MSAC Application 1161: Final Decision Analytic Protocol (DAP) to guide the assessment of testing for mutations in the epidermal growth factor receptor (EGFR) gene in patients with locally advanced or metastatic non small cell lung cancer (NSCLC) to determine eligibility for subsidised gefitinib

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MSAC and PASC

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

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

Purpose of this document

This document is provides a decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The protocol has taken into account input from various stakeholders.

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

Patients – specification of the characteristics of the patients in whom the intervention is to be considered for use

Intervention – specification of the proposed intervention and how it is delivered

Comparator – specification of the therapy most likely to be replaced 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

Acknowledgements

The PASC and the MSAC wish to thank Professor Wendy Cooper for her valuable contributions to the development of this protocol.

Summary of matters for consideration by the application

The PASC requests that the applicant note the following issues and consider addressing the issues in its application:

- The applicant has indicated that testing be limited to adenocarcinoma samples. *PASC has indicated that it would be more appropriate to limit testing to patient with non-squamous NSCLC and NSCLC not otherwise specified.*
- *The costs and consequences of re-biopsy need to be considered, as well as the consequences of not conducting a re-biopsy.*
- *The possibility that a proportion of patients diagnosed via cytology alone (30% as estimated by the applicant) may be candidates for biopsy.*
- *Consideration of all available tests, including an assessment of their comparative diagnostic accuracy and analytical sensitivity. Costs of all tests should also be included in the modelled analysis.*
- *Clear description of how samples may be obtained, ie bronchoscopy can provide both cytological and histological samples, as can fine needle aspiration.*
- *The eligibility of patients who test negative to EGFR mutation for erlotinib treatment needs to be amended.*
- *Consideration of erlotinib as a comparator, given its potential use as first-line therapy.*
- *Sensitivity analysis be undertaken to include a quality of life analysis for those patients who are negative.*

Purpose of application

A proposal for an application requesting a MBS listing of testing for activating mutations in the epidermal growth factor receptor gene (EGFR testing) in patients with locally advanced or metastatic non small cell lung cancer (NSCLC) was received from AstraZeneca by the Department of Health and Ageing in April 2011. Testing for activating mutations in the EGFR gene is currently not funded under the Medicare Benefits Schedule (MBS) however, in December 2010, it was recommended for inclusion on the Medicare Benefits Schedule (MBS) for use in identifying patients who are suitable candidates for second-line treatment with gefitinib by MSAC. The proposed application seeks to extend availability to also include use for the purposes of identifying suitable candidates for first-line treatment with gefitinib.

EGFR testing and gefitinib, a chemotherapeutic agent, can be considered to be co-dependent technologies. AstraZeneca advises that, on the basis that the chemotherapeutic agent gefitinib is more efficacious in patients with an EGFR mutation in comparison to those who test negative for the EGFR mutation (Armour and Watkins, 2010[1]), concurrent MBS and PBS listings are being sought for EGFR testing and gefitinib to facilitate use of gefitinib for the first-line treatment, as monotherapy, of locally advanced or metastatic NSCLC in patients with an activating mutation of the EGFR gene with a WHO performance status of 2 or less.

Background

Current arrangements for public reimbursement of EGFR testing

Testing for activating mutations in the EGFR gene is currently not funded by MBS (although as discussed below it has been recommended for subsidy by MSAC for a subgroup of patients with NSCLC). Until the recommendation is implemented, patients must either pay for the test themselves or seek to have the cost of the test funded through the hospital with which their specialist is affiliated.

There have been two prior MSAC considerations of applications requesting reimbursement of genetic testing for mutations in the EGFR gene in patients with locally advanced or metastatic NSCLC.

March 2010 MSAC consideration

In March 2010, MSAC considered an application by the Pathology Services Table Committee (PSTC) requesting reimbursement of DNA sequencing of the EGFR gene for the purposes of determining whether a patient should have access to gefitinib under the Pharmaceutical Benefits Scheme (PBS). MSAC determined that there was not yet a sufficiently agreed framework to enable proper consideration of the proposal that EGFR gene mutation testing should be publicly funded. MSAC determined that there is a need to clarify the relative roles of PBAC and MSAC in progressing this type of proposal relating to the cost-effectiveness of co-dependent technologies such as EGFR mutation

testing of patients with locally advanced or metastatic NSCLC to determine eligibility for therapy with gefitinib. MSAC agreed that consideration of public funding of EGFR mutation testing should be deferred pending further advice from the Economics Sub-Committee (ESC) of MSAC regarding the appropriate basis for appraising such services, in accordance with the recommendations from the Review of Health Technology Assessment in Australia (HTA Review).

December 2010 MSAC consideration

In December 2010, MSAC considered further information supplied by AstraZeneca to enable the reconsideration of EGFR gene mutation testing to determine whether a patient should have access to gefitinib under the PBS. The use of EGFR gene mutation testing prior to both first-line and second-line treatment with gefitinib was considered. The appropriate comparator was considered to be "no testing". MSAC noted that several test methods can be used to establish the presence of EGFR gene mutations in tumour samples. The test proposed for subsidy, specifically, involved use of the High Resolution Melt (HRM) method followed by direct DNA sequencing for those samples exhibiting an abnormal HRM trace. The application to MSAC assumed the use of HRM followed by direct DNA sequencing of samples with an identified mutation – with adequate tumour material – was associated with 100% sensitivity and specificity, however no comparative data versus direct DNA sequencing alone were presented for either this test combination or any other testing methodologies.

MSAC identified there were issues relating to questions of when and how frequently EGFR testing should be conducted, the amount of tumour tissue in a biopsy sample (tumour load), the stability of the mutation over time in a patient and between primary and secondary tumours (mutation frequency), the relative importance of some mutations in EGFR over others, the impact of mutations in other genes and the optimal test(s) for the detection of activating mutations of the EGFR gene. MSAC also noted that there were uncertainties around the development of resistance to gefitinib.

Limited data were presented to MSAC to enable an assessment of cost-effectiveness of EGFR testing. MSAC noted the evidence provided was insufficient for a full appraisal of the safety, performance and cost of the options available for EGFR testing and so was unable to draw an adequately informed conclusion on the usefulness of these tests in clinical management. For this reason, MSAC decided not to support the general use of EGFR testing.

MSAC considered whether the test should be made available for determination of whether gefitinib should be used as a second-line agent to treat NSCLC. It was noted by MSAC that, since December 2004, the detection of an activating mutation in the EGFR gene in tumour samples has been a prerequisite for patient eligibility for PBS-subsidised gefitinib as second-line therapy for locally advanced or metastatic NSCLC but, to date, there had been no MBS funding for such testing. Currently such patients either have to pay for EGFR testing themselves or seek to have the test funded through the public hospital system. MSAC was concerned that this represented poor equity of access to the tests required to determine eligibility for gefitinib as currently subsidised on the PBS. MSAC also considered that the use of gefitinib was reserved for a small group of patients who meet certain clinical criteria, have exhausted all other therapeutic options including erlotinib but still have good health status. Although a small number of patients would be eligible for PBS-subsidised gefitinib, a larger number of patients would undergo EGFR testing to determine whether an activating mutation in the EGFR gene was present. For these reasons, and despite the lack of adequate evidence provided

on the safety, performance and cost of the test options available, MSAC agreed to advise the Minister that public funding should be made available in this limited and clinically well-defined setting. MSAC was concerned to ensure that public funding should not be extended to allow use of EGFR gene testing for other purposes, and advised that an item descriptor for the MBS service should reflect the current PBS conditions for use of gefitinib. A listing as shown in Table 1 was proposed by MSAC. MSAC noted that if the PBAC were to reconsider PBS subsidy of gefitinib for use in the first-line treatment setting, it was anticipated that MSAC would be closely involved.

Table 1: Current MBS item descriptor for [item]

Category 6 – Pathology services Group P7 – Genetics
MBS [item number] A test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: between $400 and $606

MSAC noted that the PBAC, at its meeting in November 2010, had rejected a submission requesting extension of the PBS for gefitinib to include first-line monotherapy for locally advanced or metastatic NSCLC in patients with an activating mutation of the EGFR gene. The committee indicated that an integrated submission would be needed across the co-dependent EGFR gene testing and gefitinib in any future re-consideration of this request. It was noted that the consequences of an extension beyond the current PBS listing would be a large increase the number of patients who would require EGFR gene testing to determine eligibility for gefitinib and the adverse consequences of a false positive test resulting in inappropriate exposure to gefitinib are more serious than in the last-line setting where no other treatment options are available. AstraZeneca is currently pursuing PASC consideration to inform a re-application for PBS listing of gefitinib via the co-dependent technology evaluation process.

Current arrangements for public reimbursement of gefitinib

Gefitinib is currently listed on the PBS as shown in Table 2. Notably the current restriction includes an amendment that removed the requirement that analysis of the DNA sequence of the EGFR gene must be used to detect a mutation in the EGFR gene. In November 2009, the PBAC noted that the analysis by DNA sequencing methodology was not MBS reimbursed and it was therefore considered reasonable to use other methodologies to detect the specific activating mutations in the EGFR gene.

Table 2: Current PBS listing of gefitinib

Name, Restriction, Manner of administration and form	Max. Qty	Max. Rpts	Dispensed Price for Max. Qty	Proprietary Name
Gefitinib Tablet 250mg	30	1	$3,851.36	Iressa®
Authority Required Initial PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with a WHO performance status of 2 or less, where: (1) disease progression has occurred following treatment with at least 1 chemotherapy agent; and (2) there is evidence that the patient has an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene in tumour material. The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Gefitinib (Iressa) PBS Authority Application for Use in the Treatment of Locally Advanced or Metastatic Non-Small Cell Lung Cancer - Supporting Information Form [may be downloaded from the Medicare Australia website (www.medicareaustralia.gov.au)]; and (3) details of the prior chemotherapy including the name(s) of drug(s) and date of the most recent treatment cycle; and (4) details of the patient's WHO performance status; and (5) a copy of the pathology report providing evidence of the presence of activating mutation(s) of the EGFR gene from an Approved Pathology Authority. Continuing PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic non-small cell lung cancer in patients with a WHO performance status of 2 or less, where the patient has previously been issued with an authority prescription for gefitinib.				

