Australian Government

Department of Health

Application 1454:

Diagnostic testing for ROS proto-oncogene 1 (ROS1) rearrangements in non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment

PICO Confirmation

(to guide a new application to MSAC)

(Version 1.0)

This PICO Confirmation Template is to be completed to guide a new request for public funding for new or amended medical service(s) (including, but not limited to the Medicare Benefits Schedule (MBS)). It is relevant to proposals for both therapeutic and investigative medical services.

Please complete all questions that are applicable to the proposed service, providing relevant information only.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment (HTA Team) on the contact number and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

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Background

Diagnostic testing for ROS proto-oncogene 1 (ROS1) gene rearrangement is a new test that is not available to Australian patients outside of participation in clinical trial assessing the pharmaceutical agent crizotinib. This application is requesting a Medicare Benefits Schedule (MBS) listing for testing of ROS1 rearrangements in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment.

This application is part of a co-dependent assessment. Patients who harbour ROS1 gene rearrangement may respond to treatment with crizotinib. Crizotinib is currently listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive advanced NSCLC.

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Summary of PICO/PPICO criteria to define the question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Component	Description
Patients	Patients with NSCLC, which is of non-squamous histology or histology not otherwise specified, with documented absence of activating mutations of either the EGFR gene or the ALK gene. The applicant requests that only patients with documented evidence of a positive ROS1 IHC examination result, defined as a staining intensity score of 2+ or 3+ are to be eligible for ROS1 testing.
Prior tests (for investigative medical services only)	Tests required to confirm diagnosis of NSCLC. Tests required to confirm negative for EGFR and ALK. Pre-screening for evidence of ROS1 immunoreactivity by IHC examination.
Intervention	FISH testing for ROS1 gene rearrangement to determine if the proposed PBS requirements relating to access to crizotinib are fulfilled. Alternative assays include: IHC [a]; reverse-transcriptase-polymerase-chain reaction (RT-PCR); Sanger sequencing; and next-generation sequencing (NGS)
Comparator	Management without genetic testing (no testing and standard care).
Outcomes	For analytic performance: • Sensitivity, specificity, positive predictive value, negative predictive value Comparative performance of methods:

Component	Description
	• Concordance with evidentiary standard; ROC; reclassification index Relating to ROS1 rearrangement testing: • Rates of re-testing, rates of re-biopsy, estimated number of patients tested; cost of testing per case of detected ROS1 positive Relating to co-dependent drug crizotinib: • Overall survival, progression free survival, quality of life, adverse events.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; FISH = fluorescent in-situ hybridisation; IHC = immunohistochemical; NSCLC = non-small cell lung cancer; ROC = receiver operating characteristics; ROS1 = ROS proto-oncogene 1

[a] The applicant proposes IHC be performed as a complementary test with FISH testing.

PICO or PPICO rationale for therapeutic and investigative medical services only

Population

The proposed population for ROS1 testing are patients with locally advanced or metastatic NSCLC, which is of non-squamous histology or histology not otherwise specified, with documented absence of activating mutations of either the epidermal growth factor receptor (EGFR) gene or the ALK gene.

The outcome of this test will determine whether the patients are eligible for subsequent treatment with crizotinib. Crizotinib is currently only PBS-listed for the treatment of patients with ALK-positive advanced NSCLC. **REDACTED**

ROS1 gene rearrangement in NSCLC

The ROS1 encodes an orphan receptor kinase related to ALK. ROS1 proto-oncogene receptor tyrosine kinase is activated by chromosomal rearrangement in a variety of human cancers including NSCLC [1]. Rearrangement leads to fusion of a portion of ROS1 that includes the entire tyrosine kinase domain with 1 of 12 different partner proteins. The resulting ROS1 fusion kinases are constitutively activated and drive cellular transformation.

ROS1 has high homology with ALK in its protein kinase domain [2]. The ALK and ROS1 rearrangements rarely occur in the same tumour, with each defining a unique molecular subgroup of NSCLC [1].

The National Comprehensive Cancer Network Guidelines for NSCLC (2017) report that crizotinib also stops growth signals from ROS1 [3], similar to ALK.

