MSAC Application 1173: Final Decision Analytical Protocol (DAP) to guide the assessment of Epidermal Growth Factor Receptor (EGFR) gene mutation testing for eligibility for erlotinib treatment as a first-line therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

January 2012

Table of Contents

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MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Australian Government Health Minister to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Commonwealth Minister for Health and Ageing 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 EGFR gene mutation analysis as a marker for first-line treatment with erlotinib in patients with locally advanced or metastatic NSCLC. The DAP is intended to guide the assessment of the safety, effectiveness and cost-effectiveness of EGFR gene mutation testing in order to inform the assessment of the intervention and thus MSAC's decision-making regarding its public funding. It was finalised after inviting relevant stakeholders to provide input to the protocol. PASC noted that other matters were raised in the public and stakeholder feedback and the response from the applicant, but judged that addressing these would not substantially alter the final DAP.

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

Patients – specification of the characteristics of the population or patients in whom the intervention is to be considered for use;
Intervention – specification of the proposed intervention
Comparator – specification of the therapy most likely to be replaced, or added to, by the proposed intervention
Outcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

Purpose of application

In June 2011, an application was received from Roche Diagnostics Australia by the Department of Health and Ageing, requesting an MBS listing for genetic testing for mutations in the epidermal growth factor receptor (EGFR) gene in previously untreated locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC) patients, to determine eligibility for first-line treatment with erlotinib. EGFR gene mutation testing is a co-dependent technology with the treatment of NSCLC with first-line erlotinib. Erlotinib, a tyrosine kinase inhibitor (TKI), has been previously approved by PBAC for use as a monotherapy for unselected NSCLC patients who have received prior platinum-based chemotherapy for NSCLC. In this application, it is being proposed as a first-line treatment for NSCLC patients with locally advanced or metastatic tumours who test positive for EGFR activating mutations. EGFR gene mutation testing has also been proposed as a marker for first-line treatment of NSCLC with the TKI gefitinib.

An independent evaluator group, as part of its contract with the Department of Health and Ageing, has drafted an earlier version of this DAP.

Background

Current arrangements for public reimbursement

There is currently no MBS listing for EGFR gene mutation testing to determine eligibility for treatment with erlotinib in *previously untreated* locally advanced or metastatic NSCLC patients. Approval is being sought for public funding for EGFR gene mutation testing in association with first-line erlotinib treatment for NSCLC. Erlotinib has been PBS listed for treatment of *unselected* NSCLC patients *who have received prior platinum-based chemotherapy*, and has not yet been assessed by the PBAC for use in *previously untreated patients* with locally advanced or metastatic NSCLC with confirmed EGFR gene mutation. EGFR gene mutation testing is *not* a requirement for eligibility for PBS subsidised erlotinib treatment in patients with locally advanced or metastatic NSCLC who have received prior chemotherapy.

MSAC has previously considered an application for public funding for EGFR gene mutation testing as a co-dependent service relating to gefitinib treatment for NSCLC. In December 2010, MSAC's recommendation to the Minister was *'MSAC supports public funding for testing in the limited circumstance of determining tumour EGFR activating mutation status to contribute to a determination of eligibility for currently PBS-subsidised gefitinib for a patient with locally advanced or metastatic non-small cell lung cancer.' (DoHA 2010).*

With regard to EGFR gene mutation testing approval for second- and third-line gefitinib treatment, MSAC noted that there was potential for possible expansion of the gefitinib PBS listing to include first-line treatment of locally advanced or metastatic NSCLC. Another application is currently being assessed by MSAC to also consider EGFR gene mutation testing to determine eligibility for first-line gefitinib.

An MBS fee of between $400 and $606 was estimated by MSAC in 2010 when considering EGFR gene mutation testing for *gefitinib* eligibility (DoHA 2010). The cost of EGFR gene mutation testing would be expected to be similar for *first-line erlotinib* eligibility however it may vary depending on the choice of assay and testing platform used. EGFR gene mutation testing at the time of application was available in five Australian laboratories, namely the Peter MacCallum Cancer Centre (Melbourne), SA Pathology (South Australia), PathWest (Western Australia), Healthscope Ltd (Victoria) and Royal Brisbane Hospital (Queensland).

Erlotinib and gefitinib are tyrosine kinase inhibitors that are potentially effective in treating NSCLC patients with an activating EGFR gene mutation (EGFR M+). The intervention discussed here considers only EGFR gene mutation testing for NSCLC patients as a prerequisite for treatment with first-line erlotinib, that is, as a co-dependent service. EGFR tests are available that identify these mutations. A broader application of EGFR gene mutation testing without a co-dependent pharmaceutical treatment was not considered appropriate by MSAC.

While there are several methods for detecting EGFR gene mutation status in tumours, there are a number of factors that affect accuracy and reliability. In its assessment of EGFR gene mutation testing for access to gefitinib, MSAC noted that there were issues relating to when best to perform the test, the tumour load in the biopsy sample, mutation stability in and between primary and secondary tumours, and the impact of mutations in other genes. MSAC also noted that there are issues with interpretation of test results such as classification of mutations as activating, neutral or resistant, and prioritisation in cases of multiple mutations. PBAC has advised (with respect to EGFR gene mutation testing for gefitinib eligibility) that the method of determination of EGFR gene mutation status does not need to be specified and should not be limited to direct DNA sequencing, but should allow for use of other appropriate methods. In this application the testing method is not specified, however all EGFR gene mutation testing must be performed in laboratories accredited by the National Association of Testing Authorities (NATA) for genetic testing in humans if MBS reimbursement is to be sought.

Regulatory status

An assay designed for EGFR gene mutation testing is classified as an in vitro diagnostic medical device (IVD). IVDs are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical

diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2009).

The Therapeutic Goods Administration (TGA) regulatory framework for IVDs changed in July 2010. All IVDs now require premarket approval by the TGA (unless they were offered prior to July 1 2010 in Australia where a transition period up to 2014 applies). The new framework also requires all in-house assays (laboratory developed tests) to also be subjected to a review. Class 4 in-house assays now receive the same level of regulatory scrutiny as commercial kits. EGFR gene mutation testing is a Class 3 IVD and as such is subject to the National Pathology Accreditation Advisory Committee (NPAAC) standard for in-house assays. This provides some oversight (as assessed by NATA audits) by professional peers but it is not subject to the same vigour as commercially available Class 3 IVDs. EGFR gene mutation tests provided as in-house IVDs would be classified as Class 3 in-house IVDs that will require each performing laboratory to obtain NATA approval for their respective laboratory developed test (see Figure 1).

Figure 1: Classification of Class 3 in vitro diagnostic medical devices

Therapeutic Goods (Medical Devices) Regulations 2002 –Schedule 2A

1.3 Detection of transmissible agents or biological characteristics posing a moderate public health risk or high personal risk

1. An IVD is classified as Class 3 IVD medical devices or a Class 3 in-house IVD if it is intended for any of the following uses:
    a. detecting the presence of, or exposure to, a sexually transmitted agent;
    b. detecting the presence in cerebrospinal fluid or blood of an infectious agent with a risk of limited propagation;
    c. detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested;
    d. pre-natal screening of women in order to determine their immune status towards transmissible agents;
    e. determining infective disease status or immune status where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient;
    f. the selection of patients for selective therapy and management, or for disease staging, or in the diagnosis of cancer;
    g. human genetic testing;
    h. to monitor levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient;
    i. the management of patients suffering from a life-threatening infectious disease;
    j. screening for congenital disorders in the foetus.

    Note: For paragraph (f) An IVD medical device would fall into Class 2 under clause 1.5 if:
    k. a therapy decisions would usually be made only after further investigation; or
    l. the device is used for monitoring.
2. Despite subsection (1) an IVD is classified as a Class 3 IVD medical device or a Class 3 in-house IVD if it is used to test for transmissible agents included in the Australian National Notifiable Diseases Surveillance System (NNDSS) list as published from time to time by the Australian government.

Source: http://www.tga.gov.au/industry/ivd-framework-overview.htm [accessed 2nd August 2011]

Laboratories that manufacture in-house Class 3 IVDs are required to notify the TGA of the types of IVDs manufactured in each laboratory for inclusion on a register. These laboratories

must have NATA accreditation for the specific laboratory developed test, in this case EGFR gene mutation testing, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the NPAAC, for each test manufactured. In contrast, commercial manufacturers of Class 2, Class 3 and Class 4 IVDs must hold certification from a regulatory body to show compliance with a suitable conformity assessment procedure (Therapeutic Goods Administration 2009).