In 2009 and 2010, 309 and 277 prescriptions for gefitinib, with associated costs of $1.2 million and $1.1 million, were dispensed respectively.

A submission requesting extension of the current listing to permit use of gefitinib in the first-line setting was rejected by the PBAC in November 2010. AstraZeneca is currently pursuing PASC consideration to inform a re-application for PBS listing of gefitinib via the co-dependent technology evaluation process.

November 2010 PBAC consideration

At its consideration in November 2010, the PBAC accepted that the most relevant evidence was the IPASS direct randomised trial. The results of three other relevant direct randomised trials (NEJ002, Study 0054 and WJTOG 3405) were not yet fully available but broadly support the IPASS results. The trial design allowed for switching such that patients randomised initially to chemotherapy could later commence gefitinib and patients randomised initially to gefitinib could later commence chemotherapy. The former arm represented current clinical practice because gefitinib was currently available second-line, and the latter arm represented clinical practice with first-line gefitinib as requested, so an ITT analysis including switching was a relevant comparison. Results from the key trials, as shown, in Table 2 were considered by the PBAC. The PBAC accepted that these results supported the conclusion of first-line gefitinib treatment effect modification by EGFR mutation status for progression-free survival (PFS). The PBAC noted that an examination of the IPASS PFS data from EGFR M+ and EGFR M- patients in the chemotherapy arm did not indicate there was a prognostic effect, independent of treatment effect, associated with EGFR mutational status (although it is documented in the literature that some EGFR mutation types are independent prognostic factors). The results for median PFS in

the carboplatin plus paclitaxel arm for EGFR M+ patients and EGFR M- patients were similar (6.3 months and 5.8 months respectively).

However, a source of concern in relation to the applicability of the trial results to the Australian population was that, of 1217 randomised patients, only 437 (36%) provided tissue samples that were evaluable for mutation testing. Of the remaining 64%, 179 (15%) did not provide consent for biomarker analyses, 355 (29%) provided consent, but tissue samples were not obtained, and 246 (20%) provided samples that did not give an evaluable result. Another source of concern was that the primary evidentiary basis for the submission was one of multiple pre-specified exploratory subgroup analyses, focussing on EGFR mutation positive (M+) patients of the IPASS trial. Further, in the subgroup of 437 patients with evaluable samples, 261 (60%) were M+, which is a much higher proportion than in unselected Australian non-small cell lung cancer (NSCLC) patients (9.5% estimated in the submission).

This concern was further complicated because IPASS (like the supportive trials) was enriched so that, compared with an unselected Australian population presenting with NSCLC, there were higher proportions of Asians (97.7% vs. 8% of Asian descent in Australia), females (81% vs. 41%), never smokers (93.9% vs. 15% never smokers or passive smokers), younger (median age 57 years vs. 72 years) and non-squamous histology tumours (100% adenocarcinoma or bronchioalveolar vs. approximately 45% adenocarcinoma or unspecified). Although there was a higher proportion of EGFR activating mutations in this enriched population, the evidence available was not sufficient to determine whether these other patient characteristics may also independently modify the comparative treatment effect of first-line gefitinib beyond the modification attributed to the status of the EGFR mutation. In other words, there was little direct evidence for patients with EGFR activating mutations who were non-Asians, males, smokers, older and/or who had squamous or uncertain histology tumours.

In the subgroup of EGFR M+ patients, updated overall survival (OS) data (78% maturity) showed no difference between those initially randomised to gefitinib and those initially randomised to carboplatin and paclitaxel (HR 1.0, 95% CI: 0.76, 1.33; median OS 21.6 months compared with 21.9 months). As already noted, these ITT analyses were relevant to the requested listing and did not support the claim of an overall survival advantage for gefitinib generated by the submission's model (0.09 years for the deterministic model or 0.152 years for the probabilistic model). The PBAC therefore concluded that the submission's estimate of first-line gefitinib's overall effectiveness was an overestimate and its estimate of first-line gefitinib's cost-effectiveness was therefore also more favourable than was supported by the evidence provided.

Table 2 Key results from the randomised controlled trials comparing gefitinib and carboplatin + paclitaxel in patients with NSCLC

Trial ID	Gefitinib Median (95% CI) months	Carboplatin + paclitaxel Median (95% CI) months	Absolute difference (months)	Hazard ratio (between treatment comparison) (95% CI)
IPASS				
ITT (all patients randomised)	N = 609 5.7	N = 608 5.8	-0.1	0.74 * §§ (0.65, 0.85)
EGFR M+ subgroup	N = 132 9.6 (8.0, 11.2)	N = 129 6.3 (5.6, 7.0)	3.2	0.48* (0.36, 0.64)
EGFR M- subgroup	N = 91 1.5 (NR)	N = 85 5.8 (NR)	-4.3	2.85* (2.05, 3.96)
NEJ002 (all EGFR M+)				
Per protocol population	N = 114 10.8 (NR)	N = 110 5.4 (NR)	5.4	0.30** (0.22, 0.41)
Study 0054				
	Gefitinib	Cisplatin + gemcitabine		
EGFR M+ subgroup	N = 26 8.4 (NR)	N = 16 6.7 (NR)	1.7	0.61^ (0.31, 1.22)
EGFR M- subgroup	N = 27 2.1 (NR)	N = 27 6.4 (NR)	-4.3	1.52^^ (0.88, 2.62)
WJTOG 3405 (all EGFR M+)				
	Gefitinib	Cisplatin + docetaxel		
Per protocol population	N = 86 9.2 (8.00, 13.90)	N = 86 6.3 (5.80, 7.80)	2.9	0.49* (0.34, 0.71)

Bolded: EGFR M+ population

* p<0.0001; ** p<0.001; ^ p = 0.84; ^^ p = 0.71

§§ The HR was not constant over time, with the probability of being progression free in favour of carboplatin / paclitaxel doublet chemotherapy in the first 6 months., and in favour of gefitinib in the following 16 months. In such a case, the use of HR is not valid. This was not the case for the EGFR M+ mutation status

CI = Confidence interval; NR = Not reported; ITT = Intention to treat; PP = per protocol; HR = hazard ratio.

In relation to testing, the PBAC affirmed that the mutation testing in any PBS restriction should be limited to tumour material because this was supported by the trial evidence available, and should not be extended to possible alternative sample options such as sputum or pleural fluid. In addition, the PBAC advised that mutation testing should be restricted to detecting exon 19 deletions and exon 21 L858R point mutations because: (a) these account for 247/261 (95%) of patients with the mutations detected; and (b) some resistance mutations such as exon 20 T790M have already been documented.

Although the test used in determining EGFR mutation status was a commercially available dideoxy sequencing test, the PBAC advised that it would not be necessary to specify this particular test in any PBS or MBS restriction. Rather a minimal performance of eligible tests should be specified in terms of analytical validity, in order to minimise both false positives and false negatives. *The PASC confirmed that this would be appropriate, indicating that it is important to identify in the submission the tests used, or possibly used, and their diagnostic accuracy (see Description of the intervention below), and the implications of any differences for effectiveness and cost-effectiveness.*

The PBAC rejected the submission on the basis of unacceptably high and uncertain cost-effectiveness. The main uncertainties related to the prevalence of EGFR M+ in unselected Australian NSCLC patients, EGFR testing performance and cost, the effect of these on the comparative treatment effect of first-line gefitinib, and the extent of the incremental QALY gain based on quality of life advantages without any overall survival advantage.

Regulatory status

Until July 2010, National Association of Testing Authority (NATA) accreditation was the only requirement to be satisfied in order for laboratories to be able to undertake testing for activating mutation(s) of the EGFR gene. NATA undertakes assessment of laboratories using standards set by the National Pathology Accreditation Advisory Council (NPAAC). NATA accreditation provides a means of determining, formally recognizing, and promoting the competence of facilities to perform specific types of testing, inspection, calibration, and other related activities.

The new Medical Devices (MD) Amendment Regulations that were introduced on 1 July 2010 implemented a new regulatory framework that incorporates in-vitro diagnostic medical devices (IVDs), which includes diagnostic tests, under Chapter 4 of Therapeutic Goods Act (TGA) 1989. This amendment of the TGA regulation mandates that laboratories manufacturing Class 1-3 in-house IVDs (which includes DNA sequencing) in Australia notify all in-house tests to the TGA for entry onto a database by July 2014. AstraZeneca's proposal for an application requesting subsidy of EGFR gene mutation testing advises that all current EGFR gene testing service providers are aware of the newly imposed TGA requirements for notification.

In December 2010, MSAC resolved that all EGFR gene mutation testing should be performed by a NATA-accredited laboratory that has been demonstrated, in a suitable External Quality Assurance Program (QAP), to be proficient in the technique employed. The Department of Health and Ageing was to ensure appropriate mechanisms are in place before any MBS listing of the test. There are only four laboratories in Australia that currently perform EGFR gene mutation testing on a routine basis, the Peter MacCallum Cancer Centre (Victoria), the Institute of Medicine and Veterinary Science (South Australia), Path West Laboratory Medicine (Royal Perth Hospital, Western Australia), and Healthscope Advanced Technology (Clayton Laboratory). A national quality assurance program does not yet exist.

Gefitinib (Iressa®) is registered by the TGA. It is currently indicated for the treatment of "patients with locally advanced or metastatic non small cell lung cancer (NSCLC) whose tumours express activating mutations of the EGFR tyrosine kinase".

Intervention

Description of the disease

NSCLC is the most common type of lung cancer accounting for approximately 80% of all cases[2].
There are three histological defined subgroups of NSCLC:

(i) adenocarcinoma – often found in an outer area of the lung;
(ii) squamous cell carcinoma – usually found in the centre of the lung by an air tube (bronchus);

(iii) large cell carcinoma – may occur in any part of the lung; tends to grow and spread faster than the other two types.

