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Final Decision  
Analytic Protocol to  
guide the assessment  
of diagnostic testing  
for Anaplastic  
Lymphoma Kinase  
(ALK) gene  
rearrangement in  
patients with  
advanced non-small  
cell lung cancer to  
determine eligibility  
for treatment with  
crizotinib.

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September 2012

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## MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

### Purpose of this document

This document is intended to provide a decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients and provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use
- I**ntervention – specification of the proposed intervention and how it is delivered
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

### Purpose of application

An application requesting MBS listing of diagnostic testing for Anaplastic Lymphoma Kinase (ALK) gene rearrangement by fluorescent in-situ hybridisation (FISH) for patients with advanced non-small cell lung cancer (NSCLC) was received from Pfizer Australia Pty Ltd and Abbott Australasia Pty Ltd by the Department of Health and Ageing in December 2011.

## Background

### Current arrangements for public reimbursement

Diagnostic 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.

This application is part of a co-dependent assessment. Patients that harbour ALK gene rearrangement may respond to treatment with crizotinib. The applicant has indicated that it has concurrently

submitted to PBAC to have crizotinib listed on the PBS as a second line treatment option for patients with advanced NSCLC. The applicant has further signalled that a further PBAC submission to list crizotinib as a first line agent may be lodged in the future pending the outcome of current clinical trials.

## Regulatory status

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 has advised that the Vysis Break Apart FISH Probe Kit has been granted TGA approval and was listed on the ARTG on 3rd April 2012 (ARTG identifier 186286).

## Intervention

### Description

ALK gene rearrangement in NSCLC: In a subset of NSCLC patients a deletion and inversion (gene rearrangement) event within chromosome 2p results in the fusion of the ALK gene with the gene encoding the echinoderm microtubule-associated protein-like 4 (EML4). The resulting EML4-ALK fusion gene encodes a protein with constitutive kinase activity. Both preclinical and clinical studies have shown that cancer cells harbouring the EML4-ALK rearrangement are sensitive to treatment with ALK inhibitors such as crizotinib (McDermott et al. 2008).

ALK gene rearrangement has been associated with resistance to EGFR tyrosine kinase inhibitors (e.g. gefitinib and erlotinib). Initial clinical evidence indicated that the presence of EML4-ALK gene rearrangement is mutually exclusive to the presence of both activating EGFR and KRAS mutations (Shaw et al. 2009). However, with the increased utilisation of ALK gene rearrangement alongside other molecular assays associated with NSCLC there have been case reports of patients harbouring concurrent ALK gene rearrangement and activating EGFR mutations (Popat et al 2011). Despite these case reports, concurrent EGFR mutation and ALK rearrangement remain rare. Future planned collaborative group studies will better inform on the clinical and molecular demographics of ALK rearrangement.

FISH testing for ALK gene rearrangement: The applicant is seeking to have FISH listed on the MBS as the diagnostic testing strategy for ALK gene rearrangement. Patients enrolled in clinical trials informing the efficacy of crizotinib accessed treatment solely on the basis of testing patients for ALK disruption using the Vysis Break Apart FISH assay. While FISH was the testing methodology employed throughout the conduct of clinical trials assessing crizotinib, testing for gene rearrangements may be undertaken using a range of techniques including chromogenic in-situ hybridisation (CISH), immunohistochemistry (IHC), and reverse-transcriptase polymerase chain reaction (RT-PCR) tests (Kwak et al., 2010; Yi et al., 2011; Kim et al., 2011).

Should ALK gene rearrangement testing become MBS-funded it could be expected that there will be inter-laboratory variation in the methodological approaches to testing. In response to this PASC

determined that this assessment not be limited to FISH, rather it was determined that FISH be considered the evidentiary standard and that other testing strategies be assessed against this standard for potential eligibility for MBS-funding.

Due to the relatively low number of patients expected to harbour ALK gene rearrangements it was advised by the PASC that the use of IHC as a screening method should also be considered in the assessment. This scenario would result in all samples sent for ALK gene rearrangement testing initially receiving ALK IHC screening, with only those samples returning equivocal or positive IHC results undergoing confirmatory ALK gene rearrangement testing.

Treatment of advanced NSCLC: The choice of treatment for advanced NSCLC will and should vary in response to individual patient tolerances and molecular profile. As a guide, the 2004 NHMRC guidelines recommend that first line treatment is undertaken using combination chemotherapy that includes a platinum-based compound and another agent such as gemcitabine. Patients that fail to respond to first line treatment may receive treatment with a range of agents including: pemetrexed, docetaxel, erlotinib and gefitinib. Patients eligible to receive gefitinib must have been determined to carry EGFR activating mutations.

The PBAC submission that accompanies this MSAC application is seeking to add crizotinib to the list of therapeutic agents for advanced lung cancer, initially as a second line treatment but with a potential re-submission for use as a first line treatment option as well.

### **Delivery of the intervention**

Testing for ALK gene rearrangement 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.

Testing would be carried out in laboratories that have received accreditation from the National Association of Testing Authorities (NATA) with an established quality assurance program specific to ALK gene rearrangement testing developed by the Royal College of Pathologists of Australasia (RCPA). Advice from clinical experts is that the development of a formalised quality assurance program is underway.

It is anticipated that ALK gene rearrangement testing would be limited to specialised pathology laboratories based in major capital centres, however testing could be carried out in any laboratory meeting the appropriate accreditation and quality assurance standards. Access to ALK gene rearrangement testing for patients in regional or remote areas would be facilitated by the collection of a tissue sample at their local specimen collection or treatment centre and transportation to an accredited pathology laboratory for testing.