Roche Products Australia has submitted to the TGA for erlotinib use in previously untreated EGFR M+ patients in the third quarter of 2011. Roche Diagnostics Australia will be making an application to the TGA for approval of the COBAS EGFR gene mutation Test in Q4 2011, with an estimated approval time in the first quarter of 2012. Earlier recommendations made by MSAC regarding EGFR gene mutation testing stated that *'Testing should be performed in a NATA accredited laboratory, and be ordered by an oncologist. It should also be supported by suitable quality standards and a quality assurance (QA) program specific to EGFR testing developed by the Royal College of Pathologists of Australasia (RCPA).'* (DoHA 2010).

Intervention

Description of the disease

In Australia in 2007 lung cancer was the fourth most commonly reported cancer, comprising 9% of all cancer cases. Lung cancer was also the highest cause of cancer mortality in 2007 with 7,626 deaths reported (62% of deaths were male) and numbers are expected to have increased to an estimated 8,100 deaths in 2010 (59% male) (AIHW 2010). AIHW statistics show a trend of increasing incidence in females with case numbers increasing from 18 to 31 per 100,000 females between 1982 and 2007, and a decreasing rate in males, with case numbers dropping from 85 to 58 per 100,000 in males over the same time period (AIHW 2010).

Lung cancer is diagnosed most often in the later stages of the disease (43% in Stage IV or metastatic cancer and 25% in stage IIIB or locally advanced cancer) with as few as approximately 35% of patients expected to survive beyond one year after diagnosis (MSAC 2010). The median survival for patients with stage III or stage IV lung cancer is two years and the number of lung cancer deaths for one year is predictive of the total number of patients with advanced disease two years prior. For example there were an estimated 7,826 deaths from lung cancer in 2010 which is indicative of a total of 7,826 patients with locally advanced or metastatic disease in 2008.

NSCLC is by far the most common form of lung cancer, accounting for between 80% and 90% of cases (Armour & Watkins 2010; Cataldo et al. 2011), and can be further defined by the following subgroups: i. adenocarcinoma, ii. squamous cell carcinoma, and iii. large cell

carcinoma. Until recently when developed targeted molecular therapies became available, treatment for all three subgroups was similar (Armour & Watkins 2010). While treatment for NSCLC diagnosed in the early stages has made advances, patients with locally advanced or metastatic tumours face chemotherapy (platinum-based doublet chemotherapy is most common) and its subsequent symptoms of toxicity, with response rates reported at less than 30% (Cataldo et al. 2011).

Studies have found that approximately 10% to 20% of NSCLC tumours harbour somatic mutations in the EGFR gene (Ishibe et al. 2011; Keedy et al. 2011). EGFR activation can be the result of protein over-expression, increased gene copy number or mutation of the EGFR gene. Recent trials with drugs targeted towards tumours harbouring activating mutations in the EGFR gene (such as gefitinib, and erlotinib in the first-line setting) have significantly improved the response rate in a subgroup of patients who test positive for one of these mutations (Sequist et al. 2011).

An NSCLC sub-group with activating EGFR gene mutations

The EGFR gene encodes a transmembrane receptor protein with tyrosine kinase activating ability and has a role in the regulation of various developmental and metabolic processes. Under normal circumstances, ligand binding on the cell surface triggers dimerisation of the receptor and phosphorylation of the intracellular tyrosine kinase domain, followed by a cascade of molecular reactions in the EGFR signalling pathway, leading to changes in cell survival and proliferation. There are several known receptors in the EGFR family including HER1 (known as EGFR), HER2 (known for its involvement in breast and gastric cancers), HER3 and HER4. Ligand molecules including epidermal growth factor and other growth factors are known to bind the receptors and trigger the signalling cascade (Armour & Watkins 2010; Cataldo et al. 2011).

A sub-group of NSCLC patients harbour EGFR gene mutations which result in an over-activated intracellular kinase pathway (an activation mutation) and is associated with a form of NSCLC tumour which tends to be resistant to standard platinum-based doublet chemotherapy. Approximately 90% of these mutations occur between exons 18 and 21 of the tyrosine kinase activation domain, with the majority occurring in exon 19 (in-frame deletion or insertion mutations) or in exon 21 at codon 858 (a missense mutation resulting in a leucine to arginine substitution - L858R) (Mazzoni et al. 2011). These mutations increase activation of the EGFR pathway by triggering phosphorylation at the tyrosine kinase binding site, adenosine triphosphate (ATP) binding, and downstream signalling which leads to cell proliferation and development of metastases.

Erlotinib is a tyrosine kinase inhibitor (TKI) designed to compete at the ATP binding site of the kinase domain, thereby inhibiting phosphorylation and receptor signalling, restoring cellular apoptosis (cell death). Its effectiveness stems from the fact that erlotinib has a greater affinity

for the binding site than ATP. The EURTAC and OPTIMAL trials found that first-line erlotinib provides significant clinical benefit when compared with platinum-based doublet chemotherapy in patients with activating EGFR gene mutations (Rosell et al. 2009; Zhou et al. 2011).

It is proposed that by identifying those patients with tumours carrying activating EGFR gene mutations (M+), first-line erlotinib treatment can be allocated most effectively, and those without the mutations (M-) can be treated with other first-line platinum-based chemotherapy regimens.

While inhibiting EGFR has been shown to improve clinical outcomes for patients with activating mutations, resistance to treatment with TKIs eventually develops through a variety of mechanisms. Two primary mechanisms of resistance have been identified. One is a second EGFR point mutation (exon 20, T790M) which acts to prevent erlotinib binding but allows constitutive binding of ATP, and the other is an amplification of the MET receptor tyrosine kinase. Binding of the MET ligand HGF activates an independent cell-proliferative pathway (Cataldo et al. 2011). Although patients with a secondary mutation are resistant to TKIs, once they have stopped treatment the tumour can lose the secondary mutation, and TKIs can be effective once again (Sequist et al. 2011). Patients with a primary resistance mutation of this type will not benefit from erlotinib treatment.

Pre-selection is another factor in the consideration of NSCLC patients for testing. Studies have shown that female sex, Asian origin, never smoking and lung adenocarcinoma are all predictors of activating EGFR gene mutations (Mazzoni et al. 2011; Rosell et al. 2009). While pre-selecting for these factors would increase the proportion of patients testing positive for EGFR gene mutations, there would be those outside these criteria who would be excluded from effective treatment. Further data indicate that 30% of EGFR gene mutations occur in males, 33% in current or former smokers, and 9% occur in large cell carcinomas (Rosell et al. 2009). However squamous cell carcinoma (SCC) has rarely been found harbouring EGFR gene mutations and where a mutation has occurred, response to TKI treatment has been poor when compared to adenocarcinoma. Exclusion of SCC patients on the basis of histological diagnosis has been suggested (Shukuya et al. 2011).

Methods for identification of EGFR gene mutation

EGFR genetic status can be determined by testing cells retrieved from the lung tumour using one of a number of laboratory methods. Genetic sequencing (Sanger sequencing) is a commonly used method for mutation detection in Australia and has the advantage that it can detect any mutation (Ishibe et al. 2011), however this method requires at least 20% tumour cells present in the sample, and can be inaccurate if there is a lower proportion. Many M+ EGFR tumours are heterozygous for the mutant allele (Soh et al. 2009), with biopsy samples needing tumour cells present at a rate of at least 20% to provide reliable sequencing results.

Low tumour cell numbers can lead to false negative results. Tissue preparation techniques can also cause artefacts as formalin fixation and paraffin embedding used for biopsy preparation can cause fragmentation and chemical modification of the DNA sequence of interest (John, Liu & Tsao 2009). There are currently no TGA approved methods available for EGFR gene mutation detection.

There are some in-house (laboratory developed) methods that are used for EGFR gene mutation screening, for example the High Resolution Melt (HRM) method. HRM is currently used at the Peter MacCallum Cancer Centre. HRM identifies samples harbouring an EGFR gene defect but must be followed by sequencing for confirmation and specific identification of the mutation (John, Liu & Tsao 2009). A dual HRM and direct DNA sequencing method was proposed by AstraZeneca in its submission to MSAC for approval of funding for EGFR gene mutation testing for access to PBS listed gefitinib.

Various other methods of EGFR identification are available in kit form and often include PCR amplification of the DNA of interest (this can overcome the need for at least 20% tumour cells in the tissue sample) followed by mutation detection. Most kits are capable of detecting only a specific mutation or set of mutations. The TheraScreen EGFR29 kit is able to detect 29 EGFR gene mutations and was used to test for enrolment of patients in the IPASS gefitinib study (Fukuoka et al. 2011). In the Canadian based erlotinib trial BR.21, EGFR gene mutation status was identified using Sanger sequencing. Roche Diagnostics has developed the cobas® 4800 EGFR gene mutationTest which is a Real Time PCR diagnostic assay capable of identifying 41 mutations in exons 18 to 21. The analysis, including the DNA isolation process, can be completed in less than 8 hours providing the results in one day.