Adenocarcinomas of the lung predominate in women in Japan (72%), Korea (65%), and in Singapore Chinese (61%) and now also in western countries. The percentage of lung cancer cases classified as adenocarcinoma is higher in Asia than in North America or Europe. Adenocarcinoma is currently the most prominent form of lung cancer in younger persons, women of all ages, lifetime non-smokers and long-term former smokers[3]. *PASC indicated that adenocarcinoma is increasing in prevalence compared to squamous cell carcinomas in Australia.*

Regardless of the subtype, but in common with all cancers, NSCLC arises as a consequence of either acquired (somatic) and/or inherited (germ-line) mutations. Over time and many cellular divisions, a mutation will translate into the abnormal cellular proteins and enzymes. This can lead to disruption of physiological cell function, abnormal cell regulation, proliferation, survival and migration; this is otherwise referred to as tumour development and metastases.

Somatic mutations often arise as a consequence of exposure to factors capable of causing damage to the genetic code within cells. Known examples include tobacco smoke, ionising radiation, some organic solvents, viruses, alcohol and asbestos. There are numerous theories as to why some people do and others do not develop cancer. Overall, the number of mutations acquired by individuals as a consequence of lifestyle, diet, and working environment, in combination with predisposed inherited genetic risk factors together contribute to the overall risk for an individual.

In terms of NSCLC some of these mutations are known to translate directly into pathological processes associated with cancer, whereas other 'bystander' mutations may only become pathological as a consequence of the tumourigenesis processes itself.

Epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases (TKs) regulate many developmental, metabolic and physiological processes. In tumour cells, the TK activity of EGFR may be dysregulated by various oncogenic mechanisms, including EGFR gene mutation, increased gene copy number and EGFR protein overexpression[4]. Improper activation of EGFR TK results in increased malignant cell survival, proliferation, invasion and metastasis. EGFR overexpression is observed in tumours from more than 60% of patients with metastatic NSCLC, and is correlated with poor prognosis[4,5]. Because of the high frequency of EGFR mutations in NSCLC, these somatic mutations are thought to represent very early genetic events leading to the development of lung cancer[4,6]. These findings are the rationale for the development of novel anticancer agents that target EGFR.

EGFR mutation

EGFR is a cellular transmembrane receptor found on the surface of cells. Activation of the EGFR occurs when specific ligands, including EGF or other growth factors, bind to the extracellular domain. This stimulates intracellular tyrosine kinase activity and a cascade of intracellular reactions leading to DNA synthesis and cell proliferation. Mutations of the EGFR gene may cause the gene to be constitutively "active" resulting in overexpression or activity and contributing to the development of cancers through tumour cell proliferation. There is some evidence that the mutant allele is also amplified[15].

EGFR mutations are found in exons 18-21 of the EGFR gene. They include point mutations, insertions, and deletions in the EGFR gene. Around 90% of all activating mutations are accounted for by exon 19 deletions and a point mutation in exon 21 (L858R)[7]. A patient with locally advanced or metastatic NSCLC is said to be mutation positive (M+) if an activating EGFR gene mutation is detected. If an activating mutation is not detected, the patient is said to be mutation negative (M-). EGFR mutations are more common in patients who have never smoked (or have only smoked very little), patients with adenocarcinoma histology, females, and Asian patients[8,9].

The public summary document (PSD) relating to MSAC's consideration of EGFR testing in December 2010 noted that PBAC had proposed limiting any extension of the PBS listing for gefitinib to particular exon 19 deletions and exon 21 L858R point mutations, so this might obviate the need to obtain larger samples with minimum thresholds of tumour volume in order to test for all possible mutations, for example by DNA sequence analysis.

In regard to testing for specific mutations, AstraZeneca proposed an approach in which testing is limited to adenocarcinoma samples for the purpose of determining the appropriateness of first-line gefitinib. *PASC has determined that it would be more appropriate to limit testing to patient with non-squamous NSCLC and NSCLC not otherwise specified.* Access to gefitinib may then be restricted via a change in the PBS listing to use amongst patients with evidence of exon 19 deletions and/or exon 21 L858R point mutations only.

The PSD relating to MSAC's consideration of EGFR testing in December 2010 also indicated that reliable estimates of the prevalence of the particular mutations of interest in the tested population will be important. Prevalence is also likely to vary with any proposal to pre-select the population for testing based on clinical or histological criteria. Studies that have pre-selected their populations using clinical profiling report a high likelihood of a EGFR mutation (59.7%[10], 34%[11]) compared with 12.1% and 14.8% in the unselected populations[12],[13]. The PSD relating to MSAC's consideration of EGFR testing in December 2010 also suggested that EGFR gene mutation results may change with exposure to radiotherapy and other therapies and thus the results of testing the primary tumour may not be representative of EGFR gene mutation status in NSCLC metastases in some patients. MSAC also noted that there were uncertainties around the development of resistance to gefitinib, interpretative challenges in the laboratory, such as whether mutations in EGFR gene testing may be activating, neutral or resistant, and that a gene may have multiple mutations requiring a determination as to which one would take precedence biologically. Additionally some atypical EGFR mutations, in particular, insertion 20 mutations are gefitinib insensitive[6]. MSAC noted that knowledge in this area was evolving as more data accumulates.

Clinical expert advice has indicated that a single test should probably be sufficient to determine eligibility for treatment with an EGFR tyrosine kinase inhibitor (such as gefitinib). However, it was also noted that, if a patient has metastatic NSCLC involving multiple sites, it is currently unclear which is the most appropriate site to biopsy for EGFR mutation testing as the mutation status may differ between primary and metastatic sites and that there is currently only limited data addressing this issue. As noted above regarding the November 2010 PBAC consideration of gefitinib, the PBAC considered that mutation testing should be limited to testing of tumour material. This is consistent

with recommendations that mutation testing be undertaken on tissue from the most accessible tumour site until further information is known. It was also noted that, although the majority of patients with EGFR activating mutations who develop resistance to tyrosine kinase inhibitor treatment (e.g., gefitinib) don't currently undergo repeated biopsies, it is possible that, in future, serial sampling of tumours over the course of treatment may become important to detect emergence of drug resistant mutations as newer drugs are being developed that overcome some resistance mechanisms (e.g., irreversible EGFR inhibitors).

Description of the intervention

Testing for EGFR gene mutation in patients with locally advanced or metastatic NSCLC involves: (i) collection of an appropriate sample of lung cancer tissue for testing; (ii) preparation of the tissue sample; and (iii) testing the prepared sample for an activating mutation of the EGFR gene.

(i) Collection of tissue sample

The proposal stated that in Australia, there are two common methods for obtaining tumour tissue for EGFR gene mutation testing: (i) bronchoscopically and (ii) percutaneous fine needle aspiration (FNA). Bronchoscopy is commonly performed by respiratory physicians, and may allow sampling of endobronchial disease (biopsies, wash, brush); mediastinal masses or lymph nodes (transbronchial needle aspiration with or without endobronchial ultrasound-guidance (EBUS); or sampling of peripheral lung lesions (transbronchial biopsies, brushes or washes with or without endobronchial ultrasound-guidance (EBUS). When bronchoscopy is not suitable, CT guided percutaneous FNA is an alternative approach. This is generally performed by radiologists. FNA has the disadvantage of providing smaller tissue volumes and carries greater risk of complications for patients and is therefore not the preferred method for obtaining tissue for EGFR mutational analysis. However, core biopsies with a larger bore needle can also be performed by a CT guided percutaneous approach and can provide a larger specimen.

In order to be able to conduct EGFR testing on a sample of lung tissue, it is imperative that a sufficient quantity of lung cancer tumour tissue be available for analysis. MSAC noted in its December 2010 consideration that, currently, the amount of tumour material collected by biopsy from the lung is often insufficient for molecular testing, particularly where tissue samples are retrieved by fine needle aspiration.

MSAC, in December 2010, noted that if EGFR testing was not required to be performed at the time of initial diagnosis, consequential issues would need to be considered such as the need to re-biopsy to obtain a new sample or to retrieve a stored sample if available (which may be assisted by appropriate attention to managing cell blocks). This is important given the comparatively small tumour samples which are retrieved in NSCLC through standard cytological techniques such as FNA. Obtaining multiple samples and performing multiple tests over time would have consequences for the patient and the healthcare system which would need to be assessed

In regard to the timing of tests, AstraZeneca proposed that the biopsy and testing for EGFR mutation status be conducted at the time of, or as close as possible, to initial diagnosis of NSCLC. *PASC agreed that EGFR mutation testing should occur as close as possible to initial diagnosis of NSCLC. However,*

PASC also noted that re-biopsy may need to occur in the case of sample failure, or for patients who may be eligible for second-line gefitinib therapy. AstraZeneca also proposed that mutation testing occur only once following an assessment by a pathologist that the lung tumour sample is 1) histologically defined as adenocarcinoma, that 2) sufficient numbers of cells are present for genetic testing and 3) that there is a sufficiently high ratio of malignant to normal cells present. *PASC has determined that the need for histological definition of the lung sample tissue as adenocarcinoma is not necessary PASC agreed that the viability of a biopsy for mutation testing is the ratio of malignant to normal cells within a sample, and this is crucial for the detection of tumour specific mutations. However, they noted that this is difficult to ascertain prior to mutation testing being performed. PASC indicated that the MBS item descriptor should not limit the number of tests as there may be a need for re-biopsy.*

(ii) Preparation of tissue sample

The proposal stated that qualified pathology department personnel undertake preparation of biopsy material, i.e., chemical fixation, slicing, staining and mounting onto glass slides. Interpretation of histopathology and selection of biopsy samples or section slices containing appropriate cells for EGFR mutational analysis is performed by pathologists.

Tumour samples collected at time of diagnosis/surgery are typically stored by the pathology department of the hospital where the diagnosis/surgery was undertaken. When a request to test for the presence of mutations in the EGFR gene is made by the treating physician, preparation and packaging of pathology samples or slides for dispatch to an accredited centre that conducts EGFR gene mutation testing is undertaken by pathology department administrative staff.

