLC histology	non-squamous histology or histology not otherwise specified	none (resubmission agrees with November 2013 MSAC, which excluded other options)
<i>EGFR</i> mutation test result	none in item descriptor, but economic and financial analyses assume ALK testing is limited to <i>EGFR</i> -negative NSCLC	include <i>EGFR</i> mutation negative in item descriptor
Other mutation test results	none in item descriptor, on the basis that there is no evidence to support any	possibly add other mutation types as evidence becomes available
ALK IHC triage	included in item descriptor, and in economic and financial analyses, and a case is put for both its exclusion and an optional note if included	exclude ALK IHC triage (or optional note) from item descriptor
When to test		
NSCLC stage	limited to patients with locally advanced or metastatic NSCLC	exclude NSCLC stage from item descriptor
How to test		
Pathologist	included in item descriptor	exclude 'pathologist' from item descriptor, but make item "pathologist determinable"
Type of ISH	limited to FISH in item descriptor	limit to ISH in item descriptor
Source of tumour tissue	not specified	none (resubmission agrees with November 2013 MSAC, which excluded sources other than tumour tissue)

In terms of proposed implementation, ESC noted the views that:

- the existing seven pathology laboratories conducting *ALK*-FISH testing are of high quality
- *ALK*-FISH testing is no more complex than *EGFR* mutation testing
- the RCPA will implement a QAP that will include *ALK* IHC testing
- standardisation of *ALK* IHC immunostaining will improve test performance.

15. Co-applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

16. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website at: www.msac.gov.au.