



Australian Government

Medical Services Advisory Committee

## Public Summary Document

### ***Application No. 1161 – Assessment of EGFR mutation testing for the use of gefitinib in locally advanced or metastatic non-squamous NSCLC***

**Sponsor/Applicant/s:** AstraZeneca

**Date of MSAC consideration:** 29-30 November 2012

#### **1. Purpose of application**

In April 2011, the Department of Health and Ageing received a proposal for an application from AstraZeneca requesting 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).

This application seeks to extend availability of a test already funded on the MBS for use of gefitinib for first-line treatment (seeking PBS listing) in patients with locally advanced or metastatic NSCLC.

#### **2. Background**

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 was 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 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 that 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. MSAC noted 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 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 regarding 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.

<b>Table 1: Current MBS item descriptor for [item]</b> 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

### 3. Prerequisites to implementation of any funding advice

AstraZeneca’s proposal for an application requesting subsidy of EGFR gene mutation testing advised that all current EGFR gene testing service providers are aware of the newly imposed TGA requirements for notification.

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.

Only a limited number of Australian laboratories currently perform this test.

### 4. Proposal for public funding

#### Proposed (and current) MBS listing

Category 6 – Pathology services Group P7 – Genetics
73328
A test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: \$397.35

The proposal 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.

### 5. Consumer Impact Statement

No issues were identified.

### 6. Proposed intervention’s place in clinical management

The current and proposed algorithms are for the base case scenario, which only allows testing for patients who would be immediately eligible for gefitinib treatment if EGFR mutation positive (M+). EGFR mutation testing would be an additional intervention to the current practice of no testing for first-line treatment. However, as EGFR mutation testing can be

undertaken to determine eligibility for second-line gefitinib treatment, it will likely just change the timing of testing for some patients.

MSAC noted expert advice that current clinical practice guidelines recommend gefitinib for the first-line treatment of EGFR M+ NSCLC in patients with a good performance status (NHMRC; Azzoli et al. 2011; Felip et al. 2011; and NCCN Clinical Practice Guidelines in Oncology 2012).

The current clinical management algorithm 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).

#### Proposed management algorithm

The proposed clinical management algorithm 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, PASC has disagreed with the use of adenocarcinoma as the defining feature of the population. Patients whose tumour tests 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).

#### **7. Other options for MSAC consideration**

Not applicable.

#### **8. Comparator to the proposed intervention**

The proposed comparator for the use of EGFR mutation testing to triage patients for first-line treatment with gefitinib was 'no testing'. Current practice includes EGFR mutation testing to triage patients for second-line treatment with gefitinib and so this is included in the economic analysis.

MSAC agreed with the nominated comparator 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 would need to be considered.

## Proposed (and current) MBS listing

<b>Category 6 – Pathology services Group P7 – Genetics</b>
73328 A test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.
Fee: \$397.35

### 9. Comparative safety

No safety concerns regarding EGFR mutation testing were reported in the resubmission. No unexpected serious adverse events occurred during any of the pre-clinical, clinical validation and clinical utility studies.

### 10. Comparative effectiveness

#### Evidence for the test performance

Prognostic evidence on the biomarker (not systematically acquired)	Retrospective cohort studies investigating clinical outcomes of patients with biomarker positive or negative status.	<input checked="" type="checkbox"/> k = 5      n = 1127
Comparative analytical performance	Studies that compared different testing methodologies from archival specimens or samples. Concordance data were presented <sup>a</sup> .	Resubmission: <input checked="" type="checkbox"/> k = 13      n = 1199 Evaluation: <input checked="" type="checkbox"/> k = 3      n = 189

<sup>a</sup> reference standard not available. k=number of studies; n=number of patients.

The resubmission identified 13 studies that compared at least two EGFR mutation testing methods but presented only one of these. A further three studies that met the inclusion criteria were identified during the evaluation. Most of the included studies compared a test method to DNA sequencing.

**Table 4: Concordance of EGFR mutation testing methodologies**

	<b>Positive % agreement</b>	<b>Negative % agreement</b>	<b>Overall % agreement</b>	<b>Kappa</b>
<b>Concordance with DNA sequencing using LCM enrichment of tumour cells:</b>				
<b>HRM</b>				
Takano et al. 2007	91.9% (95% CI 78.7%, 97.2%)	100% (95% CI 87.1%, 100%)	95.2% (95% CI 86.9%, 98.4%)	0.903
Fukui et al. 2008	100% (95% CI 82.4%, 100%)	100% (95% CI 89.9%, 100%)	100% (95% CI 93.1%, 100%)	1.00