(iii) Testing for an activating mutation of the EGFR gene

The proposal stated that if not prepared prior to being sent to the EGFR gene mutation testing laboratory, formalin-fixed, paraffin-embedded (FFPE) tissue blocks will be processed into sections and presented onto glass slides by qualified molecular pathology clinical scientists. An initial review of these slides is performed by a pathologist at the testing centre to determine sample quality and likelihood of yielding sufficient cancer cells required for analysis. If tumour cells of appropriate quality and quantity are identified, these are dissected from the pathology slide(s) by the pathologist. These cells are then processed in terms of their DNA extraction, followed by the amplification of DNA from candidate exons by qualified molecular pathology clinical scientists. These DNA samples are then analysed via validated platforms (e.g., direct gene sequencing) for the presence of EGFR mutations by qualified molecular pathology clinical scientists.

Process review, interpretation and reporting of results of the EGFR gene mutation test are performed by qualified senior molecular pathology clinical scientists and/ or qualified molecular pathologists and reported to the referring doctor.

As discussed above, although collection of a sample of tumour tissue is necessary to conduct EGFR gene mutation testing, the proposal indicated that EGFR gene mutation testing will be undertaken using a sample of tumour tissue obtained at the time of diagnosis. On this basis, it was proposed that

the submission to MSAC will assume that no healthcare resources will be utilised prior to the conduct of the EGFR test. However, the proposal indicated that approximately 5% of samples cannot be analysed due to low tumour load and in such cases a re-biopsy would be required. Furthermore, the clinical management algorithms provided in the proposal suggest that 23% of patients may have EGFR status unknown due to poor samples. As noted by the PBAC in November 2010, 20% of patients in the IPASS trial provided samples that did not yield an evaluable result.

In regard to the use of resources in collecting a tissue sample, and whether they should be included in the economic evaluation, AstraZeneca has proposed that it be assumed that all EGFR gene mutation testing will be undertaken using a sample of tumour tissue obtained at the time of diagnosis and therefore no healthcare resources will be utilised prior to the conduct of the EGFR testing. *AstraZeneca has also proposed that consideration of the need for re-biopsy, and associated costs, should be included in the sensitivity analysis of the economic model. PASC agreed that the need for re-biopsy could be dealt with in sensitivity analyses of the economic model and also indicated that the proportion requiring re-biopsy for first-line and second-line may differ.*

AstraZeneca, stated that, based on real world data, 5% of biopsy samples presented to the Peter MacCallum Cancer Centre Pathology Department had insufficient tumour cells to enable EGFR mutation testing, but the proportion of samples provided to other pathology service providers without sufficient quality is unknown. AstraZeneca proposed to advocate the provision of guidance to hospitals and other pathology departments as a mechanism of ensuring only appropriate samples are sent for testing. *This was not accepted by the PASC. As PASC noted, it is the ratio of malignant to normal cells within a sample that is crucial for the detection of tumour-specific mutations. A sample may appear to be sufficient at the time of collection, but only at the time of testing can it be determined if there is a minimum level of tumour load to provide the basis for an accurate result. It was noted that there may be significant risk involved in in obtaining repeat biopsies in some patients.*

Testing techniques

The proposal did not advocate limiting funding of testing for EGFR gene mutations to any one particular technique. Several techniques can be used to establish the presence of EGFR gene mutations in tumour samples. All techniques fall into two categories: (i) screening technologies which detect all EGFR mutations including novel mutations; and (ii) targeted technologies which detect specific known EGFR mutations. Screening technologies include polymerase chain reaction (PCR)/sequencing, nested PCR/sequencing, PCR/High resolution melt analysis (HRMA)/denaturing high performance liquid chromatography (dHPLC) (melt analysis), and pyrosequencing. Targeted mutation technologies include DxP (QIAGEN®) amplification refractory mutation system (ARMS)/Scorpions PCR, peptide nucleic acid-locked nucleic acid (PNA-LNA) PCR clamp, SnaPshot® (Applied Biosystems™), PCR/Fluorescent fragment length polymorphism (RFLP), mutant-enriched (ME) PCR/sequencing, Sequenom® OncoCarta™ MassARRAY®, and PCR-Invader® (Hologic)[1].

[1] AstraZeneca EGFR M+ website (accessed June 9 2010) http://www.egfr-mutation.com/EGFR-exon/egfr-dection

The proposal stated that currently, the majority of the techniques used to test for EGFR gene mutations are developed in-house by Australian advanced molecular pathology service providers using established, validated and published procedures.

In addition, there is no generally accepted standard approach for determining EGFR mutation status, i.e., screening (sequencing) or targeting (ARMS/Scorpions etc) approaches to testing, but that sequencing is considered to be the gold standard for detecting any/all mutations that might be present. The proposal acknowledged that in the future, other approaches, including commercial assays such as those that employ the ARMS/Scorpions technique, may be used.

In December 2010, MSAC noted that any future considerations of EGFR testing should identify the available test options and any strategies to combine test options. A comparative assessment of their analytical performance based on empirical data would also be needed. This comparative assessment should refer to the testing approach used in the clinical trial evidence provided to support the co-dependency between EGFR gene testing and the proposed wider use of gefitinib, including the type, collection and handling of samples. This comparative assessment should also refer to the reference or gold standard test. The collection and handling of samples should also be considered to assess the impact on test performance of inadequate samples.

MSAC, in December 2010, also indicated that analyses of comparative test performance should be incorporated appropriately into overall clinical and economic evaluations, taking into account PBAC's proposal to limit any extension of the PBS listing for gefitinib to particular mutations (exon 19 deletion and exon 21 L858R point mutations) and the likely prevalence of these mutations in any proposal to select the population for testing. This should appropriately address the impact on patient outcomes and overall cost-effectiveness of both false negative results and false positive results of identified testing approaches. Sensitivity analyses of these clinical and economic evaluations would help determine the required thresholds for test performance. Similarly, scenario analyses of these clinical and economic evaluations would help assess the different options of when best to test in the clinical pathway. Other useful measures to help interpret and compare these scenario analyses are the number of patients needing to be tested for each patient treated and the associated cost of testing per treated patient.

AstraZeneca proposed that the MBS item descriptor should not specify a test for EGFR mutation testing beyond the statement that the test used should be a validated, established method for detecting the presence of mutations associated with the eligibility criteria for PBS listed gefitinib and be provided by a NATA accredited pathology service. AstraZeneca stated that any restricting of the methodological approach to EGFR testing is likely to negatively impact the innovative drive of testing providers to deliver improved techniques with greater sensitivity and/or the ability to deliver results faster. PASC noted there is, as yet, no validated test. *PASC noted that it is important for a submission for listing EGFR mutation testing on the MBS to include the identification of all tests, an assessment of their comparative diagnostic accuracy and analytical sensitivity. The sensitivity and specificity of the test will affect the positive predictive value of the test.*

Delivery of the intervention

The proposal indicated that it is anticipated that medical oncologists will be the main professional group who order and use the test results. However, as respiratory physicians and thoracic surgeons often perform the biopsy and may care for the patient without a referral to a medical oncologist, they may also order and use the test results to choose the most appropriate therapy.

The laboratory conducting the testing will require the services of pathologists to identify the most appropriate tumour sample for testing and to interpret the molecular testing results.

MSAC, in December 2010, noted the possibility of preselecting patients for mutation testing on the basis of the likelihood of harbouring an activating mutation in the EGFR gene should be considered. Selection of patients could be based on clinical profiling or histological criteria known to be prognostic of progression. If proposed, these options should be assessed according to the confidence of unequivocally differentiating between factors at diagnosis with different prognostic impact. The PSD relating to MSAC's considerations in December 2010 also states that any proposal to further confine EGFR testing to any pre-selected group based on clinical or histological criteria would also need to be communicated in any MBS item descriptor. *AstraZeneca has proposed that the MBS item descriptor would be limited to patients who have histologically defined adenocarcinoma, however PASC has indicated that this limitation is not appropriate, and instead the patient population should be limited to patients with non-squamous NSCLC and NSCLC not otherwise specified.*

Prerequisites

Although the proposed listing does not include any limitations on who might provide a referral for EGFR gene mutation testing, the information provided by the applicant notes that requests for EGFR gene mutation testing typically originate from either oncologists, respiratory physicians or thoracic surgeons.

In terms of limitations on who could deliver EGFR gene mutation testing, the proposal indicated that the application will assume that EGFR gene mutation testing will be undertaken at NATA accredited molecular pathology laboratories. It is claimed that expansion of the availability of EGFR gene mutation testing will not be associated with increases in staffing numbers, training, or skill set for molecular pathology service providers. Similarly, it is anticipated that no changes to the inventory of capital equipment will occur as a result of expansion of the availability of EGFR gene mutation testing.

It is suggested that there are no specific requirements in terms of geography, facilities, access to equipment, or location for undertaking EGFR gene mutation testing in patients with locally advanced or metastatic NSCLC. If a suitable tumour sample is available (e.g., one that was taken at time of diagnosis/surgery), it is assumed that this sample can be retrieved from the relevant pathology department and sent to an accredited centre for EGFR gene mutation testing. The cost of shipping samples is addressed below in Health care resources.

Co-administered and associated interventions

Gefitinib (IRESSA®) is an EGFR tyrosine kinase inhibitor, administered orally once daily (250mg). The proposal states that in gefitinib clinical trials, drug treatment is ceased on, or soon after, disease progression. EGFR gene mutation testing and gefitinib can be considered to be co-dependent technologies. AstraZeneca advised that, on the basis that gefitinib is more efficacious in patients who test positive for an EGFR gene mutation in comparison to those who test negative for an EGFR gene mutation (Armour and Watkins, 2010[14]), concurrent MBS and PBS listings are being sought for EGFR gene mutation testing and gefitinib to facilitate use of gefitinib for first-line treatment, as a monotherapy, in patients with locally advanced or metastatic NSCLC who have an activating mutation of the EGFR gene. If an activating mutation is not detected, treatment with gefitinib has a greater likelihood of being futile and chemotherapy and/or radiotherapy would be assessed as an alternative treatment approaches.

Listing proposed and options for MSAC consideration

Proposed MBS listing

The proposed MBS listing for EGFR testing is shown in Table 3.