Characteristics of patients with ROS1 rearrangement

Clinical characteristics of NSCLC patients with ROS1 rearrangements are similar to patients with ALK-rearranged NSCLC [4]. ROS1 rearrangements are more commonly found in patients who have never smoked or who have a history of light smoking and who have histological features of adenocarcinoma [1, 2, 5].

Estimates of the size of the testing population

The 2014 incidence and pathology estimates for lung cancer presented by the applicant are given below.

Table 1: Incidence estimates for NSCLC - applicant submitted

Incidence	Estimated number
Incidence estimate of all lung cancers in 2014	11,580
Incidence of NSCLC	9,843 (85% of all lung cancers)

References for applicant supplied data are: Francis and Solomon 2010 [6]; AIHW 2014 [7].

The 2016 incidence and 2007 pathology estimates for lung cancer are available and are presented in the table below. The applicant should consider whether these represent more reliable estimates.

Table 2: Incidence estimates for NSCLC - more recent estimates identified during evaluation

Incidence	Estimated number
Incidence estimate of all lung cancers in 2016	12,203 [8]
Incidence of NSCLC	7,663 (62.8% of all lung cancers) [9]

ROS1 rearrangements occur in approximately 1% of patients with NSCLC [1, 10], although this estimate varies. Studies have reported incidence rates between 0.9% and 1.7% [5, 11]. The National Comprehensive Cancer Network Guidelines for NSCLC report that about 2 out of every 100 lung cancers (2%) consist of cells with a ROS1 gene rearrangement.

Rationale

The applicant has requested that ROS1 rearrangement testing be conducted at diagnosis.

The applicant has indicated that in Australia, tumour tissue samples are collected by a respiratory physician/surgeon/interventional radiologist as part of routine clinical practice during the initial diagnosis of NSCLC patients. 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; and percutaneous transthoracic core biopsy. The applicant has noted that bronchoscopy is preferred as the amount of tissue obtained using fine needle aspiration is often insufficient for molecular testing. The applicant has further noted that fine needle aspiration carries a greater risk of complications for the patient. The tissue samples acquired from biopsy (specimen) are then sent to the pathologist who performs and interprets the laboratory testing.

Based on the outcome, the patient is referred back to the respiratory physician/surgeon, or to a medical oncologist, who then communicates the clinical diagnosis. Medical oncologists may also request that the pathologists conduct additional molecular tests, in situations where the clinical profile, or results of the diagnostic reports warrant further investigation.

Thus, the applicant has proposed that ROS1 rearrangement testing is for newly diagnosed patients, as part of a screening algorithm sequential to the existing ALK and EGFR testing. The clinical evidence for the proposed population consists of a phase 1 study (PROFILE 1001), a single-arm, dose-finding trial. In the PROFILE 1001, only 14% of patients were treatment naïve for metastatic

disease [11] The applicant may consider whether the ROS1 test could be reserved for patients who have undergone at least one prior line of chemotherapy.

Prior test (investigative services only - if prior tests are to be included)

The applicant has suggested that ROS1 fluorescent in-situ hybridisation (FISH) testing be conducted as part of a screening algorithm sequential to the existing ALK and EGFR testing. According to the proposed MBS descriptor, only those patients who are documented to be both ALK- and EGFR-negative should be eligible for the proposed medical service for ROS1 gene rearrangement FISH testing, to inform the eligibility for crizotinib.

In addition, the applicant requested that patients be pre-screened for evidence of ROS1 immunoreactivity by immunohistochemical (IHC) examination. The applicant specified that only patients with documented evidence of a positive ROS1 IHC examination result, defined as a staining intensity score of 2+ or 3+, are to be eligible for the proposed medical service for ROS1 testing.

Studies have shown that IHC could also be considered an alternate method to FISH [12, 13], which is discussed below.

Intervention

The applicant is seeking to have FISH listed on the MBS as the diagnostic testing strategy for ROS1 gene rearrangement to identify patients eligible for crizotinib treatment.

<u>FISH testing for ROS1 gene rearrangement:</u>

The presence of ROS1 rearrangement can be clinically detected by FISH.