Timing of EGFR identification within disease progression

Currently, erlotinib is approved as a second or third-line therapy for NSCLC in all patient groups. In contrast, it is proposed that *previously untreated* NSCLC patients with locally advanced or metastatic cancer should receive erlotinib only if they test positive for an activating EGFR gene mutation[1]. The base case that will be assessed is the use of EGFR gene mutation testing at the time of diagnosis of non-squamous NSCLC or NSCLC not otherwise specified.

A strong case has been made to test all patients with NSCLC at diagnosis regardless of the stage of the disease due to the fact that the majority will either present with or eventually progress to advanced or metastatic disease. The advantage of having the test performed at initial diagnosis is having the test result recorded in the patient's medical record, thereby

[1] It should be noted that eligibility for erlotinib as a *second- or third-line* treatment will continue to be available without the requirement for an activating EGFR gene mutation

avoiding the 2-3 week delay in commencing treatment. There would also be considerable time and cost savings by having the reporting pathologist arranging for the test to be performed while actively reporting the case rather than having the test laboratory having to retrieve the samples from another laboratory. Similarly, it would become apparent early in the course of the disease that a sample was unsuitable for testing and a biopsy could be performed before the patient's condition deteriorated.

Although outright cure may be achieved in a small proportion of early stage NSCLC patients through surgery and chemo- or radiotherapy, relapse rates are high (Saijo 2011).The majority of patients progress quickly on to late stage cancer requiring EGFR gene mutation testing to determine the best treatment strategy. It is likely that a relatively low absolute number of tests would be performed on patients who present with early stage disease and never progress to advanced stage disease. The clinical and cost benefits of early testing and treatment planning may outweigh the cost of unnecessary testing.

An alternative is to restrict the timing of EGFR gene mutation testing to be carried out at the time when patients become eligible to receive first-line erlotinib, that is, when they are initially diagnosed with, or their disease progresses to stage IIIB or IV cancer. Approximately 60% to 70% of patients diagnosed with NSCLC present with Stage IIIB or Stage IV disease and could therefore undergo EGFR gene mutation testing at the time of biopsy and diagnosis (DoHA 2010; Mazzoni et al. 2011). The consequences of testing closer to the diagnosis of locally advanced or metastatic disease should be quantitatively addressed in the assessment.

Multiple tumours in patients with metastases present another issue relating to the timing of sample collection as it cannot be assumed that all tumours will carry the EGFR gene mutation, or that a primary tumour EGFR gene mutation will remain stable through the course of the disease. However EGFR gene mutations have been found to occur in the precursor to lung adenocarcinoma, atypical adenomatous hyperplasia, indicating that the mutations can occur very early in the tumour development or are even founder events of NSCLC (Sartori et al. 2008). Current research indicates that there is some discrepancy between the EGFR gene mutation status of primary and corresponding metastatic tumours in advanced NSCLC patients (Sun et al. 2011), although differences in assay technique and sensitivity may account for the variation in results.

Sample collection and preparation

The two methods commonly used in Australia for tissue sampling for EGFR gene mutation testing are (i) bronchoscopy and (ii) percutaneous fine needle aspiration (FNA). Bronchoscopy may allow sampling of endobronchial disease (biopsies, wash, brush); mediastinal masses or lymph nodes (transbronchial needle aspiration with or without endobronchial ultrasound guidance or EBUS); or sampling of peripheral lung lesions (transbronchial biopsies, brushes or washes with or without EBUS). Bronchoscopy is usually carried out by a respiratory physician

and is the preferred method for sample collection as a greater cell mass can usually be obtained. When bronchoscopy is not possible FNA is the method used, usually carried out by radiologists, and is guided by computed tomography (CT) (DoHA 2010). However, core biopsies with a larger bore needle can also be performed by a CT guided percutaneous approach and can provide a larger specimen.

It is critical that sufficient tissue is obtained to carry out a reliable DNA preparation and screening procedure. As previously mentioned, a tumour proportion of at least 20% is required for detection of EGFR gene mutations with Sanger sequencing, due to the heterogeneous nature of the tumour, and the sensitivity of the technique. Tissue biopsy is preferred to FNA, as the latter method is less likely to supply sufficient material for testing (John, Liu & Tsao 2009), and MSAC has noted previously that the quantity of tissue currently collected by either method is often insufficient to conduct satisfactory mutation testing (DoHA 2010). FNA also carries a higher risk to the patient than sample collection via bronchoscopy. Sputum samples and bronchial brushings are unlikely to provide sufficient cellular material for DNA analysis. To reduce the necessity for repeat sampling and testing, sample size and quality should be made a priority. It should be noted that there may be clinical consequences of more invasive sampling, such as an increased rate of adverse effects associated with tissue retrieval, as well as additional costs associated with resampling.

For the detection of somatic EGFR gene mutations, tissue samples are normally processed into formalin-fixed, paraffin-embedded tissue blocks (FFPE) which are then sectioned, stained and mounted onto glass slides. Following mounting, samples would be examined by a suitably qualified clinical scientist. For direct sequencing, samples with a low tumour cell proportion should be enriched by micro-dissection after which DNA extraction can be carried out using a commercially available kit. PCR amplification of the EGFR TK domain exons is followed by sequencing for identification of mutations (John, Liu & Tsao 2009). Where necessary, samples will be transported to a laboratory accredited to carry out EGFR gene mutation testing.

Delivery of the intervention

The applicant proposes that NSCLC patients would require one EGFR gene mutation test in their lifetime. This test would be performed immediately following pathological diagnosis of NSCLC and irrespective of the stage of disease, utilising the same biopsy material used for this diagnosis (base case). Alternatively, this could be performed by retrieving and retesting the biopsy sample when the patient's disease status reaches Stage IIIB or IV (alternative scenario). Approximately 60% to 70% of NSCLC cases are first diagnosed at Stage IIIB or IV (Mazzoni et al. 2011; Molina et al. 2008), with the remaining 30% to 40% diagnosed at earlier stages which would make them ineligible for erlotinib treatment. If the DNA analysis was inconclusive a repeat test may be necessary. At the Peter MacCallum Cancer Centre the rate of re-testing is estimated at 10% of EGFR tests however this rate may be reduced if testing is limited to bronchoscopy and core biopsy samples. In pre-clinical studies reported by Roche

Diagnostics the cobas® EGFR assay exhibited an invalid rate of 3.0% compared to 23.8% by the Sanger method when utilising FFPET as the specimen of choice (Roche Diagnostics Internal data). FNA and pleural effusion samples give a lower cellular yield and the highest re-test rates. Where possible, the repeat test should be carried out using the original biopsy sample, however in some cases further biopsy may be required.

Apart from the situation of inconclusive EGFR gene mutation test results, there are other circumstances in which more than one biopsy or EGFR gene mutation test may be required. Where there are multiple tumours present, more than one biopsy and EGFR gene mutation test may be required to guide treatment, although in practice, it may be decided to sample only the most accessible tumour. Further mutations can occur in the development of the disease, changing EGFR gene mutation status from negative to positive, and inducing resistance to chemotherapy (Sequist et al. 2011). The decision to order further EGFR gene mutation testing under these circumstances is at the oncologist or treating specialist's discretion. However these circumstances would be considered unusual and it is expected that on average there would be one test requested per patient.

EGFR activating mutations occur with greatest frequency in adenocarcinoma NSCLC patients, however they are also known to occur in large-cell NSCLC (Rosell et al. 2009). By restricting EGFR gene mutation testing to those with a diagnosis of non-squamous cell and NOS NSCLC the testing regime will include patient populations most likely to be affected by the mutation (adenocarcinoma and large-cell carcinoma). EGFR gene mutations have been reported to be found in only 0-1.1% of squamous cell NSCLC (Shukuya et al. 2011). NSCLC that has not been categorised by histological diagnosis (i.e. not otherwise specified or NOS) should also be included in the testing regime so as to avoid missing patients who may benefit from first-line erlotinib treatment. Further pre-selection of patients (the frequency of activation mutations is higher in females, Asians and non-smokers) is a consideration however a significant proportion of M+ cases fall outside these demographics.