Table 3: Proposed MBS item descriptor for EGFR testing

Category 6 – Pathology services Group P7 – Genetics
[MBS item number] To establish the presence or absence of an activating EGFR mutation in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) for consideration of treatment with gefitinib therapy. Fee: $394.11

In response to discussion of the proposed item descriptor, PASC considered a more appropriate wording would be that shown in Table 4. The alternative wording is aligned with the listing recommended by MSAC in December 2010 but also uses the preferred term "non-squamous NSCLC" as NSCLC is considered to be a non-specified label. Given the link to the PBS listing of gefitinib through the use of the phrase "access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled", it is not necessary for the item descriptor to specify whether testing is performed for access to gefitinib in the first- or second-line treatment setting.

Table 4: Alternate MBS item descriptor for EGFR 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 non-small cell lung cancer, or non-small cell lung cancer not otherwise specified, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $394.11

Clinical place for proposed intervention

Implicitly, it is claimed that listing of the co-dependent EGFR testing and gefitinib technologies as requested will improve clinical management and outcomes for patients with locally advanced or metastatic NSCLC. In their response to the draft DAP, the applicant provided revised clinical management algorithms, one for current management of patients with NSCLC (Figure 1) and the second for management should gefitinib be listed for first-line use (Figure 2). This second algorithm has been altered to reflect the decisions made at the PASC meeting regarding the defined population.

Current management algorithm

In the current management algorithm (**Error! Reference source not found.**), no EGFR testing is conducted prior to first-line therapy and all patients are treated with platinum-based doublet chemotherapy. Recommendations for the type of platinum-based therapy are determined by whether the patient has a squamous or non-squamous cell tumour[12]. In the case that platinum-based doublet chemotherapy is contraindicated or not tolerated or upon progression of disease, it is assumed that 25% of patients will be tested for activating mutations of EGFR.

AstraZeneca has indicated they do not agree with the limiting of second-line gefitinib therapy to patients with a WHO status less than or equal to 2. Consequently they have proposed an alternate current management algorithm, which is depicted in Figure 1. In this algorithm it is assumed that patients positive for NSCLC are separated into those with histologically confirmed adenocarcinoma or those without adenocarcinoma. *As indicated above, PASC did not agree with the use of adenocarcinoma to define the patient population.* All patients are treated with platin-based doublet chemotherapy. Patients with adenocarcinoma with disease progression after platin-based doublet chemotherapy then have their biopsy retrieved for EGFR testing or require a re-biopsy (possibly up to two times). Patients who are EGFR mutation positive are eligible for gefitinib. *PASC agreed that one of the claims for gefitinib is that it is better tolerated than traditional chemotherapy therefore sicker*

patients may be able to access this treatment. PASC disagreed with the inclusion of erlotinib for use in patients who have tested EGFR negative.

The current clinical management algorithm (Figure 1), reflects the MBS listing for EGFR mutation testing to access the current PBS listing of gefitinib for second-line treatment. In this algorithm it is assumed that patients positive for NSCLC are separated into those with histologically confirmed adenocarcinoma or those without adenocarcinoma (this group includes patients who have cytology alone and have no biopsy undertaken; 30%). All patients are treated with platin-based doublet chemotherapy. Patients with adenocarcinoma with disease progression after platin-based doublet chemotherapy then have their biopsy retrieved for EGFR testing or require a re-biopsy (possibly up to two times). *PASC has indicated that adenocarcinoma is not an appropriate determination of patient elgigibility, and instead the defining characteristic of the patient population should be non-squamous NSCLC or NSCLC not otherwise specified.* Patients who are EGFR mutation positive are eligible for gefitinib. *PASC stated that the allowance in the algorithm for patients who test negative to EGFR mutation to be eligible for erlotinib, therapy needs to be amended.*

Proposed management algorithm

The proposed clinical management algorithm, (Figure 2), reflects the likely requested listing for gefitinib for first-line therapy. *PASC has stated that the population, instead of those with histologically confirmed adenocarcinoma as proposed by the sponsor, should be patients with non-squamous NSCLC or NSCLC not otherwise specified.*

Reflecting the current clinical management algorithm, patients positive for NSCLC are separated into those with histologically confirmed adenocarcinoma or those without adenocarcinoma (this group includes patients who have cytology alone and have no biopsy undertaken; 30%). At this stage patients with adenocarcinoma are eligible for EGFR mutation testing. *As stated above, and as for Figure 1, PASC has disagreed with the use of adenocarcinoma as the defining feature of the population.* Patients who test positive to EGFR mutation are treated with gefitinib monotherapy. *The algorithm does not indicate what happens to patients whose biopsy sample is insufficient for EGFR mutation testing. Under this algorithm, access to second-line gefitinib does not appear to be a possibility for patients who have their NSCLC diagnosed by cytology, and then have failed first-line platin-based doublet therapy (or potentially patients with insufficient biopsy sample for EGFR testing who are treated with platin-based doublet therapy in lieu of re-biopsy).*

In addition, as for Figure 1, the possibility of biopsy for patients with initial cytology diagnosis (30%) needs to be taken into consideration. Also, the use of "70% via histology" in both Figures 1 and 2 does not provide an accurate description of how samples may be obtained. Bronchoscopy can provide both cytological samples (cell suspension eg washes, transbronchial needle aspiration, brushes) and histological samples (cell or tissue block, ie bronchoscopic endobronchial or transbronchial biopsy). Furthermore, some cytology specimens can be spun down and made into a histology block. Fine needle aspiration can provide a cytological sample, but if a core biosy is taken, ie with a larger needle, sections can be made for the core to be examnined as histology. Given these possibilities, it would be appropriate for the application to consider the different approaches to biopsy.

PASC also indicated that the allowance in the algorithm for patients who test negative to EGFR mutation to be eligible for erlotinib, therapy needs to be amended.

Figure 1: Revised current management algorithm for NSCLC second-line gefitinib therapy

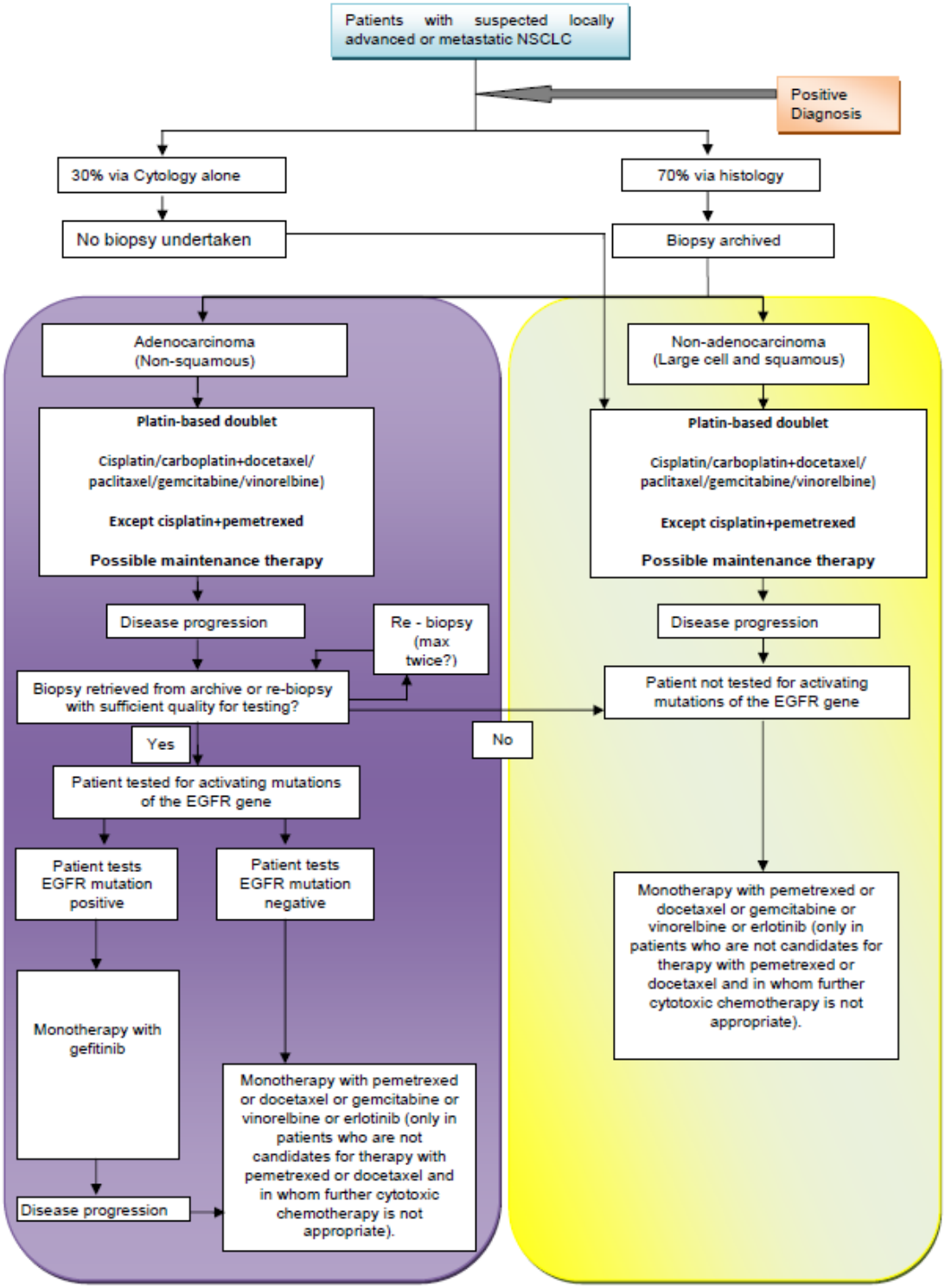
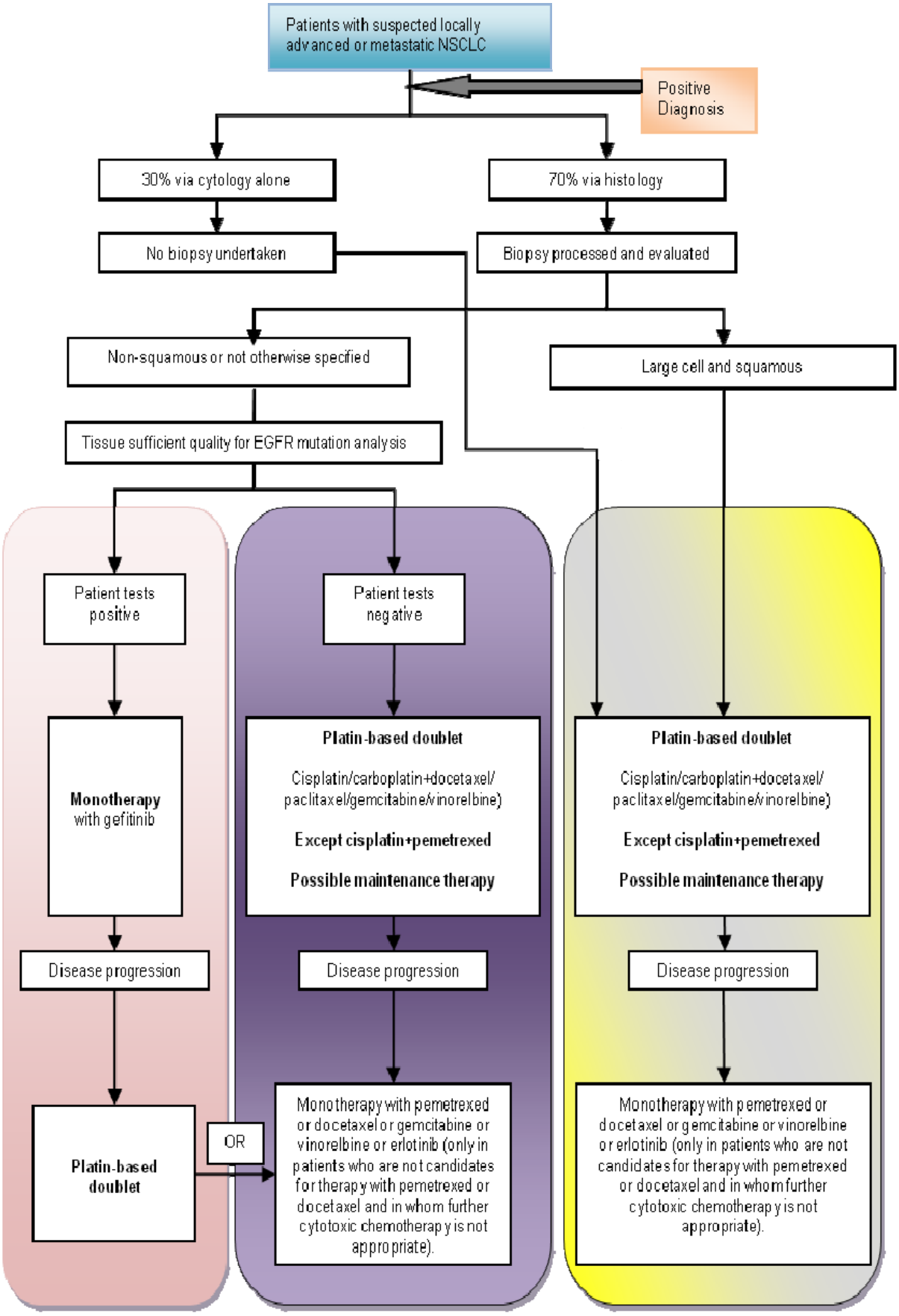