The FISH technique is performed on formalin-fixed paraffin-embedded tumour tissue, using commercially available ROS1 probes such as the Zytolight SPEC ROS1 dual-colour break-apart arrangement probe and other commercial products [10]. Several different ROS1 FISH assays have been developed, which generally use red or orange and green fluorescent probes to hybridise with sequences adjacent to or including a portion of the ROS1 gene, which is located on chromosome 6.

If a ROS1 gene rearrangement is present, the two probes become separated, resulting in a 'split' signal. Isolated 3' signals can also be observed in the setting of ROS1 rearrangements. Specimens are deemed positive (i.e. rearranged) if more than 15% of tumour cell nuclei demonstrate split or isolated 3' signals [14, 15]. The FISH test required at least 15% of a minimum of 50 evaluated nuclei containing a ROS1 gene rearrangement to be classified as ROS1 positive [10].

In the absence of a ROS1 rearrangement, the overlapping probes produce a fused or yellow signal.

Pre-requisites for ROS1 gene rearrangement testing

An adequate tissue sample must be collected ahead of ROS1 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; and percutaneous transthoracic core biopsy. For patients who have developed metastatic disease following treatment for earlier stage NSCLC, pathology testing is typically performed on surgically resected tumours.

The applicant stated that in the majority of cases, the sample obtained during the initial biopsy is sufficient for conducting testing for both activating mutations of the EGFR gene and ALK gene rearrangement. Thus, the applicant has noted that additional procedures are rarely required. However, the proposed sequential testing algorithm increases the probability that there will be insufficient sample material for testing and increase the repeat biopsy rate, leading to patient harm and increased costs (12% of samples were not tested due to insufficient tissue; [16]) In addition, the demand for biopsy sample for pathology testing is increasing with the number of tests being performed. This is likely to increase further with ROS1 rearrangement testing. Further, the original biopsy sample may be of insufficient quality to perform ROS1 testing.

The applicant may consider simultaneous testing rather than sequential testing to reduce the probability that there will be insufficient sample material for testing and to reduce repeat biopsy rate.

Delivery of the intervention

Testing for ROS1 gene rearrangement in NSCLC patients would be ordered by the medical oncologist or respiratory physician. A pathologist would be responsible for examining and interpreting the results of sample testing.

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 ROS1 gene rearrangement testing developed by the Royal College of Pathologists of Australasia.

Consistent with the final protocol for ALK testing, it is anticipated that ROS1 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 ROS1 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.

Similar to the ALK gene rearrangement, the ROS1 gene rearrangement is stable and not affected by prior treatment. Therefore, each patient would require testing only once (albeit that retests might be required if the initial sample is of insufficient quality or quantity at the time of testing).

The applicant has noted that there are currently no commercially available FISH tests for ROS1 testing in Australia; only ROS1 Break Apart FISH probes are commercially available at present. The applicant has further noted that individual centres currently develop and validate their own modified 'in house' FISH protocols for detecting ROS1 rearrangements.

Rationale: *Testing for the ROS1 gene rearrangement using tests other than FISH*

The applicant stated that FISH was considered the gold standard assay for detection of ALK rearrangements and consequently, many early ROS1 screening studies used FISH as the predominant testing tool [14]. FISH was also the predominant diagnostic method used in the Phase I study of crizotinib in advanced ROS1-rearranged NSCLC [1]. Nevertheless, there are potential limitations with using FISH testing for ROS1 rearrangement [14]:

- FISH is a technically challenging technique and is not uniformly available in all laboratories;
- Certain ROS1 rearrangements may be missed with break-apart FISH assays; and
- FISH does not provide detail on specific ROS1 fusion partners [5].

Alternative, complementary methods that could be used to confirm the presence of known ROS1 rearrangements and identify the translocation partner in specimens with sufficient tissue to obtain RNA include:

- IHC alone;
- Reverse-transcriptase-polymerase-chain reaction (RT-PCR); and
- Next generation sequencing (NGS).