It is believed that the ALK gene rearrangement is stable and not affected by prior treatment, therefore each patient requires testing only once (albeit that retests might be required if the initial sample is of insufficient quality or quantity at the time of testing).

## Prerequisites

ALK gene rearrangement testing: An adequate tissue sample must be collected ahead of ALK gene rearrangement testing. Biopsy samples for pathology testing will often be taken during initial diagnosis of disease and be collected using a range of techniques including: bronchoscopy; percutaneous transthoracic fine needle aspiration (FNA); and percutaneous transthoracic core biopsy. In the case of patients that have developed metastatic disease following treatment for earlier stage NSCLC, pathology testing is typically performed on surgically resected tumours.

The demand for biopsy sample for pathology testing is increasing with the number of tests being performed, and may be expected to further increase with the discovery of additional lung cancer biomarkers such as ROS1. Further, the original biopsy sample may be of insufficient quality to perform ALK testing. In response to these factors PASC determined the assessment should consider re-biopsy rates (and related safety outcomes) associated with the potential introduction of ALK testing.

Access to crizotinib: In line with the associated PBAC submission to have crizotinib listed on the PBS as a second line therapy, patients must have been treated with first line combination chemotherapy prior to being eligible to access crizotinib.

## Co-administered and associated interventions

As detailed in Intervention section above it was determined by PASC that the use of IHC as a screening method be considered in the assessment. Only IHC screening using the anti-ALK antibody clones 5A4 or D5F3 is to be assessed, with other anti-ALK antibodies not to be considered. This scenario would result in all samples sent for ALK gene rearrangement testing initially receiving ALK IHC testing, with only samples returning equivocal or positive results from IHC testing going on to receive confirmatory testing.

EGFR testing is required ahead of PBS-subsidised access to gefitinib as a second line therapy. As testing laboratories have outlined that there are technical efficiencies associated with conducting EGFR and ALK testing at the same time, EGFR associated with second-line access to gefitinib may be considered as a co-administered intervention.

It was noted by PASC that an extension of MBS-funding for EGFR testing associated with access to first-line therapies was not supported by MSAC at the time of drafting this protocol. Despite this, it can be reasonably expected that EGFR testing associated with first line access to EGFR-sensitive treatment will be the basis of further MSAC assessments and as such it was requested that first-line EGFR testing be included in contingency planning.

## Listing proposed and options for MSAC consideration

### Proposed MBS listing

In order to facilitate the potential MBS-funding of ALK IHC screening and confirmatory ISH testing two MBS item descriptors are required.

ALK IHC testing may be funded through the existing MBS item numbers 72846 or 72847. Given that this assessment requires that only ALK antibodies available as commercial reagents be considered, then this would have to be adequately reimbursed if a unique ALK IHC MBS item number and fee are required for this class of test. Justification of the ALK IHC fee must be provided in-line with Department of Health and Ageing guidelines for input-based fee determination.

Table 1: Current MBS item descriptors for IHC testing

Category 6 – Pathology Service	
<p>MBS item number: 72846</p> <p>Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen 1 to 3 antibodies except those listed in 72848</p> <p>(Item is subject to rule 13)</p> <p>Fee: \$60.00 Benefit: 75% = \$45.00 85% = \$51.00</p> <p>Rule 13.(7) If more than 1 of the services mentioned in items 72846, 72847, 72848; 72849 and 72850 or 73059, 73060, 73061, 73064 and 73065 are performed in a single patient episode, a medicare benefit is payable only for the item performed that has the highest scheduled fee.</p>	
<p>MBS item number: 72847</p> <p>Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies</p> <p>(Item is subject to rule 13)</p> <p>Fee: \$90.00 Benefit: 75% = \$67.50 85% = \$76.50</p> <p>Rule 13.(7) If more than 1 of the services mentioned in items 72846, 72847, 72848; 72849 and 72850 or 73059, 73060, 73061, 73064 and 73065 are performed in a single patient episode, a medicare benefit is payable only for the item performed that has the highest scheduled fee.</p>	

Table 2: Proposed MBS item descriptor for ISH testing.

Category 6 – Pathology Service	
<p>MBS item number: to be advised</p> <p>An in situ hybridization 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 classified, 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.</p> <p>Fee: \$350-500 [A final proposed fee is to be advised by the applicant upon the completion of a cost survey of reference laboratories]</p> <p><b>Proposed relevant explanatory notes:</b> Testing must be performed in an accredited pathology laboratory participating in a quality assurance program specific to ALK gene rearrangement testing developed by the Royal College of Pathologists of Australasia.</p>	

It is proposed that ALK gene rearrangement testing would be undertaken on patients with advanced or metastatic, non-squamous or not otherwise classified NSCLC patients when treatment with crizotinib was being considered. Should the applicant seek the removal of the current access restriction to non-squamous or not otherwise classified NSCLC's then evidence substantiating the inclusion of squamous carcinomas and an assessment of the implications of removing this restriction must be provided.

### Clinical place for proposed intervention

ALK gene rearrangement testing and treatment with crizotinib is a novel treatment approach to NSCLC and will add to current therapeutic options. Currently the second line treatment options available for patients with advanced NSCLC include:

1. The untargeted therapies pemetrexed and docetaxel. Pending the outcome of this application and its companion PBAC submission, the use of these agents may be substituted with crizotinib in patients harbouring ALK gene rearrangement.
2. The targeted therapies erlotinib and gefitinib. Gefitinib is only available to patients that have activating EGFR mutations. Erlotinib as a second line (or later) therapy is not restricted to patients with activating EGFR mutations but restricted for patients that have either failed or are contraindicated to treatment with pemetrexed or docetaxel.