Figure 2: Revised proposed management algorithm for NSCLC-first-line gefitinib therapy



Comparator

The proposal stated that the first appropriate comparator is no EGFR testing under the current PBS treatment algorithm. Patients in the current setting (where gefitinib is not available for first-line treatment) are assumed to be treated with platinum-based doublet chemotherapy for fit patients (single agents can be offered in elderly or patients).

The proposal also claimed that the availability of an accurate EGFR test will improve the effectiveness and hence cost-effectiveness of gefitinib treatment to the extent that it would be an appropriate first line treatment for EGFR mutation+ patients. Consequently the proposal suggested that a second comparison would be first line EGFR testing and gefitinib treatment versus the current treatment algorithm, and in this comparison gefitinib would replace doublet chemotherapy as a first line treatment for NSCLC.

PASC agreed with the nominated comparators proposed and noted that with gefitinib used as first-line therapy there is greater risk associated with false positive EGFR results, as such patients would receive an ineffectual treatment (gefitinib) and not receive effective treatment (doublet chemotherapy). Evidence relating to the diagnostic accuracy of the available tests and a comparison between the selected tests will need to be considered, Then, evidence demonstrating the claimed benefits of EGFR testing and gefitinib use will be required – in this case the comparison would be the proposed first-line EGFR testing and gefitinib use versus the current scenario.

PASC also stated that erlotinib should be considered as a comparator, given its potential use as first line therapy.

Clinical claim

The clinical claim made by the applicant is that testing for EGFR status and treating patients on the basis of the results of that test (patients with EGFR activating mutation are treated with gefitinib; those without EGFR activating mutation or not tested are treated with platinum-based doublet chemotherapy) is associated with advantages over the current scenario. The proposal for application made the following claims:

- Clinical trial data show EGFR mutation status to be a crucial indicator of response to gefitinib, and therefore it is vital that patients are tested for mutation status before the best treatment decisions can be made.
- Patients with EGFR mutation who are treated with gefitinib have a significant quality of life (QoL) advantage over patients receiving platinum-based chemotherapy.
- Improvements in QoL associated with gefitinib treatment are likely to be reflective of the efficacy and tolerability benefits that gefitinib offers over chemotherapy.

- In addition to improved QoL, improvements in progression free survival are also likely to lead to improved survival.
- Gefitinib has significant safety advantages over chemotherapy.

On the basis of a claim for superiority, it was proposed that a cost-effectiveness/cost-utility analysis will be presented in the application. *PASC agreed that the proposed outcome claim was that patients with EGFR mutation who are treated with gefitinib have significant quality of life advantages over patients receiving platinum-based chemotherapy and in these patients improvements in progression-free survival are also likely to lead to improved survival. A cost-utility/cost effectiveness model is appropriate. PASC agreed with the PBAC finding that the presence of the EGFR mutation was a treatment effect modifier and PASC considered that evidence of a prognostic effect was equivocal.*

Outcomes and health care resources affected by introduction of proposed intervention

Clinical outcomes

The following outcomes were identified as the most appropriate:

Efficacy

- Diagnostic accuracy of EGFR testing*: in order to calculate PPV & NPV prevalence of EGFR gene mutation status will need to be known. The prevalence of the population is likely to differ depending on whether the accuracy of the test has been determined in a NSCLC population that has been pre-selected for the likelihood of having the EGFR mutation or the accuracy of the test has been determined in an unselected population with NSCLC.*
- Comparison of test performance
- Objective tumour response rates
- Progression-free survival
- Overall survival
- Quality-adjusted survival

Although diagnostic accuracy of EGFR testing is nominated as an outcome that is integral to the determination of the comparative effectiveness of targeted use of gefitinib in EGFR mutation positive patients (and use of platinum based doublet therapy in mutation negative patients) versus use of platinum-based doublet therapy in all patients, there is no generally accepted standard approach to determining EGFR mutation status, i.e. screening (gene sequencing) or targeting (Scorpion ARMS, QIAGEN etc.) approaches to testing.

MSAC, in its December 2010 consideration and clarification of the information it would need in a rec-consideration of EGFR testing, stated that the available test options and any strategies to combine test options (with or without HRM polymerase chain reaction pre-screening) need to be identified. A

comparative assessment of their analytical performance based on empirical data is also needed. This comparative assessment should refer to the testing approach used in the clinical trial evidence provided to support the co-dependency between EGFR gene testing and the proposed wider use of gefitinib, including the type, collection and handling of samples. This comparative assessment should also refer to the reference or gold standard test if one can be identified. The collection and handling of samples should also be considered to assess the impact of test performance of inadequate samples.

The proposal indicated the application will assume 100% sensitivity and specificity for EGFR testing (i.e., assume no false positives and no false negatives are generated by the test). *PASC did not agree with this proposal. PASC noted that as there is no validated test information about which tests are available, their diagnostic accuracy, including comparative analytical sensitivity, will need to be included in any application.*

Safety

It is claimed that there are likely to be few safety issues that might impact on the patient from the application of the test to tissue samples as the majority of tissue samples would have already been obtained for the diagnostic work-up. *PASC noted there are likely to be safety issues with the use of gefitinib as first-line therapy. False positive results could potentially expose the patient to the adverse effects of gefitinib without benefit and could potentially result in denial of other effective treatment. False negative results would deny the patient access to the potential benefits of gefitinib.*

Health care resources

The proposal included costs for the following health care resource items:

- Costs for EGFR testing. Costs associated with administration of gefitinib.
- Costs associated with administration of platinum-based doublet chemotherapy (there are four treatment regimens that have been demonstrated to have similar efficacy[16], those being carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/gemcitabine, cisplatin/docetaxel).
- Costs used in the management of adverse events associated with gefitinib (specifically, anaemia, thrombocytopaenia, diarrhoea, anorexia, rash, alopecia and insterstitial lung disease).
- Costs used in the management of adverse events associated with chemotherapy (specifically, thrombocytopenia, anaemia, bone marrow failure, febrile neutropaenia, leukopaenia, diarrhoea, vomiting and anorexia).