Prerequisites

A cytological or biopsy sample could be collected by a respiratory physician, radiologist or surgeon although this is only occasionally necessary specifically for the EGFR gene mutation test, as biopsy samples are taken at the time of diagnosis of the disease, and can then be used for DNA analysis. In the base case where patients are eligible for EGFR gene mutation testing at the time of diagnosis of NSCLC, the pathologist who utilises the biopsy sample to confirm the histological diagnosis of NSCLC may initiate a request for EGFR gene mutation testing. Results of the EGFR gene mutation test would be returned to the requesting oncologist or respiratory physician.

In the scenario where EGFR gene mutation testing is restricted to patients with Stage IIIB or IV NSCLC, information regarding the confirmation and histological diagnosis of NSCLC would

have to flow from the pathologist to the treating oncologist or respiratory physician, who would then confirm the disease staging and may send a request back to the pathologist for the patient's biopsy to be retrieved and tested EGFR gene mutation status.

Once the tissue sample has been retrieved by the testing laboratory, an anatomical pathologist would carry out macro-dissection or micro-dissection of the tumour cells so that an appropriate sample is available for DNA extraction. DNA extraction and assay would be performed by a molecular scientist or technician, under the supervision of a senior scientist or pathologist according to NPAAC laboratory supervision standards. Supervising senior scientists are required by the NPAAC to have a PhD or Fellowship in the appropriate discipline, 10 years experience and a minimum of two years as a supervisor in a clinical laboratory. Pathologists require a medical degree followed by five years of specialist training in pathology and examination by the Fellow of the Royal College of Pathologists of Australasia (FRPCA).

In December 2010 MSAC recommended that all EGFR gene mutation testing should only be performed in NATA accredited laboratories. To gain NATA accreditation a laboratory must satisfy standards set by NPAAC. In this instance, such a laboratory would have demonstrated proficiency in its Director's choice of technique for EGFR gene mutation testing. Competence to perform the test will be monitored through the RCPA Quality Assurance Program (QAP) and evaluation of a suitable QAP for EGFR gene mutation testing was in progress at the time of Roche's application submission (Roche Diagnostics Australia 2011).

While it is not proposed that a specific method for EGFR gene mutation testing should be included in the MBS item listing, the choice of technique may depend on factors such as available equipment, skill and experience of staff, case load and case mix. Where laboratories in Australia are already conducting EGFR gene mutation testing it could be expected that no further investment in equipment or staff would be required, although upgrades driven by technology changes may be necessary. Laboratories wishing to establish EGFR gene mutation testing would need to outlay for the testing platform of their choice, and additional outlays to seek NATA accreditation and staff training will be required.

Analysis of EGFR gene mutations is a complex task and depends on a number of conditions for successful completion. Sample size, proportion of tumour cells, artefacts of tissue preparation and interpretation of results all present particular challenges in the detection of somatic mutations (John, Liu & Tsao 2009). For this reason it is likely that the majority of EGFR gene mutation testing will be performed in specialist referral laboratories, located in the major metropolitan areas of Australia. Currently patients are usually required to attend a metropolitan or large regional facility to have a biopsy taken. If EGFR gene mutation testing is not available at the laboratory where the diagnostic analysis is performed, the biopsy sample would be retrieved by the testing laboratory and prepared for DNA analysis. Patients would not be further inconvenienced by this process.

Co-administered and associated interventions

EGFR gene mutation testing is a co-dependent service and is required to determine eligibility for treatment with the TKI erlotinib in *previously untreated* patients with locally advanced or metastatic NSCLC. Erlotinib (TARCEVA®, Roche) comes in tablet form taken orally, and is available as erlotinib hydrochloride in doses of 25mg, 100mg and 150mg (DoHA 2011). The proposed course of erlotinib for patients with previously untreated locally advanced or metastatic NSCLC would be a dose of 150mg daily (Cataldo et al. 2011; Riccardi S 2011; Rosell et al. 2009) until there is further disease progression or until toxicity prevent further use. In contrast the EGFR gene mutation test would on average be required only once in a patient's lifetime.

Should approval be given for MBS listing of EGFR gene mutation testing, it is likely that the utilisation of erlotinib would increase as a first-line therapy for NSCLC patients. At the same time, utilisation of standard platinum-based chemotherapy is likely to decrease for these patients, and the utilisation of erlotinib as a treatment after failure of chemotherapy is also likely to decrease.

Listing proposed and options for MSAC consideration

Proposed MBS listing

Targeted population

It is proposed that EGFR gene mutation testing would either be performed on the patient population at diagnosis of non-squamous NSCLC or NSCLC not otherwise specified (NOS) irrespective of disease stage (base case), or those that have previously untreated locally advanced (Stage IIIB) or metastatic (Stage IV) non-squamous NSCLC or NSCLC not otherwise specified (possible alternative scenario).

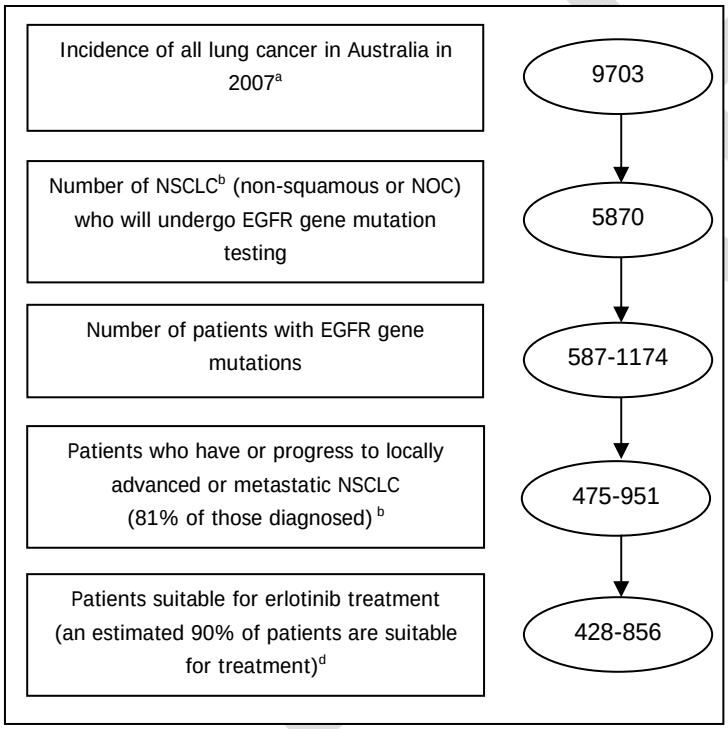
In order to estimate the likely usage of EGFR gene mutation testing and potential eligibility for first-line erlotinib (and/or gefitinib) in the base case, it has been assumed that 89% of all lung cancer is NSCLC and 68% of all NSCLC is non-squamous or NSCLC NOC, based on data from a US study of 5628 lung cancer patients (Yang et al. 2005). It can therefore be assumed that 60.5% (89% x 0.68) of all lung cancer cases are non-squamous NSCLC or NSCLC NOC. Using the incidence of lung cancer in Australia from 2007 (9703 patients; AIHW 2010), it is therefore estimated that 5870 patients per year would be eligible for EGFR gene mutation testing. Somatic EGFR gene mutations have been found to occur in 10% to 20% of patients with NSCLC (Ishibe et al. 2011; Rosell et al. 2009) (587-1174 patients). Approximately 60% to 70% of patients diagnosed with NSCLC are found to be in stage IIIB or IV of the disease (Mazzoni et al. 2011; Molina et al. 2008). However, in the absence of data outlining the percentage of patients staged I, II or IIIA at diagnosis who progress to having locally

advanced or metastatic disease, 5-year mortality data for all stages (I – IV) was used as a proxy for the percentage of all lung cancer cases who either have or progress to have locally advanced or metastatic disease. It is therefore assumed that 81% of patients are either diagnosed as having, or progress to have, locally advanced or metastatic disease each year (587 – 1174 x 0.81 patients) (Yang et al. 2005).

Based on US data on the 5-year mortality rate for all lung cancers, it is assumed that 475 - 951 patients per year would potentially be eligible for treatment with first-line erlotinib or gefitinib. However, only 90% of patients are considered suitable for chemotherapy or TKI treatment (Roche Diagnostics Australia 2011). It is therefore estimated that between 428 and 856 patients per year may receive first-line erlotinib or gefitinib, if their use is approved in patients with previously untreated locally advanced or metastatic NSCLC.

Figure 2 illustrates the number of patients treated under the proposed scenario.