Access to ALK gene rearrangement testing at the time of diagnosis was recommended for all patients diagnosed with locally advanced (Stage IIIB) or metastatic disease (Stage IV) disease. For patients diagnosed with earlier stage disease, testing was not supported until they had failed to respond to first-line treatment. Consideration of these separate patient groups should be presented in the assessment, with estimates of the number of patients anticipated to access ALK gene rearrangement testing through each pathway provided.

Estimates of the size of the testing population: The 2010 incidence and pathology estimates for lung cancer presented by the applicant are given below.

Table 3: Non-squamous NSCLC incidence estimates provided by the applicant.

Incidence estimate of all lung cancers in 2010	10,004
Incidence of all NSCLC	8,503 (85% of all lung cancers)
Squamous cell carcinoma	2,401 (24% of all lung cancers)
Non-squamous NSCLC	6,102 (61% of all lung cancers)

References for applicant supplied data are: (Francis and Solomon 2010; Tracey et al. 2009).

These figures differ slightly from those presented in the Australian Institute of Health and Welfare & Cancer 2011 report on lung cancer in Australia (AIHW 2011).

Table 4: Non-squamous NSCLC incidence estimates determined by the assessment group.

Incidence of all lung cancers in 2007	9,703
Incidence of all NSCLC	6,095 (62.8% of all lung cancers)
Incidence of non-squamous NSCLC	4,524 (46.6% of all lung cancers)

The most significant difference in the data presented by the applicant and those reported by the AIHW regards the incidence of non-squamous NSCLC, with figures of 61% and 46.6% presented respectively. The Department of Health and Ageing has indicated a preference that the most recent data published by the AIHW at the time of undertaking the assessment be used.

PASC has expressed a preference that the most recent data regarding Australian ALK-gene rearrangement prevalence in NSCLC will be presented in the assessment report, together with a range of values tested in sensitivity analysis. Literature at the time of developing this protocol suggests that ALK gene rearrangements are found in approximately 4% of all lung cancers (range 0.4% - 13.5%) and they are more frequent in younger patients, never or light smokers and those with adenocarcinoma histology (Solomon et al. 2011; Francis & Solomon 2010; Kwak et al. 2010; Shaw et al. 2009; ). More recently, it is also reported that features associated with ALK-positive NSCLC include median age of onset in fifth or sixth decade, adenocarcinoma histology and never or light smoking status (Camidge and Doebele, 2012)

Clinical algorithms for the place of ALK gene rearrangement testing for which assessments are sought are provided in Figures 1 through 4. Please note that these figures are for the purpose of illustrating the clinical algorithms associated with the various assessments outlined in this DAP and are not intended to reflect the economic models required in the final assessment.

Figure 1: Clinical algorithm for the treatment of patients with advanced non-squamous or otherwise not classified NSCLC to be assessed.