IHC offers an alternative and universally available option for pathology laboratories unable to carry out FISH [13]. The applicant has presented key studies that investigated the sensitivity and specificity of the IHC screening method used to predict ROS1 rearrangement. Jin et al. (2015) reported that the best criterion to detect ROS1- rearrangement by IHC was an H-score ≥100, with a sensitivity and specificity of 90% and 93.5% respectively [17]. However, other studies have shown that IHC testing for ROS1 is not particularly sensitive and specific (sensitivity ranges from 33%-100% and specificity ranges from 15%-99% [18]).

Fusion specific RT-PCR kits are commercially available. NGS provides massive parallel sequencing, and is considered as a quicker technique. When combined with NGS, RT-PCR allows specific identification of the fusion partners [13].

Should ROS1 gene rearrangement testing become MBS-funded it could be expected that there will be inter-laboratory variation in the methodological approaches to testing.

REDACTED The applicant has advised that considering that genetic mutation testing in cancer is a rapidly evolving field, the applicant is willing to work with the Department of Health to finalise the details of the restriction.

Clinical evidence

The role of ROS1 testing in predicting patient response to crizotinib was identified in a phase 1 study. The phase 1 study was originally designed to include an initial dose-escalation phase, followed by an expansion phase in which the maximum dose established in the initial phase would be evaluated in molecularly defined cohorts of patients [1]. The protocol was later amended to include an expansion cohort of patients with advanced, ROS1-rearragened NSCLC.

Patients had histologically confirmed, advanced NSCLC with a ROS1 rearrangement. Of the 50 patients, 98% (49/50) were identified with ROS1 rearrangement using the break-apart FISH test. All patients with positive results on FISH had more than 15% split signals. For the remaining patient, a RT-PCR assay was used [1]. Other eligibility criteria included an age of at least 18 years, an Eastern Cooperative Oncology Group performance status of 0 to 2 (on a scale of 0 to 5, with 0 indicating the patient is fully active and able to carry on all pre-disease activities without restriction and 5 indicating that the patient has died), adequate organ function, and measurable disease according to the Response Evaluation Criteria in Solid Tumours (RECIST).

Treatment of advanced NSCLC with ROS1 rearrangement

Currently, there are no treatments either TGA approved or listed on the PBS for the targeted treatment of patients with NSCLC with ROS1 rearrangement (although non-targeted treatments are available, refer to Comparator section). Patients with advanced NSCLC are referred to a medical oncologist for ongoing management.

Crizotinib is the co-dependent pharmaceutical medicine. The applicant has advised that crizotinib may only be prescribed by a specialist medical practitioner. Crizotinib is currently TGA-registered and PBS-listed for the treatment of patients with ALK-positive NSCLC. **REDACTED**

In the phase 1 study (described above), crizotinib was administered orally at the standard dose of 250mg twice daily in continuous 28-day cycles. Treatment continued until the occurrence of RECIST-defined disease progression or clinical deterioration, unacceptable toxic effects, withdrawal from the study, or death. In patients with RECIST-defined progression, the study treatment could be continued at the investigator's discretion with approval from the sponsor [1]. In the expansion cohort of patients with advanced, ROS1-rearranged NSCLC, the primary end point was the response rate [1].

Among the 50 patients, three patients had a complete response (6%), 33 patients had a partial response (66%), and nine patients had stable disease as their best response (18%). The overall response rate was 72% (95% confidence interval (CI): 58% - 94%). The median time to the first response was 7.9 weeks and the estimated median duration of response was 17.6 months (95% CI: 14.5 – not reached) [1]. The median duration of treatment for the 50 patients was 64.5 weeks (range 2.3; 182.0) and the median progression-free survival was 19.2 months (95% CI: 14.4 – not reached).

In terms of safety, the most common events (all grades) were visual impairment (82%), diarrhoea (44%), nausea (40%), peripheral oedema (40%), constipation (34%), and vomiting (34%). Other

common events were elevated aspartate aminotransferase level (22%), fatigue (20%), dysgeusia (18%) and dizziness (16%). The majority of treatment-related adverse events were Grade 1 or 2 (94%) and the most common treatment-related Grade 3 adverse events were hypophosphatemia (10%), neutropenia (10%) and elevated aspartate aminotransferase level (4%).