AstraZeneca proposed that the proportion of patients who would require a repeat biopsy will be modelled in the sensitivity analysis. *As stated above, PASC agreed that the need for re-biopsy could be dealt with in sensitivity analyses of the model. Separate estimated costs for performing EGFR mutation testing from each of the four nominated providers will need to be provided.*

AstraZeneca considered that costs which may be incurred to send biopsy samples intra or inter-state are likely to be insignificant. Samples that are shipped are formalin fixed and embedded in paraffin, hence stable, and are usually sent by post rather than courier. *PASC did not comment on the need to include shipping costs in the modelled evaluation.*

Proposed structure of economic evaluation (decision-analytic)

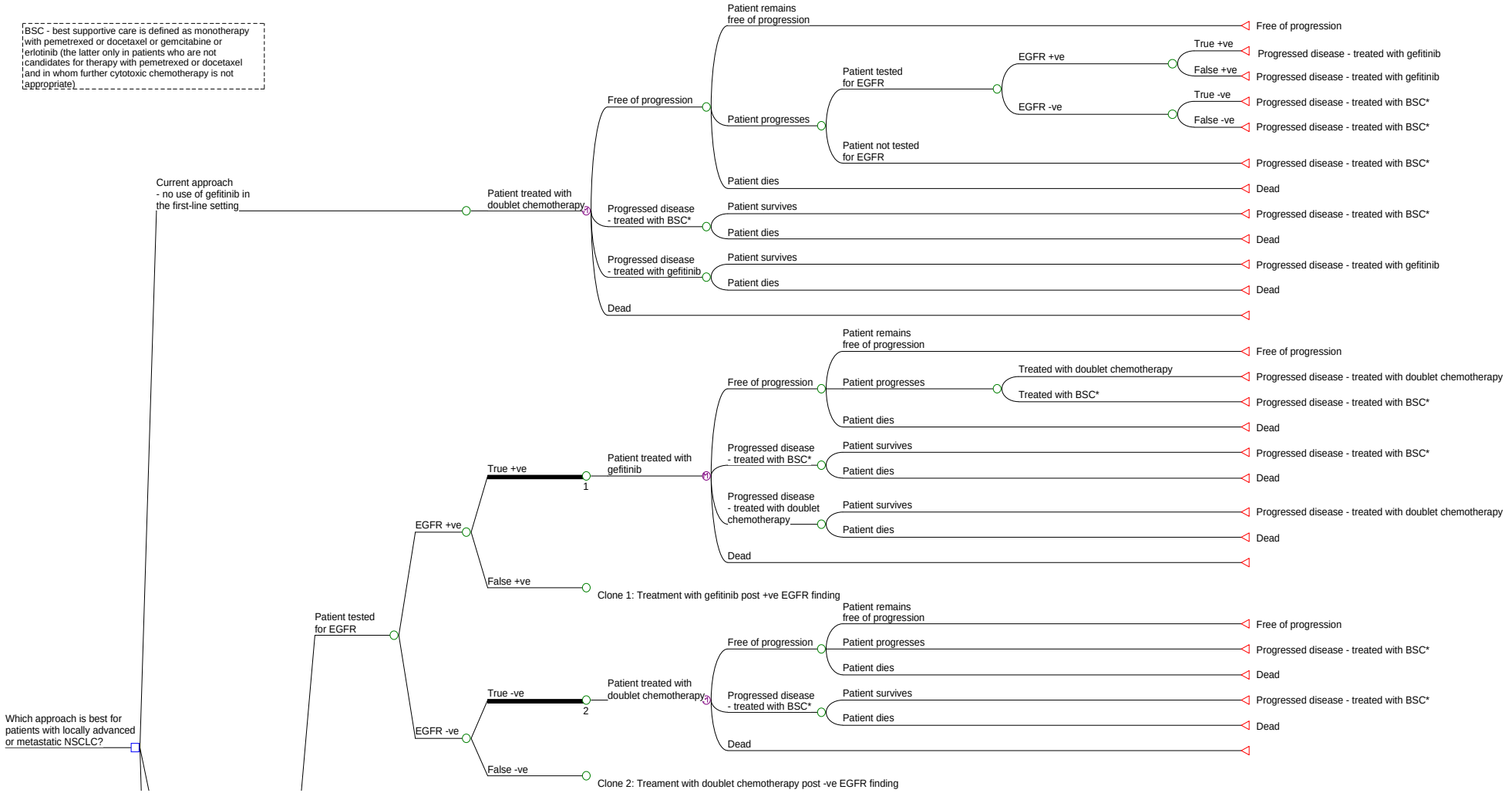
Table 5 presents a summary of the extended PICO for comparison of EGFR testing and targeted gefitinib and no EGFR testing and treatment with doublet chemotherapy.

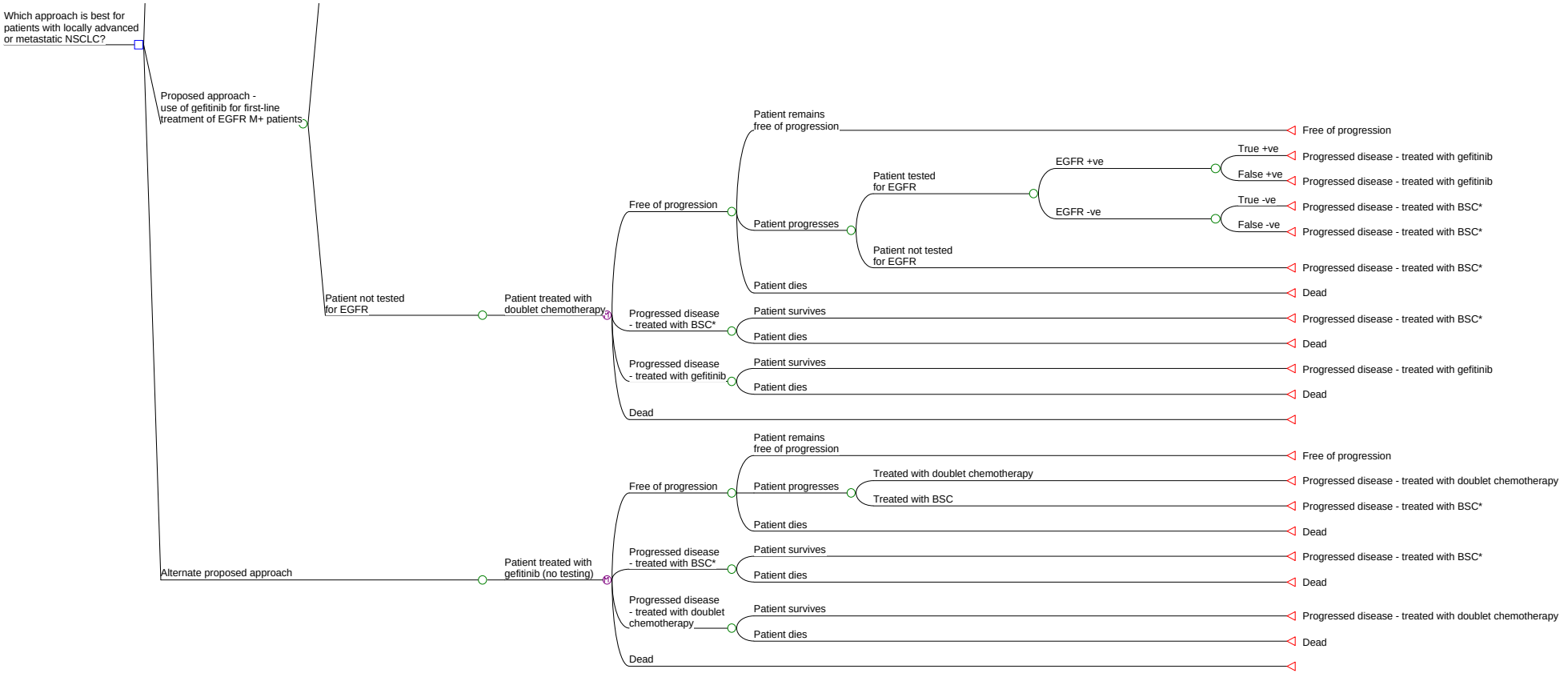
Table 5: Summary of extended PICO to define the question for public funding that assessment will investigate

Patients	Intervention	Comparator	Outcomes to be assessed	Healthcare resources to be considered
Patients with non-squamous locally advanced or metastatic non small cell lung cancer NSCLC not otherwise specified	EGFR testing and targeted use of gefitinib (on the basis of result of EGFR testing)	No EGFR testing and treatment with doublet chemotherapy	Diagnostic accuracy of EGFR testing Comparison of test performance Objective tumour response rates Progression-free survival Overall survival Quality-adjusted survival	Costs for EGFR testing Costs associated with administration of gefitinib Costs associated with administration of doublet chemotherapy Costs used in the management of adverse events associated with gefitinib (specifically, anaemia, thrombocytopaenia, diarrhoea, anorexia, rash, alopecia and insterstitial lung disease) Costs used in the management of adverse events associated with doublet chemotherapy (specifically, anaemia, bone marrow failure, febrile neutropaenia, leukopaenia, diarrhoea, vomiting and anorexia)

The draft DAP included an alternate model structure (see Figure 5 below) and the applicant has agreed with the majority of the model structure.