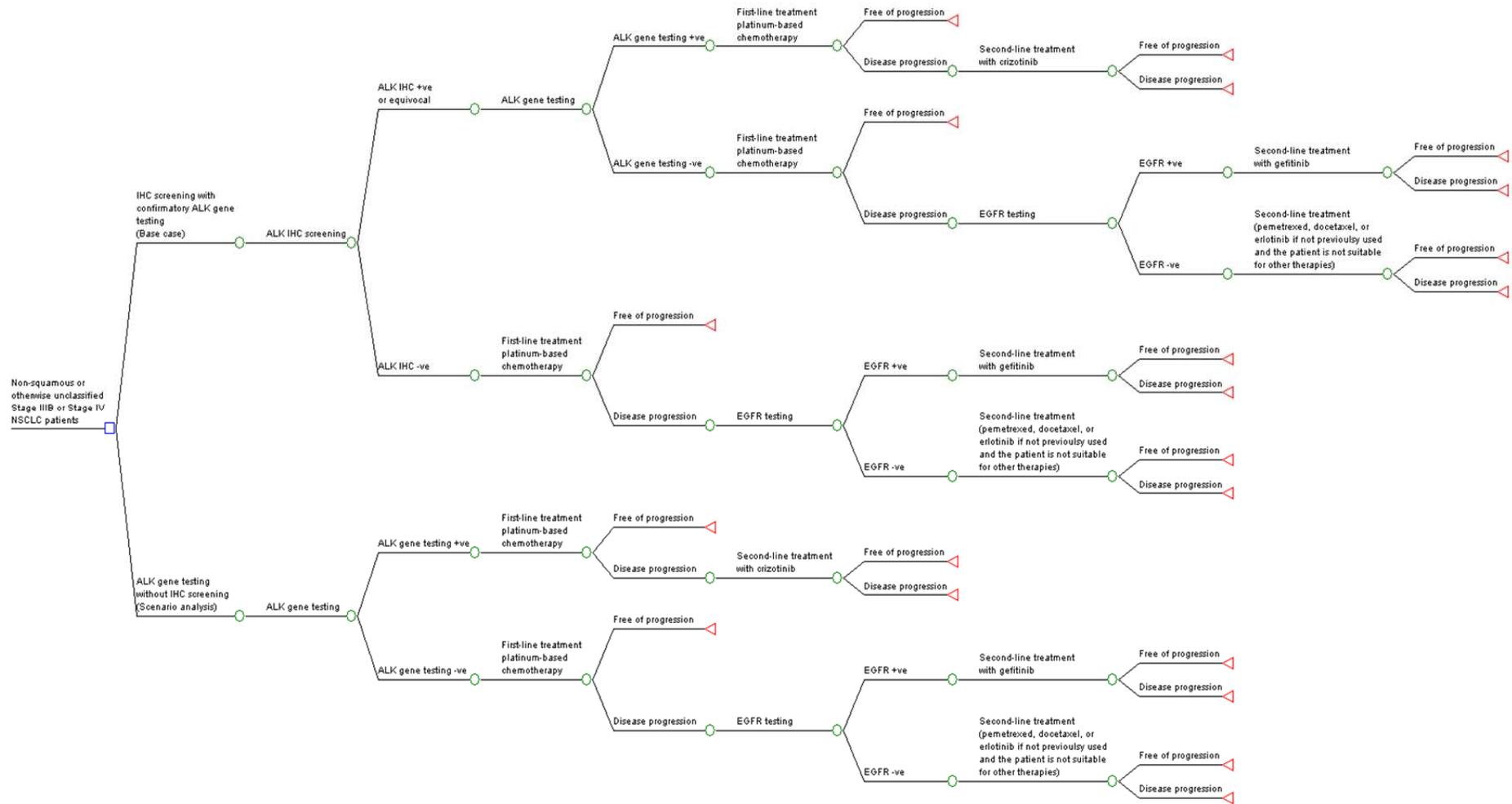


Figure 2: Clinical algorithm for the treatment of patients with advanced NSCLC without histology subtype restriction to be assessed.

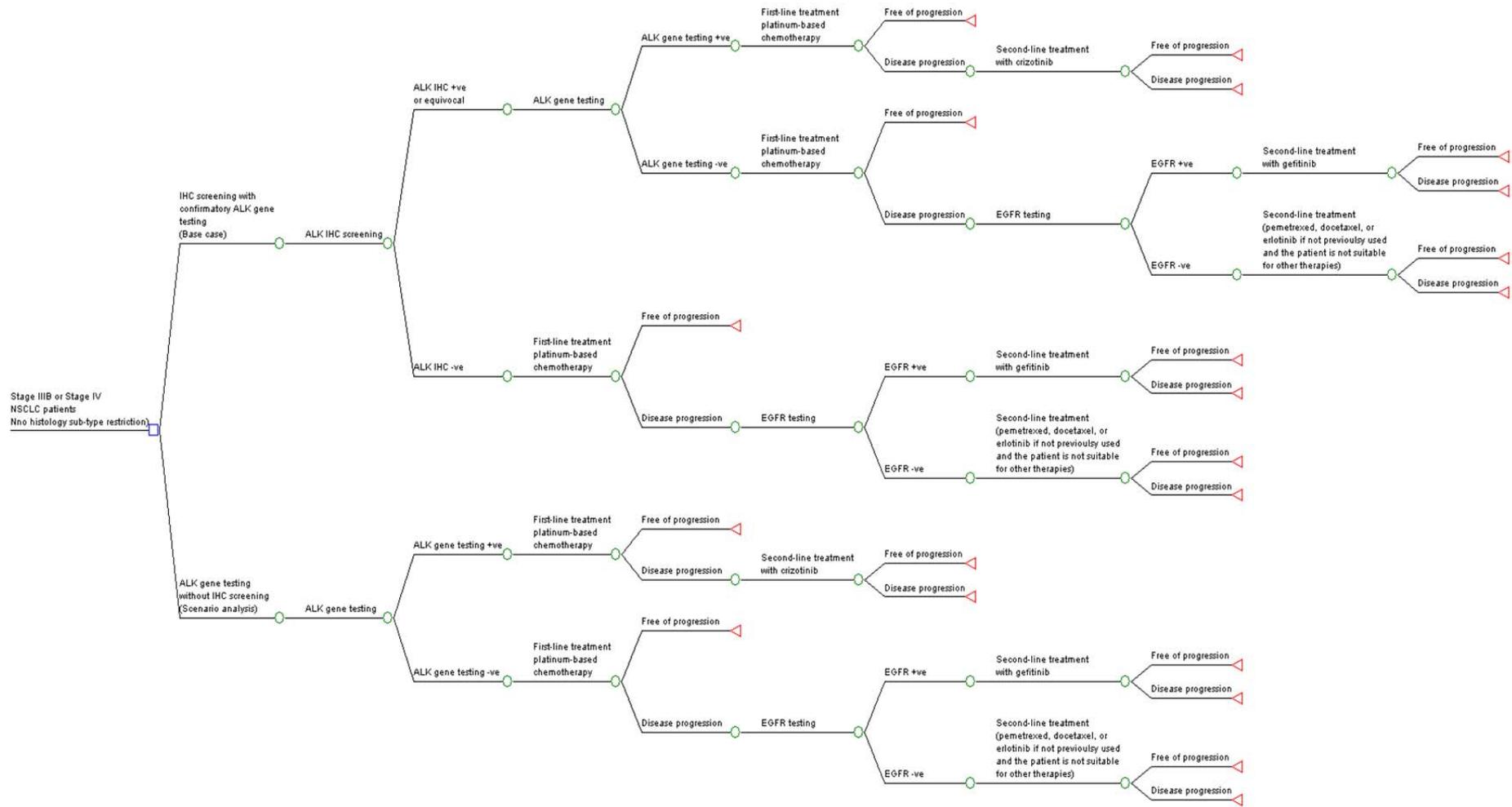
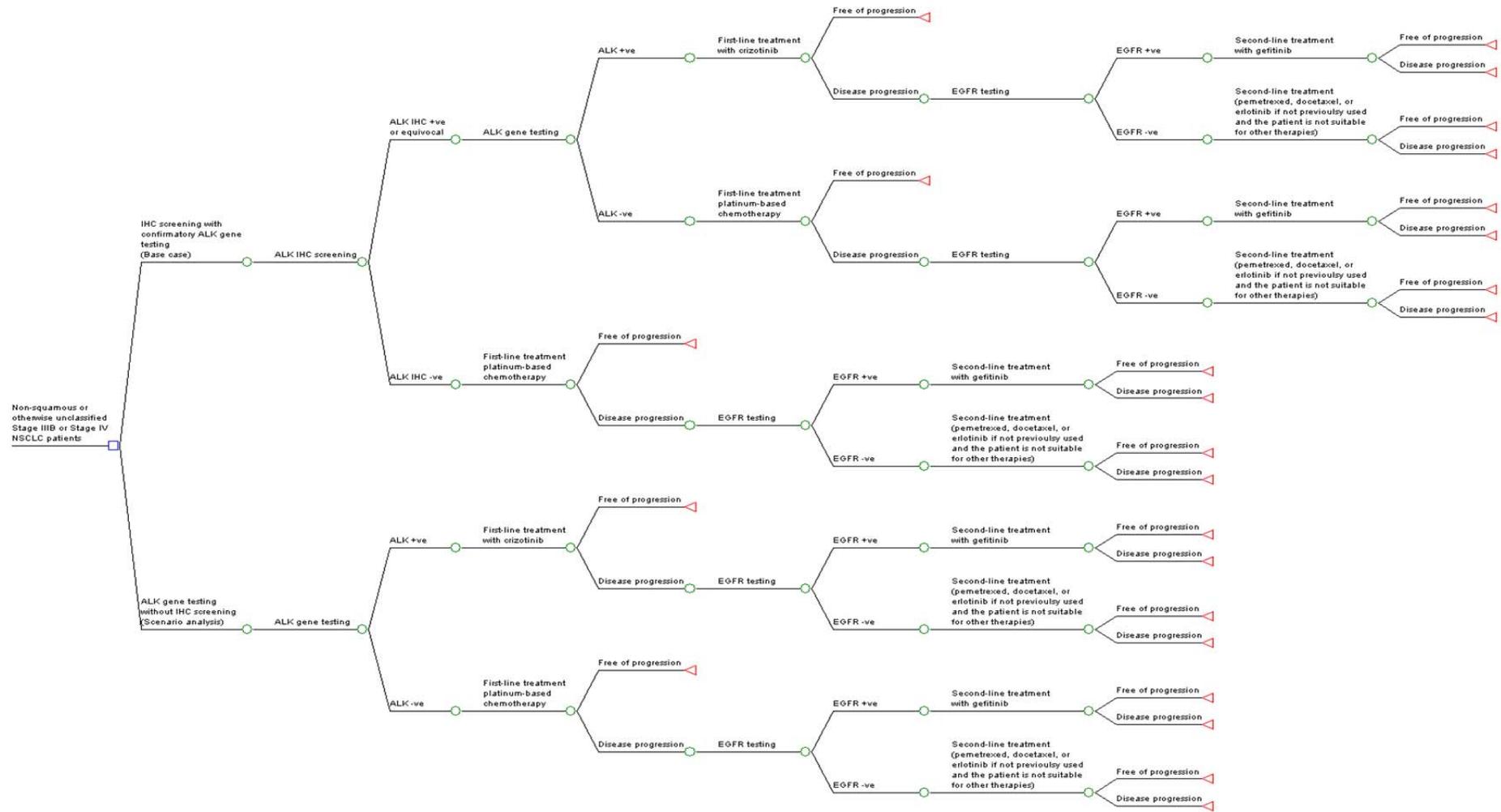