Figure 2: Estimated number of patients treated with first-line erlotinib per year for the proposed base case scenario



Sources: [a](AIHW 2010), [b]calculated from US data (Yang et al. 2005), [c](Ishibe et al. 2011; Rosell R et al 2011), [d]assumption: not all patients will be eligible for treatment due to poor performance status (Roche Diagnostics Australia 2011),

Eligibility for treatment with first-line erlotinib could be determined by (i.e. limited to) the presence of an EGFR activating mutation indicated by a genetic allele harbouring an in-frame deletion mutation in exon 19 (around codons 746 to 750) or a missense mutation leading to leucine to arginine substitution at codon 858 (L858R) in exon 21. The range of mutations that could be used to determine eligibility would be dependent on the assays available and utilised in NATA accredited testing laboratories. The EGFR substitution mutation T790M in exon 20

confers resistance to TKI double inhibitor/inhibition and if detected may determine patient exclusion from treatment with erlotinib.

It has been argued that it would be timely and efficient to test all non-squamous cell NOC or NSCLC NOC patients for EGFR gene mutations at the time of diagnosis and histological confirmation (i.e. include the 30% to 40% of cases that are not diagnosed at Stage IIIB or IV). In most cases the same biopsy sample used for histological confirmation of NSCLC could be used for DNA analysis, and there would be likely savings in transport, handling and pathology costs. This would also reduce the time from diagnosis to EGFR gene mutation status confirmation, as the pathologist could immediately request the test, rather than having to send the information regarding diagnosis to the treating clinician, who must then confirm the disease staging, and send a request back to the pathologist to perform the test. Also, it is expected the great majority of early stage NSCLC patients will progress to advanced disease stages, so treatment of these patients with either erlotinib or platinum-based chemotherapy could be prompt, as the patient's EGFR gene mutation status would already be known and on record.

The proposed item descriptor for EGFR gene mutation testing in the base case scenario is shown in Table 1. The MBS item should not inadvertently exclude the current PBS-subsidised access to erlotinib as a second- or third-line treatment, which does not have a requirement for determining EGFR gene mutation status.

Table 1: Proposed MBS item descriptor for EGFR gene mutation testing

Category [6] – [Pathology services] Group P7 - Genetics
MBS [item number] *A test of tumour tissue from a patient with non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise classified, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for first-line access to erlotinib are fulfilled once the patient is also diagnosed with locally advanced or metastatic disease.* Fee: $[400] [Relevant explanatory notes] *The test will, ordinarily, be initiated by a pathologist, medical oncologist or respiratory physician (or occasionally a surgeon). Samples with low quality DNA or low tumour cell content relevant to the sample size available and chosen testing method may require tumour cell enrichment or the use of a method more sensitive than Sanger sequencing.*

It may be argued that restriction of EGFR gene mutation testing to those with locally advanced or metastatic NSCLC may be appropriate to limit the rate of potentially unnecessary EGFR tests performed, although this would incur other time and resource consequences. The alternative item descriptor for EGFR gene mutation testing in the scenario where tumour tissue from patients is tested for EGFR gene mutation status once they are diagnosed with locally advanced or metastatic NSCLC is shown in Table 2.

Table 2: Proposed alternative MBS item descriptor for EGFR gene mutation testing

Category [6] – [Pathology services] Group P7 - Genetics
MBS [item number] *A test of tumour tissue from a patient with locally advanced or metastatic non-squamous or not otherwise specified non-small cell lung cancer (NSCLC), to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for access to first-line erlotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.* Fee: $[400] [Relevant explanatory notes] *The test will, ordinarily, be initiated by a pathologist, medical oncologist or respiratory physician (or occasionally a surgeon). Samples with low quality DNA or low tumour cell content relevant to the sample size available and chosen testing method may require tumour cell enrichment or the use of a method more sensitive than Sanger sequencing.*

Clinical place for proposed intervention

Current scenario clinical management

In the current scenario there is no EGFR gene mutation testing for erlotinib treatment for patients with previously untreated locally advanced or metastatic NSCLC. Treatment offered to these patients is first-line chemotherapy, with platinum-based doublet chemotherapy (such as carboplatin and gemcitabine) generally being the preferred choice. Newer therapeutic agents such as bevacizumab or pemetrexed are also options for treatment (Cataldo et al. 2011; Mazzoni et al. 2011; Riccardi S 2011). The choice of agent will depend on the NSCLC sub-grouping of the tumour, with squamous cell carcinoma sometimes requiring different agents to non-squamous cell types (Riccardi S 2011). Not all patients are likely to be able to meet the requirements for chemotherapy due to poor performance status.

EGFR gene mutation testing is *not* required for eligibility for erlotinib in the second-line or third-line setting. Erlotinib is listed on the Pharmaceutical Benefits Scheme (PBS) for the treatment of patients with locally advanced or metastatic NSCLC following prior treatment with chemotherapy. The current PBS restriction does not limit erlotinib use to only EGFR gene mutation positive patients in the second- and third-line settings, and is as follows:

> *Initial PBS-subsidised treatment, as monotherapy, in a patient with locally advanced or metastatic (stage IIIB or IV) non-small cell lung cancer with a WHO performance status of 3 or less, after prior treatment with platinum-based chemotherapy, where:*
> *(1) (a) disease progression has occurred following treatment with docetaxel or pemetrexed; or (b) treatment with docetaxel and pemetrexed is either contraindicated or cannot be tolerated; and*
> *(2) further cytotoxic chemotherapy is not appropriate.*

Proposed clinical management if MBS listing of EGFR gene mutation testing is approved

Under the proposed scenario, patients diagnosed with NSCLC would be assayed for EGFR gene mutation status either after diagnosis of non-squamous NSCLC or NSCLC NOC (base case) or once their disease reaches Stage IIIB or IV (possible alternative scenario).

In the base case, patient tumour status would be recorded as EGFR M+ if an activating EGFR gene mutation is found or EGFR M- if no activating EGFR gene mutation is found. If diagnosed when the disease is at Stage IIIB or IV, patients would be treated according to their EGFR gene mutation status: erlotinib (or gefitinib if similarly PBS listed) for those who are EGFR M+ and standard platinum-based doublet chemotherapy for those who are EGFR M-. If diagnosed at an earlier stage, once the disease progresses to Stage IIIB or IV, the patient should be assessed for evidence to confirm that the previously detected EGFR gene mutation is stable, i.e. the EGFR gene mutation expressing tumour identified has not undergone further mutation. This may require a new biopsy and further EGFR gene mutation testing. In light of this evidence the patient should be treated according to their current EGFR status.

EGFR gene mutation testing

In the possible alternative scenario, patients would not be tested for EGFR gene mutation status until their disease has progressed to Stage IIIB or IV cancer, although many patients will be first diagnosed having already reached this stage. For those diagnosed at earlier stages, their biopsy sample would be retrieved and processed for EGFR gene mutation testing when Stage IIIB or IV is reached, again on the basis that the mutation is stable. Patients would then be treated according to their EGFR status: erlotinib (or gefitinib if PBS listed) for those who are EGFR M+ and standard platinum-based doublet chemotherapy for those who are EGFR M-.

In those cases where EGFR gene mutation status is unknown because insufficient tumour tissue has been retrieved for accurate EGFR gene mutation testing, and the decision is made not to re-sample, patients would receive treatment with standard platinum-based doublet chemotherapy.

Alternatively, if an EGFR gene mutation is found which renders the patient insensitive to erlotinib (i.e. T790), the patient may be ineligible to receive erlotinib. Patients who harbour these mutations and those who have squamous cell NSCLC would be eligible for platinum-based chemotherapy. If a patient receives erlotinib as a first-line treatment and is found not to respond to erlotinib treatment, they would not be given the drug in subsequent lines of treatment.

Clinical need

The proposed management algorithm will satisfy a previously unmet clinical need, as there is currently no reimbursement available for EGFR gene mutation testing. In the proposed

management algorithm, EGFR gene mutation testing follows histological diagnosis of NSCLC (with/without progression of disease to Stage IIIB or IV) and can therefore be restricted to patients with non-squamous-cell NSCLC or NSCLC NOC. If EGFR gene mutation testing is restricted to those with locally advanced or metastatic NSCLC, retrieval of the biopsy for EGFR gene mutation testing would be necessary in the 30% to 40% of patients found with early stage NSCLC at initial diagnosis, when their disease has progressed to Stage IIIB or IV. Some of these patients may remain in remission after treatment of their early stage NSCLC, or die from competing illnesses, and not require EGFR gene mutation testing.

By identifying activating EGFR gene mutation early in the patient's progression, erlotinib can be offered promptly as a first-line treatment for stage IIIB or IV NSCLC. Erlotinib treatment would not be given unless the patient's disease was diagnosed at, or progressed to, a locally advanced or metastatic stage.