Figure 3: Alternate structure for a model




Which approach is best for patients with locally advanced or metastatic NSCLC?
Proposed approach - use of gefitinib for first-line treatment of EGFR M+ patients
Patient not tested for EGFR
Patient treated with doublet chemotherapy
Free of progression
Patient remains free of progression
Free of progression
Patient progresses
Patient tested for EGFR
EGFR +ve
True +ve
Progressed disease - treated with gefitinib
False +ve
Progressed disease - treated with gefitinib
EGFR -ve
True -ve
Progressed disease - treated with BSC*
False -ve
Progressed disease - treated with BSC*
Patient not tested for EGFR
Progressed disease - treated with BSC*
Patient dies
Dead
Progressed disease - treated with BSC*
Patient survives
Patient dies
Dead
Progressed disease - treated with gefitinib
Patient survives
Patient dies
Dead
Dead
Alternate proposed approach
Patient treated with gefitinib (no testing)
Free of progression
Patient remains free of progression
Free of progression
Patient progresses
Treated with doublet chemotherapy
Progressed disease - treated with doublet chemotherapy
Treated with BSC
Progressed disease - treated with BSC*
Patient dies
Dead
Progressed disease - treated with BSC*
Patient survives
Patient dies
Dead
Progressed disease - treated with doublet chemotherapy
Patient survives
Patient dies
Dead
Dead

The alternate model structure has the following characteristics:

- The model will capture the costs and effects of the diagnostic testing
- The time horizon of the model is the patient's lifetime
- The model will capture survival gains from the use of gefitinib (if any) and quality adjusted survival
- In addition, the model will capture the costs of any adverse events from use of chemotherapy

In summary:

1. Patients with non-small cell lung cancer enter the model.
2. In the first arm of the model it is assumed that there is no use of gefitinib in first-line therapy and all patients are treated with doublet chemotherapy.
    a. Patients are progressed through a Markov process where they are either progression free, have progressed disease-treated with gefitinib, have progressed disease treated with BSC or die.
    b. Patients who are progression free are progressed through a Markov process where they continue to receive ongoing chemotherapy cycles until disease progression or death.
    c. Patients who have disease progression who are eligible for an EGFR test (WHO ≤2) will have the EGFR test, and those who are positive will receive gefitinib treatment. They can stay in this health state receiving gefitinib while the disease doesn't progress or until death. If the disease progresses they move to a new health state where they will receive BSC until they die. Patients whose EGFR test is negative will move to a new health state where they receive BSC until they die.
    d. Patients who have disease progression who are not eligible for an EGFR test will receive BSC (monotherapy) until they die.
3. In the second arm of the model, the proposed approach is one where gefitinib is used as first-line therapy.
    a. Patients are assumed to be eligible for treatment with gefitinib (i.e. their WHO status is ≤2)
    b. Patients are tested for EGFR mutation just after diagnosis of NSCLC. In the proposal put forward by the applicant most patients will be tested although a residual number will have a biopsy sample that is inadequate for the EGFR test. (The model is structured such that the proportion that will have the test can be adjusted in the model to include the scenario that only patients with clinical characteristics that increase their likelihood of having an EGFR activating mutation receive the test and the majority of the population do not receive the test). Patients will either be positive or negative.
    c. Patients who are positive for an activating mutation of the EGFR gene will be treated with gefitinib and progress through a Markov process where they are either progression free, have progressed disease or die.

i. Patients who are progression free after a course of gefitinib are progressed through a Markov process where they continue to receive gefitinib therapy until the disease progresses or they die.
ii. Patients whose disease has progressed will move to a new health state. A proportion of these patients will be well enough to continue with active chemotherapy, and the remainder will receive BSC. Patients being treated with active chemotherapy will continue until the disease progresses or they die. Once the disease progresses they will enter a new health state where they will receive BSC. Patients receiving active chemotherapy will receive this treatment until the disease progresses.
iii. Patients in the health state where they are receiving BSC will continue with BSC until they die.

d. Patients who are negative for an activating mutation of the EGFR gene will be treated with doublet chemotherapy.
    i. Patients are progressed through a Markov process where they are either progression free, have disease progression-may have a repeat EGFR test and if positive be treated with 2nd-line gefitinib, have disease progression and then are treated with BSC or dead
        1. Patients who are progression free are progressed through a Markov process where they continue to receive ongoing chemotherapy cycles until disease progression or death.
        2. Patients who have disease progression will receive BSC (monotherapy) until they die.

e. Patients who are not tested for an activating mutation of the EGFR gene will be treated with doublet chemotherapy.
    i. Patients are progressed through a Markov process where they are either progression free, have disease progression-may have a repeat EGFR test and if positive be treated with 2nd-line gefitinib, have disease progression and then are treated with BSC or dead.
    ii. Patients who are progression free are progressed through a Markov process where they continue to receive ongoing chemotherapy cycles until disease progression or death.
    iii. Patients who have disease progression may then have an EGFR test (if WHO status ≤2), and those who are positive will receive gefitinib treatment. They can stay in this health state receiving gefitinib as long as the disease doesn't progress or until death. If the disease progresses they move to a new health state where they will receive BSC until they die. Patients whose EGFR test is negative will move to a new health state where they receive BSC until they die.
    iv. Patients who have disease progression and do not have an EGFR test will receive BSC (monotherapy) until they die.

4. In the third arm of the model, it is assumed that all patients are treated with gefitinib. This arm of the model is designed to capture any prognostic effects from the presence or absence of the activating mutation of the EGFR gene.

a. Patients are progressed through a Markov process where they are either progression free, have progressed disease-treated with doublet chemotherapy, have progressed disease treated with BSC or die.
    i. Patients who are progression free after a course of gefitinib are progressed through a Markov process where they continue to receive gefitinib therapy until the disease progresses or they die.
    ii. Patients whose disease has progressed will move to a new health state. A proportion of these patients will be well enough to continue with active chemotherapy, the remainder will receive BSC. Patients being treated with active chemotherapy, will continue until the disease progresses or they die. Once the disease progress they will enter a new health state where they will receive BSC. Patients receiving active chemotherapy will receive this treatment until the disease progresses.
    iii. Patients in the health state where they are receiving BSC will continue with BSC until they die.

AstraZeneca requested modifying the structure to allow the potential for patients who do not progress to go straight to maintenance therapy, either erlotinib or mono chemotherapy. In the case of doublet chemotherapy, this maintenance therapy will be implemented after the fixed initial treatment interval. However, it is not uncommon for patients to withdraw from therapy prior to progression due to tolerability problems.

AstraZeneca agreed that EGFR testing, if it is done, be considered at two critical time points dependent upon the eventual PBS listing of gefitinib. At the time of diagnosis and prior to first-line therapy, and after progression and before second-line therapy. In both cases there may be a need for a second biopsy prior to testing.

PASC indicated that EGFR mutation testing for second-line gefitinib be presented as a comparator arm. PASC also indicated that given the different approaches to testing, and combining of tests, the cost of each individual testing methodology will need to be included in the model.

PASC indicated that the model will need to address the uncertainty around the expansion of the listing for EGFR testing beyond that already agreed by MSAC relative for use with second-line gefitinib therapy. The following issues are relevant:

- *The proportion of patients who are likely to be eligible for EGFR testing for first-line gefitinib therapy;*
- *The proportion of patients who have their NSCLC diagnosed using histology or cytology, and therefore the proportion whose biopsy sample is available for histological analysis;*
- *The proportion of patients who have their NSCLC diagnosed using cytology but may later fit the clinical profile of mutation positive cases and therefore be subject to biopsy;*
- *The limitation of patients for first-line therapy on the basis of health status, e.g. WHO ≤2*

Table 6 summarises the healthcare resources that are identified by the applicant to be included in the economic analysis.

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

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
- EGFR - mutation test - (per test)	pathology	public	100%	1						$394.11
-										
Resources provided to deliver proposed intervention										
- Gefitinib - 250mg/day - per cycle	Astra Zeneca	Private	100%	1 cycle=21 days			$2696		Assume safety net	$2696
Resources provided in association with proposed intervention										
-										
Resources provided to deliver comparator 1										
- Carboplatin+ - paclitaxel	Hospital	Public	100%	1 every 3 wks						$2549
-										
Resources used in management of adverse events, (resources used for treatment of down-stream conditions) costs per event-Gefitinib										
- Anaemia	Hospital	Public								$590
- Thrombo - cytopenia	Hospital	Public								$479
- Diarrhoea	Pharmacy	Private								$191
- Anorexia	Dietician	Public								$488
- Rash	Pharmacy	Private								$50
- Alopecia	Hairdresser	Private								$263
- Interstitial lung disease	Hospital	Public								
Resources used in management of adverse events, (resources used for treatment of down-stream conditions) costs per event-doublet chemotherapy										
- Monitoring - costs	Hospital	Public								$577
- Anaemia	Hospital	Public								$590
- Bone marrow - failure	Hospital	Public								$641
- Febrile - neutropenia	Hospital	Public								$6915
- Leukopenia	Hospital	Public								$0
- Neutropenia	Hospital	Public								$59
- Diarrhoea	Hospital	Public								$191
- Vomiting	Hospital	Public								$879
- Anorexia	Dietician	Public								$488

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

In describing the costs per event for each adverse event listed, the proposed application reports that the costs of the adverse events are based on the IPASS clinical trial and expert opinion. They represent relevant hospital costs and specific blood products. Attached to the proposed application were the relevant tables that report weighted cost per event (which are recorded in Table 6 above) provided with the PBAC submission (July 2010). Cost information was not available for interstitial lung disease.

MSAC in its considerations of December 2010 on information it would need in a re-consideration of EGFR testing for a submission to extend the PBS listing for gefitinib, commented that the basis for determining an MBS fee for EGFR gene testing to support the current PBS listing of gefitinib might

provide a suitable basis for an MBS fee for a subsequent wider use of EGFR gene testing. Alternatively wider use might generate economies of scale which should be reflected in a reduced fee. Overall costs of any additional sample collection, retrieval and handling also need to be considered. Estimates of the impact of MBS and PBS budgets should be based on an appropriate mix of prevalence data to estimate initial impacts and incidence data to estimate longer term impacts.

The information provided by the applicant in the proposed application was not sufficient to be able to determine the robustness of the weighted costs per event provided.. The following was noted:

- The cost of the test. In the PSD of the December 2010 MSAC, in which 2nd line-therapy for gefitinib is requested, the cost of the test is quoted at between $400 and $606. In this proposal, the cost of the test is quoted as being $394.11. The reasons for the discrepancy in the cost are not explored in this proposal. *PASC agreed that an estimate of the cost of the test (and breakdown) from the four nominated providers be provided in the submission. PASC also indicated that the costs for the different types of testing should be included in the model.*
- In calculating the weighted cost of an adverse event the proposed application has included the cost of the AR-DRG for that condition, and in addition then costed treatment of that condition. For example, Table 1 of the proposed application estimates the weighted cost of treating Grade 3-4 neutropenia. The AR-DRG Q60C for neutropenia ($1,327.00) is listed and in addition the cost of infusion of blood or blood products (45 events at $2,654.00) is added to the AR-DRG cost and then a weighted cost per event calculated (although the weight is not provided). *This total cost appears to include double counting. Treatment using blood products for an in-patient episode of neutropenia is likely to be included in the relevant AR-DRG.*
- Treatment per event of anorexia by a dietician is calculated at $488. *This cost appears excessive and requires some justification.*

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