Figure 4: Clinical algorithm for the treatment of patients with advanced NSCLC with first-line access to ALK testing and crizotinib treatment.



## Comparator

Comparator for ALK gene rearrangement testing: This application is seeking to have ALK gene rearrangement testing listed on the MBS. To date, all clinical trials assessing the efficacy of crizotinib have used FISH testing as the basis of determining ALK gene rearrangement status. For this reason FISH testing should be considered as the evidentiary standard for ALK gene rearrangement testing. PASC has requested that the following aspects of FISH testing also be presented in establishing the evidentiary standard during the assessment:

- Biopsy technique
- Method of sample preparation
- Details of the name and manufacturer of the FISH test
- Approach to test result interpretation

The comparative performance of alternate methods for determining ALK gene rearrangement status should be compared to FISH as the evidentiary standard.

Comparator for clinical practice: Given that both ALK gene rearrangement testing and treatment with crizotinib are novel interventions the appropriate comparator for assessment is current clinical practice. Specifically, the comparator is the scenario whereby:

upon diagnosis or failure of first line therapy, patients may access molecular profiling that does not include ALK gene rearrangement testing in order to inform eligibility to second line treatment options that does not include crizotinib.

## Clinical claim

The clinical claim is that ALK gene rearrangement testing followed by treatment with crizotinib in patients harbouring rearrangements is associated with clinical advantages with respect to disease control and survival. Hence, the clinical claim is driven by two factors:

1. The performance of the ALK gene rearrangement test.
2. The efficacy of crizotinib treatment in patients that have been identified as ALK gene rearrangement positive.

As outlined in the Health Technology Access Point Information Pack (DoHA 2011) released by the Department the assessment on co-dependent technologies will be through “a coordinated but modular assessment of applications, which reflects agreed HTA processes and timeframes and the individual responsibilities and accountability to the Minister of each of the expert advisory committees”

As a result of this approach, the assessment of this co-dependent application will be restricted to the ALK gene rearrangement test. The assessment of clinical claims associated with crizotinib treatment will be undertaken by the PBAC as per Departmental guidelines.