Estimates of the size of the testing population:

ROS1 rearrangements occur in approximately 1% of patients with NSCLC [11]. The estimated prevalence and utilisation of the proposed MBS service are presented in the table below. The estimated patient numbers were based on:

- The estimated incidence of all lung cancers;
- The estimated incidence of advanced lung cancer;
- The estimated incidence of recurrent lung cancer;
- The estimated incidence of non-squamous NSCLC;
- The assumed sensitivity **REDACTED** and specificity **REDACTED** of IHC pre-screening for ROS1 positivity;
- An assumed uptake rate of **REDACTED**.

Table 3: Estimated utilisation rates of FISH ROS1 testing – presented by the applicant

Variables	
Incidence of lung cancer in Australia	11,573 [a]
Incidence of advanced lung cancer at diagnosis	8,101 [b]
Incidence of recurrent lung cancer	530 [c]
Total new advanced lung cancer cases/ year	8,630
Incidence of non-squamous NSCLC	4,022 [d]
Advanced non-squamous NSCLC patients who are both EGFR and ALK-negative	3,223 [e]
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REDACTED	**REDACTED**

Note:

[a] The applicant assumed an incidence rate of 47.2 per 100,000 based on the AIHW ACIM books (2012 data extrapolated) [19]

[b] The applicant reported a rate of 70% based on Walter et al. 2012 [20]

[c] The applicant reported a 1-prevalence for patients diagnosed with localised disease = 63.2%; recurrence rate =28% based on Walter et al. 2012 [20]

[d] The applicant assumed 46.6% of advanced NSCLC was non-squamous, consistent with the final DAP of MSAC 1250

[e] The applicant reported that 15% of patients are EGFR positive and 4.9% are ALK positive. Thus, 80.1% will be EGFR and ALK-negative.

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The applicant has argued that by using an IHC pre-screening test, a strategy similar to that used for the current testing for ALK gene rearrangements NSCLC patients, the majority of patients who are

ROS1-negative will be excluded. This may potentially reduce the resource requirements and time associated with the proposed ROS1 FISH testing.

Comparator

Comparator for ROS1 gene rearrangement testing

This application is seeking to have ROS1 gene rearrangement testing using the FISH technique listed on the MBS. To date, most clinical trials assessing the efficacy of crizotinib have used the Vysis Break Apart FISH probe kit manufactured by Abbot Molecular Diagnostics.

However, if alternate methods of testing are considered (i.e. RT-PCR or IHC alone), the comparative performance of alternate methods for determining ROS1 gene rearrangement status should be compared with FISH as the evidentiary standard.

Comparator for clinical practice

The applicant stated that patients with ROS1-rearranged NSCLC are not currently being routinely identified. Given that both ROS1 gene rearrangement and treatment with crizotinib are novel interventions, the appropriate comparator for assessment is current clinical practice; i.e. standard care with no genetic testing. Standard care comprises platinum-based therapy (most commonly carboplatin plus gemcitabine) first-line, and pemetrexed or docetaxel second-line (refer to "Current clinical management algorithm for identified population" below).

Therefore, 'no testing' will be replaced by the new medical service which is being proposed in this co-dependent submission.

Outcomes

The applicant nominated the following efficacy and safety outcomes:

Safety outcomes:

- Adverse events
- Treatment interruptions
- Treatment discontinuations.

Efficacy outcomes:

- Objective tumour response rates
- Duration of response
- Progression-free survival
- Overall survival
- Quality adjusted survival.

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

Other outcomes measures that should also be considered are listed below.

Outcome measures suitable to assess the analytic performance of FISH testing for ROS1 gene rearrangement include:

- Sensitivity
- Specificity
- Positive predictive value
- Negative predictive value.

Measures of comparative performance of ROS1 gene rearrangement testing methods:

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

Outcomes relating to ROS1 rearrangement testing:

- Rates of re-testing
- Rates of re-biopsy
- Estimated number of patients tested
- Cost of testing per case of detected ROS1 positive.