Patients in the current management pathway, and EGFR M+ patients in the proposed management pathway who undergo disease progression after erlotinib treatment, would be offered monotherapy with (most likely docetaxel or pemetrexed) or platinum-based doublet chemotherapy (most likely gemcitabine/carboplatin) provided their performance status indicates they are likely to tolerate the treatment. PASC suggested that some patients who would not be considered suitable for treatment with chemotherapy, may be considered suitable for treatment with erlotinib. This would result in additional patients receiving active treatment rather than palliation for locally advanced or metastatic NSCLC.

Other considerations

It should be noted that there can be risks to the patient associated with obtaining a biopsy sample and this risk may increase with deterioration of the patient's health status. As has been discussed, not all biopsies provide a sufficient or suitable sample for DNA analysis and in these cases a second biopsy may be considered. By carrying out EGFR gene mutation testing immediately following histological diagnosis of the tumour, the suitability of the sample could be determined early in the history of the patient's disease and if a second biopsy is required it could be carried out at lower risk to the patient. Conversely if disease progresses, sometimes it may be easier to biopsy an accessible extrapulmonary metastasis (such as a supraclavicular lymph node or cutaneous metastasis).

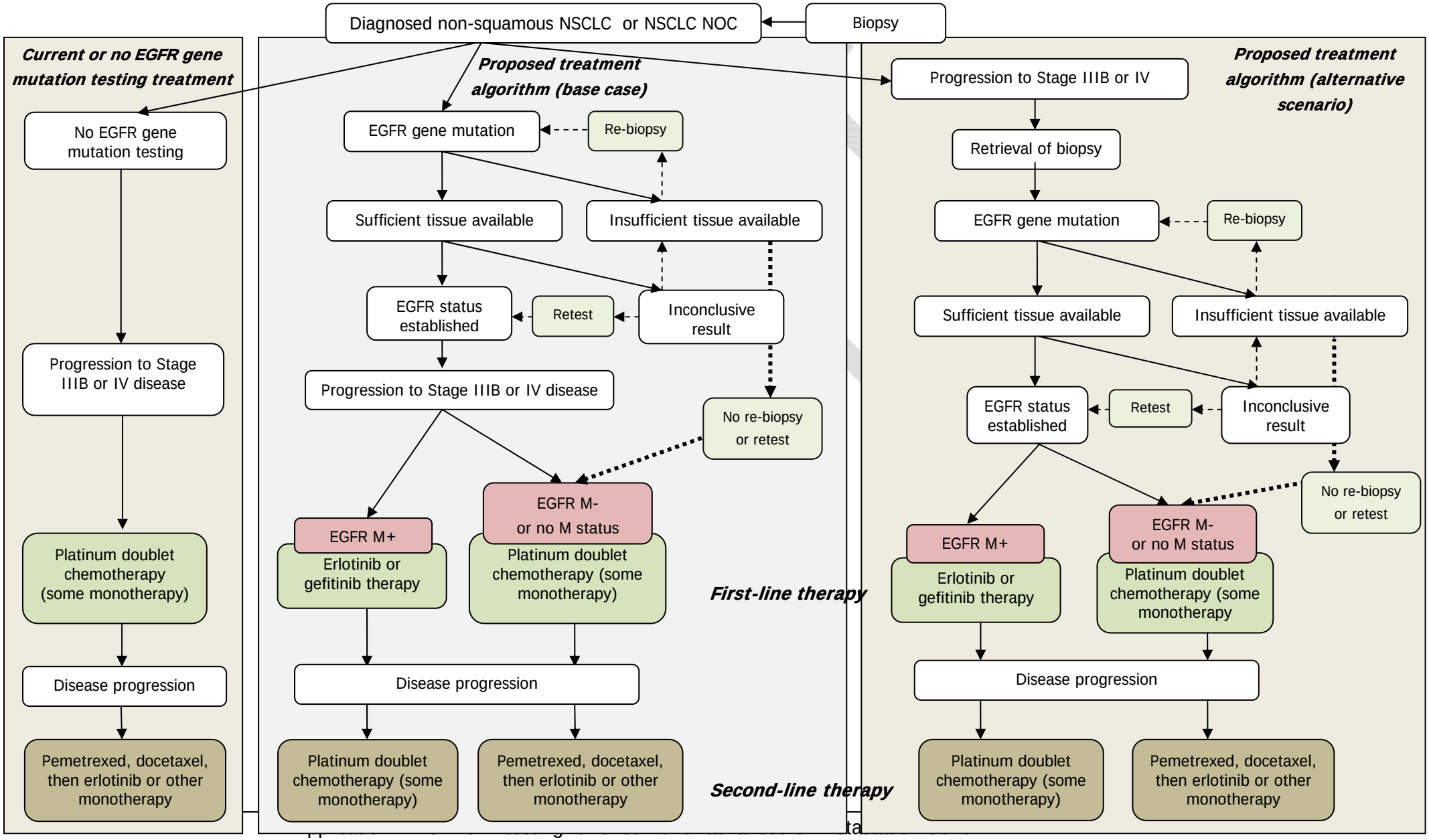
While lower risk of biopsy provides an argument for carrying out EGFR gene mutation testing on all NSCLC patients at diagnosis, both early and late stage, patients may be disadvantaged by incorrect assignment of EGFR gene mutation status. In the proposed scenario, patients who have a test result of EGFR M+ could be given erlotinib as a first-line treatment which is likely to be less effective than platinum-based chemotherapy if the test result is false (Keedy et al. 2011). Alternatively, those patients who are falsely found to be EGFR M- are likely to

miss out on the benefits of first-line erlotinib treatment. In the current scenario all patients are offered platinum-based doublet chemotherapy as a first-line treatment and do not undergo screening for EGFR gene mutation status. Erlotinib is offered to unselected patients as a second or third-line treatment.

Different EGFR gene mutation testing methods are likely to provide varying levels of accuracy. While Sanger sequencing is considered highly accurate in identifying mutations, it can also be insensitive when the proportion of tumour cells in the sample is low. A systematic assessment of EGFR gene mutation screening methods would be beneficial to the consideration of this application. Additionally, assessment of the effects of artefacts resulting from FFPE and other preparation procedures on DNA sequence would be useful.

Figure 3 illustrates the current scenario on the left-hand panel, and the proposed base case scenario in the centre panel. The right hand panel illustrates the alternative scenario in which the testing of tumour samples only occurs once the patient has otherwise become eligible for erlotinib treatment (disease has already progressed to stage IIIB or IV).

Figure 3: Current and proposed management algorithms for non-small cell lung cancer



Comparator

In the current treatment algorithm for locally advanced or metastatic NSCLC, there is no EGFR gene mutation testing for previously untreated patients. The comparator is therefore 'no testing'. In the current scenario of 'no testing', platinum-based doublet chemotherapy (mostly carboplatin + gemcitabine) is usually the preferred treatment offered to all locally advanced and metastatic NSCLC patients as a first-line therapy. Under the proposed intervention, 'EGFR gene mutation testing for erlotinib eligibility *in previously untreated* locally advanced and metastatic patients' will provide the opportunity for using erlotinib as a first-line therapy to EGFR M+ patients. As EGFR gene mutation testing is being proposed as a co-dependent service, a useful comparison would be 'EGFR gene mutation testing followed by erlotinib or chemotherapy' versus 'no testing and chemotherapy' for first-line therapy in locally advanced or metastatic NSCLC.

As there is currently no MBS listing for EGFR gene mutation testing, the MBS item descriptor for the comparator cannot be stated.

A PBAC submission for gefitinib for the treatment of patients with previously untreated locally advanced or metastatic NSCLC harbouring activating EGFR gene mutations is expected to be submitted. Therefore, if listed, gefitinib could be considered a comparator to erlotinib in this patient population. In this case, the comparison is EGFR gene mutation testing plus erlotinib or chemotherapy versus EGFR gene mutation testing plus gefitinib or chemotherapy.

Outcomes for safety and effectiveness evaluation

The health outcomes, upon which the comparative clinical performance of EGFR gene mutation testing to determine eligibility for treatment with erlotinib as a first-line therapy in patients with locally advanced or metastatic NSCLC will be measured, are:

Effectiveness

- Progression free survival
- Overall survival
- Objective tumour response rate
- Quality of life
- Comparison of test performance

Comparison of test performance

In a consideration of EGFR gene mutation testing, available test options and combination test strategies (e.g. PCR amplification and sequencing with or without HRM pre-screening) should be identified and a comparative assessment performed. Comparison should be made to the EGFR gene mutation testing methods used in clinical trials where there is evidence supporting

the co-dependent EGFR test and erlotinib treatment (i.e. EURTAC and OPTIMAL trials). If a reference or gold standard test becomes available, then a comparative assessment should refer to that standard. As currently there is no reference standard available, the decision analytic will not be able to take into account the rates of false positive and false negative results generated by EGFR gene mutation testing.