The potential benefits of the introduction of ALK gene rearrangement testing to support the proposed PBS-subsidised use of crizotinib as a second line treatment for patients with advanced NSCLC are:

- Acceptable safety and analytical performance of ALK gene rearrangement testing. (To be assessed by MSAC.)
- Non-inferior or superior effectiveness with acceptable safety of treating ALK gene rearrangement positive patients with crizotinib. (To be assessed by PBAC.)

The type of economic evaluation to be undertaken will be driven by the clinical claim(s) made and pricing sought in the PBAC submission for crizotinib. Given that crizotinib is a new treatment option for advanced NSCLC, and that the clinical utility of ALK gene rearrangement testing must be established, it would be expected that a cost-effectiveness analysis be conducted.

## **Outcomes and health care resources affected by introduction of proposed intervention**

### **Clinical outcomes**

Outcome measures suitable to assess the analytic performance of ALK gene rearrangement testing include:

- Sensitivity
- Specificity
- Positive Predictive Value
- Negative Predictive Value

Measures of comparative performance of ALK gene rearrangement testing methods:

- Concordance with evidentiary standard
- Receiver Operating Characteristic (ROC)
- Reclassification index against evidentiary standard (as a potential alternative to ROC).

Other outcomes relating to the introduction of ALK gene rearrangement testing to be presented are:

- Rates of re-testing
- Rates of re-biopsy
- Anticipated test turnaround time.

PASC also requests details on:

- The estimated number of patients being tested
- The number of patients tested per case of ALK +ve result detected
- The number of patients tested per case of ALK +ve result treated with crizotinib
- The cost of testing per case of ALK +ve NSCLC detected
- The cost of testing per case of ALK +ve NSCLC treated with crizotinib.

The assessment of outcomes regarding treatment ALK gene rearrangement testing is the remit of MSAC.

Measures of clinical efficacy for crizotinib (recommended to be the same as those used in PBAC submission) include:

- Quality-adjusted survival
- Objective tumour response rates
- Progression free survival
- Overall survival
- Safety and tolerability.

The assessment of outcomes regarding treatment with crizotinib is the remit of PBAC.

In order to achieve consistency across submissions it is recommended that the clinical endpoints and effectiveness measures regarding crizotinib treatment that the applicant submits to the PBAC are also used in the assessment of the ALK gene rearrangement testing.

### **Health care resources**

Healthcare resources that are most likely to be affected should ALK gene rearrangement testing and treatment with crizotinib become available include:

- The additional cost of performing ALK gene rearrangement testing (including IHC screening).
- The cost of treating ALK gene rearrangement positive patients with crizotinib.
- The potential reduced utilisation of any therapeutic options resulting from crizotinib treatment of ALK gene rearrangement positive patients.
  - This would also result in reduced utilisation of medical services required for intravenous drug administration.
- The potential costs for treating adverse events from treatment (with any therapeutic agent).
- Costs associated with ongoing patient monitoring, e.g. physician visits.

Health care resources and associated with initial diagnosis are assumed to remain unchanged and may be excluded from the analysis accordingly.

## Proposed structure of economic evaluation (decision-analytic)

An assessment of the cost-effectiveness of introducing ALK gene rearrangement testing that is required for access to the proposed PBS listing of crizotinib should take into account the parameters outlined in Tables 5 and 6.

PASC has proposed that multiple evaluations are conducted:

1. An assessment of patient access to ALK gene rearrangement testing upon initial diagnosis with advanced non-squamous or otherwise unclassified NSCLC (Clinical algorithm represented in Figure 1).
2. An assessment of patient access to ALK gene rearrangement testing upon initial diagnosis with advanced NSCLC without a restriction of histology sub-type (Clinical algorithm represented in Figure 2).
3. For patients diagnosed with early stage NSCLC, access to ALK gene rearrangement testing is only eligible when first-line therapy has failed and the patient has progressed to advanced disease (Clinical algorithm represented in Figure 3).
4. An assessment of the patient access to ALK gene rearrangement testing upon initial diagnosed with advanced non-squamous or otherwise unclassified NSCLC *as well as* crizotinib as a first-line treatment option (Clinical algorithm represented in Figure 4). The aim of this assessment analysis is to expedite the assessment of the ALK gene rearrangement testing associated with a potential PBAC submission to have crizotinib listed as a first line treatment option. This assessment should not be undertaken if a PBAC submission to list crizotinib as a first-line treatment option is not planned.

Evidence on the outcomes informing the performance of ALK gene rearrangement testing listed in Table 5 will be assessed by MSAC. Evidence on the clinical efficacy of crizotinib will be assessed by PBAC.