Healthcare system

Healthcare resources that are most likely to be affected should ROS1 gene rearrangement testing and treatment with crizotinib become available include:

- The additional cost of IHC pre-screening test
- The additional cost of performing ROS1 gene rearrangement testing
- The cost of re-biopsy
- The cost of treating ROS1 gene rearrangement positive patients with crizotinib
- The potential reduced utilisation of any therapeutic options resulting from crizotinib treatment of ROS1 gene rearrangement positive patients (e.g. reduced use of platinum-based therapy, pemetrexed or docetaxel noting that this reduction might not occur in all patients as crizotinib might add a line of treatment rather than replace existing treatments)
- The potential costs for treating adverse events from treatment (with any therapeutic agent)
- Costs associated with ongoing patient monitoring, e.g. physician visits.

Current clinical management algorithm for identified population

Currently, there are no tests for ROS1 gene rearrangement and no treatments either TGA approved or listed on the PBS for the targeted treatment of patients with NSCLC with ROS1 rearrangement (note that non-targeted treatments are available). Patients with advanced NSCLC are referred to a medical oncologist for ongoing management.

The first treatment option for patients with non-squamous NSCLC and negative EGFR and negative ALK testing consists of platinum doublet (chemotherapy, most commonly carboplatin plus gemcitabine). The second line treatment options available for patients with advanced NSCLC include:

- The untargeted therapies pemetrexed and docetaxel.
- The targeted therapies erlonitib and gefitinib. Gefitinib is only TGA-registered and PBS-listed for patients with activating EGFR mutations. Erlotinib is TGA-registered for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy, regardless of EGFR mutations. However, erlotinib is only PBS-listed for patients with activating EGFR mutations (unless treatment was initiated prior to 1 August 2014). Therefore, neither would be relevant to the proposed population for crizotinib.

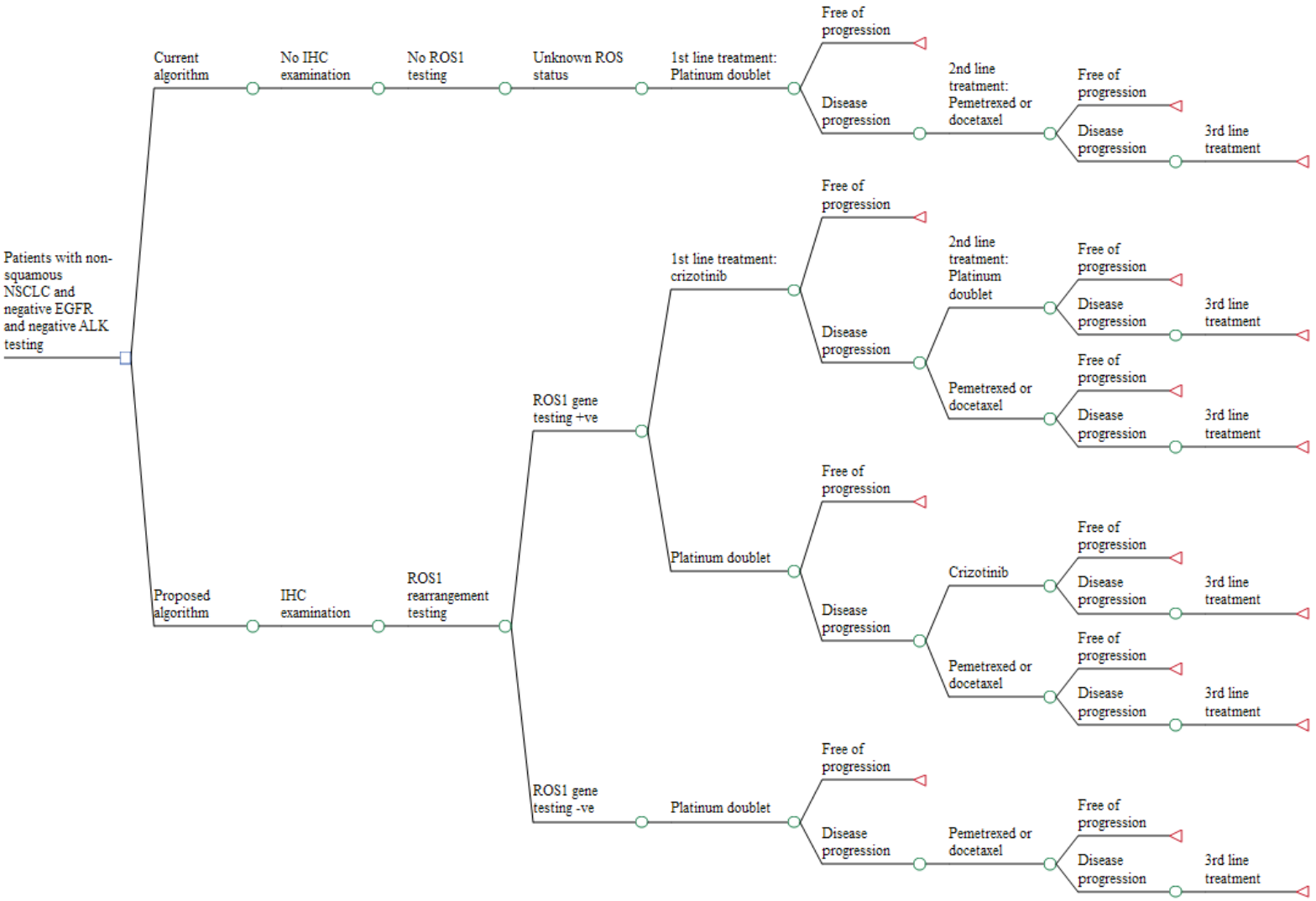
The current clinical management algorithm is presented in the upper branch of Figure 1.