A comparative assessment should consider the method of testing, analytic performance of the tests, and also include a consideration of the collection and handling methods of samples for the test to assess the impact of inadequate samples and re-sampling.

Safety

- Toxic effects from subsequent treatment (including skin rash, diarrhoea, thrombocytopenia)
- Adverse events associated with biopsies
- Rate of re-biopsy

Summary of PICO to be used for assessment of evidence (systematic review)

Table 3 provides a summary of the PICO used to:

(1) define the question for public funding,

(2) select the evidence to assess the safety and effectiveness of *EGFR gene mutation testing*, with erlotinib and

(3) provide the evidence-based inputs for any decision-analysis modelling to determine the cost-effectiveness of *EGFR gene mutation testing* with erlotinib.

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Table 3: Summary of PICO to define the question for public funding that assessment will investigate

Patients	Prior tests	Intervention	Comparator	Reference Standard (for diagnostic tests)	Outcomes to be assessed
Patients with previously untreated non-squamous NSCLC or NSCLC not otherwise classified	Histological diagnosis of non-squamous NSCLC or NSCLC not otherwise classified	EGFR gene mutation testing and, after presenting with locally advanced or metastatic disease, use of **first-line erlotinib** in patients with tumours expressing EGFR exon 19 deletions or exon 21 point mutation L858R and use of platinum-based doublet chemotherapy in patients not expressing these EGFR gene mutations and in those patients whose EGFR gene mutation status is unknown	• Primary comparator No EGFR gene mutation testing and use of treatment with platinum-based doublet chemotherapy after presenting with locally advanced or metastatic disease	No agreed reference standard currently available, but comparisons should be made against the specific tests used to generate the evidence to support the effectiveness of first-line erlotinib (the "evidentiary" standard), specifically: • PCR followed by length analysis in an ABI Prism 3130 DNA analyser for exon 19 deletions and a 5' nuclease PCR (Taqman) assay for exon 21 point mutations (EURTAC trial) • PCR-based direct sequencing (OPTIMAL trial)	Safety • Toxic effects of treatment • Adverse events from biopsies • Rate of re-biopsy Effectiveness • Progression free survival • Overall survival • Objective tumour response rate • Quality of life • Comparison of test performance Cost effectiveness • Cost per QALY
			• Secondary comparator EGFR gene mutation testing and, after presenting with locally advanced or metastatic disease, use of **gefitinib** in patients with tumours expressing EGFR exon 19 deletions or exon 21 point mutation L858R and use of platinum-based doublet chemotherapy in patients not expressing these EGFR gene mutations and in those whose EGFR gene mutation status is unknown	No agreed reference standard currently available, but comparisons should be made against the specific tests used to generate the evidence to support the effectiveness of gefitinib	

Questions

Primary question: is EGFR gene mutation testing and, after presenting with locally advanced or metastatic disease, use of erlotinib or chemotherapy (dependent on mutation status) safe, effective and cost effective compared to no testing and treatment with chemotherapy, in previously untreated patients with non-squamous NSCLC or NSCLC not otherwise classified?

Secondary question: is EGFR gene mutation testing and, after presenting with locally advanced or metastatic disease, use of erlotinib or chemotherapy (dependent on mutation status) safe, effective and cost effective compared to EGFR gene mutation testing and, after presenting with locally advanced or metastatic disease, use of gefitinib or chemotherapy (dependent on mutation status), in previously untreated patients with non-squamous NSCLC or NSCLC not otherwise classified?

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Clinical claim

The applicant claims that there will be a significant improvement in length of average progression free survival in NSCLC patients who test positive for an EGFR activating mutation and receive subsequent first-line treatment with erlotinib, when compared to those who are not tested and receive standard platinum-based doublet chemotherapy.

Clinical trials (EURTAC (Rosell R et al 2011), OPTIMAL (Zhou et al. 2011)) have demonstrated benefits associated with first-line erlotinib treatment for NSCLC patients testing positive for EGFR activation mutations:

- The OPTIMAL trial demonstrated that median progression free survival (PFS) was significantly longer in the erlotinib treated patients compared to those on chemotherapy (13.1 [95% CI 10.58 to 16. 53] vs 4.6 [4.21 to 5.42] months; hazard ratio 0.16, 95% CI 0.10 to 0.26; p<0.0001). Chemotherapy was associated with more common grade 3 or 4 toxic effects (including neutropenia and thrombocytopenia) and more treatment related adverse events (decreased platelet count, decreased neutrophil count and hepatic dysfunction (Zhou et al. 2011).
- The EURTAC trial demonstrated a significantly longer PFS associated with erlotinib treatment compared to chemotherapy. PFS was 5.2 months (95% CI, 4.4-5.8m) in the chemotherapy group compared with 9.4 months (95% CI, 7.9-12.3) in the erlotinib group (HR, 0.42; P<0.0001) (Rosell R et al 2011).

Based on the EURTAC and OPTIMAL trials, erlotinib was shown to be superior to platinum-based doublet chemotherapy in terms of effectiveness, but with a different safety profile to that of platinum-based doublet chemotherapy. Under these conditions, a cost-effectiveness analysis or cost-utility analysis is therefore required (see Table 4). It is expected that no evidence will be available directly comparing the effectiveness of EGFR gene mutation testing for erlotinib and EGFR gene mutation testing for gefitinib. Under these circumstances, the effectiveness and safety outcomes of erlotinib will be indirectly compared with gefitinib. Assuming that the effectiveness and safety of erlotinib can be demonstrated to be similar to that of gefitinib, a cost minimisation analysis would therefore be required.

Table 4: Classification if an intervention for determination of economic evaluation to be presented

<table>
<tr><td colspan="2" rowspan="2"></td><td colspan="4">Comparative effectiveness versus comparator</td></tr>
<tr><td colspan="2">Superior</td><td>Non-inferior</td><td colspan="2">Inferior</td></tr>
<tr><td rowspan="5">Comparative safety versus comparator</td><td rowspan="3">Superior</td><td colspan="2" rowspan="3">CEA/CUA</td><td rowspan="3">CEA/CUA</td><td>Net clinical benefit</td><td>CEA/CUA</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
<tr><td>Non-inferior</td><td colspan="2">CEA/CUA</td><td>CEA/CUA*</td><td colspan="2">None^</td></tr>
<tr><td rowspan="3">Inferior</td><td>Net clinical benefit</td><td>CEA/CUA</td><td rowspan="3">None^</td><td colspan="2" rowspan="3">None^</td></tr>
<tr><td>Neutral benefit</td><td>CEA/CUA*</td></tr>
<tr><td>Net harms</td><td>None^</td></tr>
</table>

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

Outcomes and health care resources affected by introduction of proposed intervention

Outcomes for economic evaluation

An economic evaluation will compare health outcomes for the proposed scenario of EGFR gene mutation testing plus erlotinib or platinum-based chemotherapy versus the current scenario where there is no EGFR gene mutation testing and patients with previously untreated locally advanced or metastatic NSCLC are treated with platinum-based doublet chemotherapy. The applicant claims that erlotinib results in statistically significant improvements in progression free survival and objective response rate, while overall survival data are immature and with a high rate of known crossover (Rosell R et al 2011). The primary economic evaluation outcome measure is therefore expected to be quality-adjusted life-years gained (QALYs).

Health care resources

A list of resources that would need to be considered in the economic analysis comparing EGFR gene mutation testing and first-line erlotinib or platinum-based doublet chemotherapy (depending on mutation status) versus no EGFR gene mutation testing and treatment with chemotherapy are provided in Table 5. The resources required to identify the population eligible for EGFR gene mutation testing would be identical to the resources required to identify those suitable for platinum-based doublet chemotherapy, and therefore do not need to be considered.