Table 5: Summary of extended PICO to define research question that assessment will investigate

Population	Prior tests	Intervention	Comparator	Reference standard	Outcomes to be assessed by MSAC
<p>Patients with advanced (Stage IIIB) or metastatic (Stage IV), non-squamous or otherwise not classified NSCLC at the time of diagnosis.</p> <p>AND</p> <p>Patients diagnosed with early stage non-squamous or otherwise not classified NSCLC that have progress to advanced disease and have failed at first-line therapy.</p>	<p>Tests required to confirm diagnosis of advanced NSCLC.</p>	<p>Testing for ALK gene rearrangement to determine if the proposed PBS requirements relating access to crizotinib are fulfilled.</p> <p>Testing options include: FISH CISH IHC RT-PCR</p>	<p>Current practice whereby following treatment failure with first line therapy, patients may access molecular profiling that <u>does not</u> include ALK gene rearrangement testing in order to inform eligibility to second line treatment options that <u>does not</u> include crizotinib.</p>	<p>FISH is to be considered as the evidentiary standard.</p> <p>The performance of other test methodologies is to be compared against the evidentiary standard.</p>	<p><b>Safety:</b> Safety of performing the ALK gene rearrangement testing (including safety outcomes associated with re-biopsy).</p> <p><b>Effectiveness:</b> Measures of analytic performance of ALK gene rearrangement testing including:</p> <ul style="list-style-type: none"> <li>- Sensitivity</li> <li>- Specificity</li> <li>- Positive Predictive Value</li> <li>- Negative Predictive Value</li> </ul> <p>Measures of comparative performance of ALK gene rearrangement testing methods:</p> <ul style="list-style-type: none"> <li>- Concordance with evidentiary standard (FISH)</li> <li>- Receiver Operating Characteristic (ROC)</li> <li>- Reclassification index against evidentiary standard (potential alternative to ROC).</li> </ul> <p>Outcomes relating to clinical implementation</p> <ul style="list-style-type: none"> <li>- Rates of re-testing</li> <li>- Rates of re-biopsy</li> <li>- Anticipated test turnaround time.</li> </ul> <p><b>ALK testing uptake:</b> Primary metrics on testing use and costs:</p> <ul style="list-style-type: none"> <li>- Estimated number of patients being tested</li> <li>- The number of patients tested per case of ALK +ve result detected</li> <li>- The number of patients tested per case of ALK +ve result treated with crizotinib</li> <li>- The cost of testing per case of ALK +ve NSCLC detected</li> <li>- The cost of testing per case of ALK +ve NSCLC treated with crizotinib.</li> </ul>

**Primary question for public funding**

What is the safety, effectiveness, and cost-effectiveness of diagnostic testing for ALK gene rearrangements to determine eligibility for crizotinib treatment in patients with advanced (Stage IIIB) or metastatic (Stage IV) non-squamous or otherwise unclassified NSCLC (assuming ALK-positive patients receive crizotinib as second line treatment and ALK-negative patients or those not tested are treated with pemetrexed or docetaxel as second line treatment) compared with current practice (no ALK gene rearrangement testing and pemetrexed or docetaxel used as second line treatment)?

**Secondary questions for public funding**

What is the safety, effectiveness, and cost-effectiveness of diagnostic testing for ALK gene rearrangements to determine eligibility for crizotinib treatment in patients with advanced (Stage IIIB) or metastatic (Stage IV) NSCLC without a restriction on histology subtype (assuming ALK-positive patients receive crizotinib as second line treatment and ALK-negative patients or those not tested are treated with pemetrexed or docetaxel as second line treatment) compared with current practice (no ALK gene rearrangement testing and pemetrexed or docetaxel used as second line treatment)?

What is the safety, effectiveness, and cost-effectiveness of diagnostic testing for ALK gene rearrangements to determine eligibility for crizotinib treatment in patients with early NSCLC that have failed first-line treatment and progressed to advanced disease (assuming ALK-positive patients receive crizotinib as second line treatment and ALK-negative patients or those not tested are treated with pemetrexed or docetaxel as second line treatment) compared with current practice (no ALK gene rearrangement testing and pemetrexed or docetaxel used as second line treatment)?

What is the safety, effectiveness, and cost-effectiveness of diagnostic testing for ALK gene rearrangements to determine eligibility for crizotinib treatment in patients with advanced (Stage IIIB) or metastatic (Stage IV) non-squamous or otherwise unclassified NSCLC (assuming ALK-positive patients are receive crizotinib as first line treatment and ALK-negative patients or those not tested are treated with platinum-based chemotherapy as first line treatment and pemetrexed or docetaxel as second line treatment) compared with current practice (no ALK gene rearrangement testing and no use of crizotinib as a treatment option)?

The assessment of the clinical and economic consequences of the introduction ALK gene rearrangement testing by and use of crizotinib as a second line treatment option should focus on:

1. The incremental cost of adding ALK gene rearrangement testing (including IHC screening) to the current diagnostic tests performed on patients with NSCLC (assessed by MSAC).
2. The comparative analytic performance of ALK gene rearrangement testing methods assessed by MSAC).
3. The incremental cost of crizotinib as a second line treatment option for ALK gene rearrangement positive patients over current treatment options (assessed by PBAC).
4. The incremental costs (or cost savings) associated with adverse events resulting from crizotinib treatment (assessed by PBAC).
5. The incremental effectiveness of treating ALK gene rearrangement positive patients with crizotinib over current practice. This should incorporate any differences in the grade or frequency adverse events resulting from treatment with any therapeutic intervention (assessed by PBAC).