Proposed clinical management algorithm for identified population

Should ROS1 gene rearrangement testing become MBS-funded it is expected that patients with non-squamous NSCLC and negative EGFR and ALK testing would, at diagnosis, undergo IHC screening for evidence of ROS1 immunoreactivity. Patients with a staining intensity score of 2+ or 3+ would undergo ROS1 testing.

Patients with ROS1 rearrangement would then receive crizotinib if crizotinib is PBS listed for treatment of patients with ROS1-positive NSCLC. The proposed clinical algorithm, with ROS1 rearrangement testing available, is presented in the lower branch of Figure 1. The proposed clinical algorithm assumes that crizotinib could be available as first or later line of treatment.

Figure 1: Current and proposed clinical algorithm for the treatment of patients with advanced NSCLC and ROS1 positive rearrangement



Proposed economic evaluation

The clinical claim proposed by the applicant is that ROS1 gene rearrangement testing followed by treatment with crizotinib in patients harbouring ROS1 rearrangements is associated with clinical advantages with respect to disease control. Hence the clinical claim is driven by two factors:

- The performance of the ROS1 gene rearrangement test
- The efficacy of crizotinib treatment in patients that have been identified as ROS1 gene rearrangement positive.

The applicant argued that the overall claim is for superiority.

The type of economic evaluation to be undertaken will be driven by these clinical claims. Given that crizotinib is a new treatment option for advanced NSCLC, and the clinical utility of ROS1 gene rearrangement testing must be established, it could be expected that a cost-effectiveness analysis be conducted.

Proposed item descriptor

The applicant has proposed the following MBS item descriptor based on the proposed testing algorithm for ROS1 rearrangement, in which patients have an IHC pre-screen, followed by confirmatory ROS1 FISH testing. The MBS item numbers for IHC are MBS 72846-72850. The proposed fee for the proposed MBS service is the same as the fee for FISH testing for ALK and EGFR.

Category 6 – Pathology Service
MBS item number: to be advised Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient: - with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is of non-squamous histology or histology not otherwise specified, - with documented evidence of ROS1 immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+, and - with documented absence of either activating mutations of the epidermal growth factor recept (EGFR) gene or anaplastic lymphoma kinase (ALK) gene rearrangement, requested by a specialist or consultant physician to determine if requirements relating to ROS1 gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: **REDACTED**; Benefit: 75% = **REDACTED**; 85% = **REDACTED** Proposed relevant explanatory notes: Testing must be performed in laboratories that have received National Association of Testing Authorities (NATA) accreditation.

This appears to be based on the MBS item descriptor for ALK testing (Item 73341).

The applicant acknowledged the fact that genetic mutation testing in cancer is a rapidly evolving field; e.g. methodologies other than FISH are available and continue to be developed. Therefore, the applicant is willing to work with the Department of Health to finalise the details of the restriction.

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