Table 5: 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
Resources provided to deliver proposed intervention: EGFR gene mutation testing and treatment with either first-line erlotinib or platinum-based doublet chemotherapy										
Resources associated with introduction of EGFR test										
- Block retrieval of stored sample from tissue archive (from most recent biopsy)	Pathologist		TBD (not all samples will need to be retrieved if biopsy performed at diagnosis of metastatic disease)	1						
- Biopsy (where there is an unsuitable sample form tissue archive)	Respiratory oncologist	Hospital patient	Approx 10%							
- Preparation of tissue sample	Pathologist		100% of pts eligible for treatment	1						
- Perform the EGFR test	Molecular pathologist		100% of pts eligible for treatment	1	~$400					
- Analysis and reporting on result - EGFR status determined from tumour biopsy and/or tissue markers for other prognostic tissue	Molecular pathologist		100% of pts eligible for treatment	1						
If EGFR positive, patient is eligible for treatment with first-line erlotinib										
- Specialist consultation for initiation in erlotinib (oral tablet) (MBS 116)	Medical oncologist		14.2% of all patients who have an EGFR gene mutation (EURTAC study) (Rosell R et al 2011)	TBD	$72.65					
- Cost of erlotinib (30 tabs x 150mg) (PBS cost per maximum quantity)			14.2% of patients	TBD			$3309.66			
If EGFR negative patients receives platinum doublet chemotherapy										
- Specialist consultation for initiation in chemotherapy (MBS 116)	Medical oncologist		~90% (EGFR negative pts)	TBD	$72.65					
- Cost of chemotherapy (1 x 45mg carboplatin) (PBS cost per maximum quantity)			~10% (EGFR negative pts)	TBD			$265.32			
- Cost of			~90%	TBD			$890.78			

	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
chemotherapy (1 x 300mg paclitaxel) (PBS cost per maximum quantity)			(EGFR negative pts)							
- Cost of chemotherapy (1 x 300mg paclitaxel) (PBS cost per maximum quantity)			90% (EGFR negative pts	TBD			$132.10			
Resources to deliver platinum doublet-IV drug administration										
- Drug administration cost for <1 hour infusion (MBS item 13915)		Day patient		Once every 3 weeks. No. of infusions per patient TBD	$62.60					
- Public hospital outpatient admission for administration		Out-patient	~86% (EGFR negative pts)	Once every 3 weeks. No. of infusions per patient TBD			$560.00			
- Full day hospital admission for chemotherapy administration in a public hospital setting (excluding average pharmacy component)		Day patient	~86% (EGFR negative pts)	Once every 3 weeks. No. of infusions per patient TBD			$562.00			
- Full day hospital admission for chemotherapy administration in a private hospital setting		Day patient	~86% (EGFR negative pts)	Once every 3 weeks. No. of infusions per patient TBD			$331.00			
Resources provided in association with proposed intervention										
Resources to monitor adverse effects related to core biopsy										
- Pulmonary bleeds										
Resources to manage side effects of erlotinib										
Resources to manage side effects of chemotherapy										
Resources provided to deliver the comparator: platinum-based doublet chemotherapy										
- Specialist consultation for regular follow-up (MBS 116)	Medical oncologist	Out-patient	100%	Once every 3 weeks. No. of infusions per patient TBD	$72.65					
- Cost of chemotherapy (1 x 45mg carboplatin) (PBS cost per maximum quantity)			100%	TBD			$265.32			
- Cost of chemotherapy (1 x 200mg Gemcitabine) (PBS			100%	TBD			$132.10			

	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
cost per maximum quantity)										
- Drug administration cost for <1 hour infusion (MBS item 13915)		Day patient	100%	Once every 3 weeks. No. of infusions per patient TBD	$62.60					
- Public hospital outpatient admission for administration		Out-patient	100%	Once every 3 weeks. No. of infusions per patient TBD			$560.00			
- Full day hospital admission for chemotherapy administration in a public hospital setting (excluding average pharmacy component)		Day patient	100%	Once every 3 weeks. No. of infusions per patient TBD			$562.00			
- Full day hospital admission for chemotherapy administration in a private hospital setting		Day patient	100%	Once every 3 weeks. No. of infusions per patient TBD			$331.00			
Resources provided in association with the comparator: platinum-based doublet chemotherapy										
Resources to manage side effects of chemotherapy										

* Include costs relating to both the standard and extended safety net.

It is assumed that the resources required to perform EGFR gene mutation testing for determining eligibility for first-line erlotinib would be identical to those required to identify patients eligible for first-line gefitinib. It is also assumed that the same proportion of patients would receive platinum-based doublet chemotherapy in either arm of the comparison. As such, the only costs that need assessing for the comparison between first-line erlotinib and first-line gefitinib would relate directly to these treatments and the adverse effects of these treatments.

Proposed structure of economic evaluation (decision analysis)

Figure 4 outlines the proposed decision analysis as a means of summarising the comparisons the assessment report should investigate and present for those patients with non-squamous NSCLC or NSCLC not otherwise classified, who progress to having locally advanced or metastatic disease (stage IIIB or IV). Like the clinical management algorithms in Figure 3, it assumes that all patients tested early will progress to an eligible stage of disease for erlotinib or comparator treatment. If a discernable proportion of patients would not progress to require such treatment, additional branches will be needed to reflect the true number needed to test per treated patient and true test cost per treated patient. This issue is not relevant to the alternative scenario analysis in which EGFR gene mutation testing is only performed for those patients whose stage of disease already renders them potentially eligible for erlotinib treatment.

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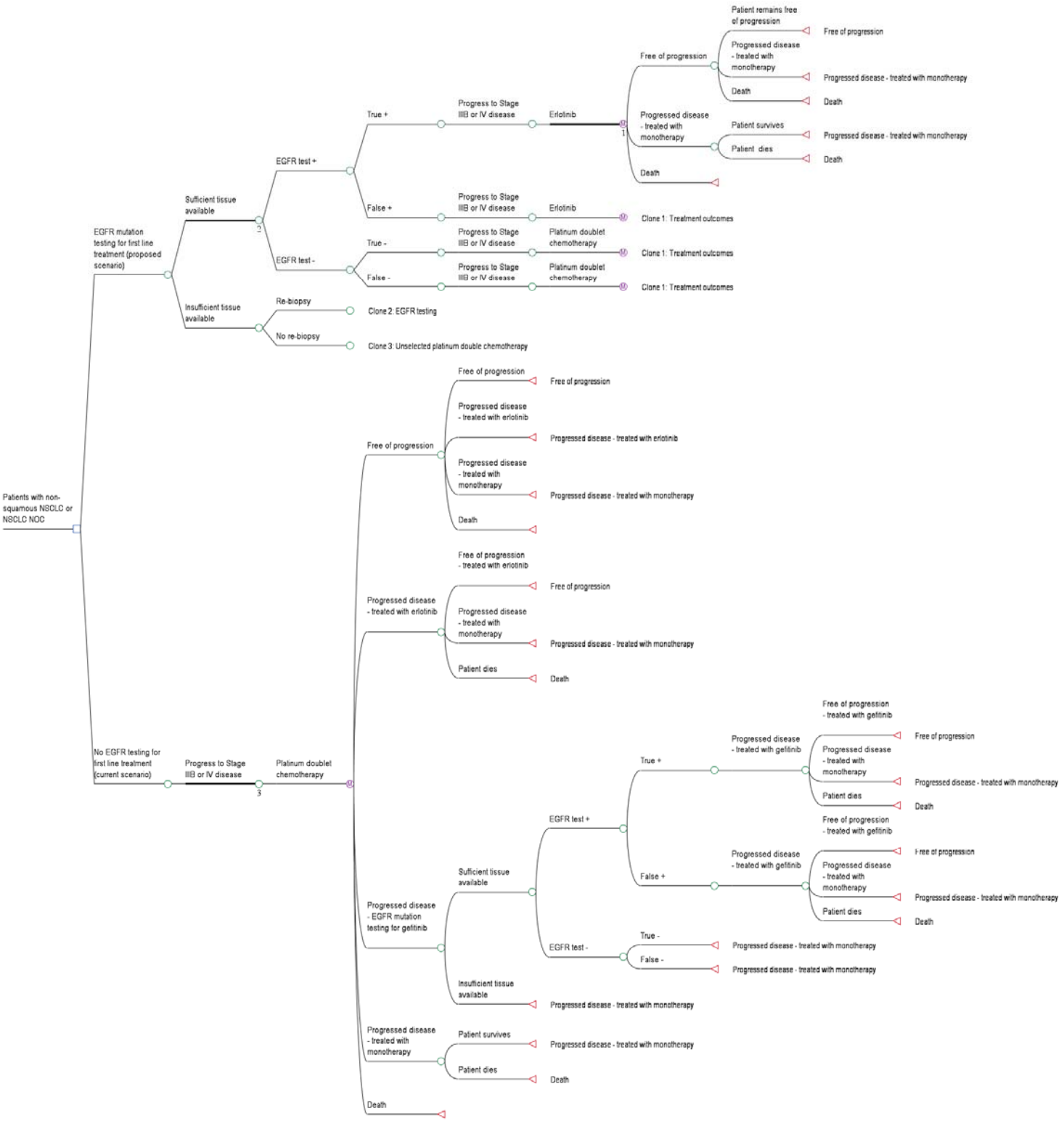
Figure 4: Decision tree representing decision options in patients with locally advanced or metastatic large cell NSCLC



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