Table 6: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
<b>Resources provided to identify eligible population</b>										
Equivalent to current practice										
<b>Resources provided to deliver proposed intervention</b>										
FISH testing (ALK)	MBS	Pathology Lab	To be provided in submission	To be provided in submission						
IHC testing	MBS	Pathology Lab	To be provided in submission	To be provided in submission						
<b>Resources provided in association with comparator (e.g., pre-treatments, co-administered interventions, resources used to monitor or in follow-up, resources used in management of adverse events, resources used for treatment of down-stream conditions)</b>										
Pharmaceuticals (crizotinib, pemetrexed or docetaxel, relevant pre-medications/ concomitant therapies)	PBS	Outpatient	To be provided in submission	To be provided in submission						
Administration cost for pemetrexed or docetaxel	Hospitals / MBS	Blend of inpatient/ outpatient and public and private hospitals	To be provided in submission	To be provided in submission						
Physician visits	MBS	Outpatient	To be	To be						

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
(Oncologist, Respiratory Physician)			provided in submission	provided in submission						
Clinical monitoring (radiological or other imaging, blood counts etc)	MBS	Outpatient	To be provided in submission	To be provided in submission						
Treatment of adverse events	Hospitals / MBS / PBS	Blend of inpatient/ outpatient and public and private hospitals	To be provided in submission	To be provided in submission						
Pharmaceuticals (crizotinib, pemetrexed or docetaxel, relevant pre-medications/ concomitant therapies)	PBS	Outpatient	To be provided in submission	To be provided in submission						
<b>Resources used to manage patients successfully treated with the proposed intervention</b>										
As above (with the exception of crizotinib costs)	See above	See above	See above	See above	As above (with the exception of crizotinib costs)					

## References

- AIHW 2011, Lung cancer in Australia: an overview., Australian Institute of Health and Welfare & Cancer Australia, Canberra.
- Camidge, DR & Doebele RC. Treating ALK-positive lung cancer—early successes and future challenges. *Nat. Rev. Clin. Oncol.* 9, 268–277 (2012); published online 3 April 2012; doi:10.1038/nrclinonc.2012.43
- DoHA 2011, Health Technology Assessment Access Point (HTAAP) Information Pack, Department of Health and Ageing, Canberra.
- Francis, H. & Solomon, B. 2010. The current status of targeted therapy for non-small cell lung cancer. *Intern.Med J.*, 40, (9) 611-618
- Kim, H., Yoo, S.B., Choe, J.Y., Paik, J.H., Xu, X., Nitta, H., Zhang, W., Grogan, T.M., Lee, C.T., Jheon, S. & Chung, J.H. 2011. Detection of ALK gene rearrangement in non-small cell lung cancer: a comparison of fluorescence in situ hybridization and chromogenic in situ hybridization with correlation of ALK protein expression. *J Thorac Oncol*, 6, 1359-66.
- Kwak, E.L., Bang, Y.J., Camidge, D.R., Shaw, A.T., Solomon, B., Maki, R.G., Ou, S.H., Dezube, B.J., Janne, P.A., Costa, D.B., Varella-Garcia, M., Kim, W.H., Lynch, T.J., Fidias, P., Stubbs, H., Engelman, J.A., Sequist, L.V., Tan, W., Gandhi, L., Mino-Kenudson, M., Wei, G.C., Shreeve, S.M., Ratain, M.J., Settleman, J., Christensen, J.G., Haber, D.A., Wilner, K., Salgia, R., Shapiro, G.I., Clark, J.W., & Iafrate, A.J. 2010. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N.Engl.J.Med.*, 363, (18) 1693-1703
- McDermott, U., Iafrate, A.J., Gray, N.S., Shioda, T., Classon, M., Maheswaran, S., Zhou, W., Choi, H.G., Smith, S.L., Dowell, L., Uikus, L.E., Kuhlmann, G., Greninger, P., Christensen, J.G., Haber, D.A., & Settleman, J. 2008. Genomic alterations of anaplastic lymphoma kinase may sensitize tumors to anaplastic lymphoma kinase inhibitors. *Cancer Res.*, 68, (9) 3389-3395
- NHMRC 2004, Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer, National Health and Medical Research Council, Canberra.
- Popat, S., Vieira de Araujo, A., Min, T., Swansbury, J., Dainton, M., Wotherspoon, A., Lim, E., Nicholson, A.G., & O'Brien, M.E.R. 2011. Lung Adenocarcinoma with Concurrent Exon 19 EGFR Mutation and ALK Rearrangement Responding to Erlotinib. *Journal of Thoracic Oncology*, 6, (11) 1962
- Shaw, A.T., Yeap, B.Y., Mino-Kenudson, M., Digumarthy, S.R., Costa, D.B., Heist, R.S., Solomon, B., Stubbs, H., Admane, S., McDermott, U., Settleman, J., Kobayashi, S., Mark, E.J., Rodig, S.J., Chirieac, L.R., Kwak, E.L., Lynch, T.J., & Iafrate, A.J. 2009. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J.Clin.Oncol.*, 27, (26) 4247-4253
- Solomon, B., Varella-Garcia, M., & Camidge, D.R. 2009. ALK gene rearrangements: a new therapeutic target in a molecularly defined subset of non-small cell lung cancer. *Journal of Thoracic Oncology*, 4, (12) 1450
- Tracey, E., Ling, L., Baker, D., Dobrovic, A., & Bishop, J. 2009, Cancer in New South Wales: Incidence and Mortality 2007, Cancer Institute NSW, Sydney.
- Yang, P., Allen, M.S., Aubry, M.C., Wampfler, J.A., Marks, R.S., Edell, E.S., Thibodeau, S., Adjei, A.A., Jett, J., & Deschamps, C. 2005. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. *Chest.*, 128, (1) 452-462

Yi, E.S., Boland, J.M., Maleszewski, J.J., Roden, A.C., Oliveira, A.M., Aubry, M.C., Erickson-Johnson, M.R., Caron, B.L., Li, Y., Tang, H., Stoddard, S., Wampfler, J., Kulig, K., & Yang, P. 2011. Correlation of IHC and FISH for ALK gene rearrangement in non-small cell lung carcinoma: IHC score algorithm for FISH. *J.Thorac.Oncol.*, 6, (3) 459-465

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