	Positive % agreement	Negative % agreement	Overall % agreement	Kappa
<b>Concordance with DNA sequencing: HRM</b>				
Do et al. 2008	<u>All EGFR mutations</u> 100% (95% CI: 94.9%, 100%)	65.1% (95% CI 56.6%, 72.8%)	77.5% (95% CI 71.2%, 82.7%)	0.570
	<u>EGFR exon 19 deletions</u> 100% (95% CI: 92.3%, 100%)	86.4% (95% CI: 80.0%, 90.9%)	89.5% (95% CI: 84.5%, 93.0%)	0.744
Takano et al. 2007	<u>EGFR exon 21 L858R</u> 100% (95% CI: 78.5%, 100%)	85.5% (95% CI: 79.7%, 89.8%)	86.5% (95% CI: 81.1%, 90.6%)	0.811
Borras et al 2011	100% (95% CI 87.9%, 100%)	82.9% (95% CI 67.3%, 91.9%)	90.5% (95% CI 80.7%, 95.6%)	1.00
Nomoto et al. 2006	100% (95% CI: 51.0%, 100%)	100% (95% CI: 90.0%, 100%)	100% (95% CI: 90.1%, 100%)	0.837
	100% (95% CI 83.2%, 100%)	83.3% (95% CI 60.8%, 94.2%)	91.9% (95% CI 78.7%, 97.2%)	
<b>ARMS technology</b>				
Ellison et al. 2010	47.1% (95% CI 26.2, 69.0)	94.9% (95% CI 90.9, 97.2)	91.1% (95% CI 86.5, 94.2)	0.409
Morinaga et al. 2008	<u>All EGFR mutations</u> 75.0% (95% CI 40.9, 92.9)	89.1% (95% CI 81.1, 94.0)	88.0% (95% CI 80.2, 93.0)	0.440
	<u>EGFR exon 19 deletions</u> 33.3% (95% CI: 6.2%, 79.2%)	97.9% (95% CI 92.8%, 99.4%)	96.0% (95% CI 90.2%, 98.4%)	0.313
	<u>EGFR exon 21 L858R</u> 100% (95% CI: 56.6%, 100%)	91.6% (95% CI 84.3%, 95.7%)	92.0% (95% CI 85.0%, 95.9%)	0.521
Goto et al. 2012 (DxS TheraScreen)	100% (95% CI 88.4%, 100%)	97.8% (95% CI 88.4%, 99.6%)	98.2% (95% CI 93.6%, 99.5%)	0.962
Kamel-Reid et al. 2012 (DxS TheraScreen)	98.4% (95% CI 91.7%, 100%)	66.7% (95% CI 30.0%, 90.3%)	93.3% (95% CI 78.7%, 98.2%)	0.762
	100% (95% CI 86.2%, 100%)			
<b>Taqman PCR assay</b>				
Endo et al. 2005	100% (95% CI 87.1%, 100%)	98.5% (95% CI 92.1%, 99.7%)	98.9% (95% CI 94.2%, 99.8%)	0.974
<b>PNA-LNA PCR clamping technology</b>				
Han et al. 2012 ( PNA Clamp EGFR Mutation Kit)	100% (95% CI 75.8%, 75.8%)	63.6% (95% CI 35.4%, 84.8%)	82.6% (95% CI 62.9%, 93.0%)	0.646

	<b>Positive % agreement</b>	<b>Negative % agreement</b>	<b>Overall % agreement</b>	<b>Kappa</b>
Goto et al. 2012	96.7% (95% CI 88.8%, 99.1%)	95.6% (95% CI 85.2%, 98.8%)	96.2% (95% CI 90.7%, 98.5%)	0.923
<b>Cycleave PCR (for exon 19 and 21)</b>				
Goto et al. 2012	98.4% (95% CI 91.7%, 99.7%)	100% (95% CI 93.1%, 100%)	99.1% (95% CI 95.3%, 99.9%)	0.981
<b>Mutation-specific PCR</b>				
Ohnishi et al. 2006	<u>All EGFR mutations</u>			
	82.6% (95% CI 62.9%, 93.0%)	92.3% (95% CI 79.7%, 97.4%)	88.7% (95% CI 78.5%, 94.4%)	0.756
	<u>EGFR exon 19 deletions</u>			0.763
	66.7% (95% CI: 39.1%, 86.2%)	100% (95% CI 92.9%, 100%)	93.6% (95% CI 84.6%, 97.5%)	0.850
	<u>EGFR exon 21 L858R</u>			
	100% (95% CI: 74.1%, 100%)	94.2% (95% CI 84.1%, 98.0%)	95.2% (95% CI 86.7%, 98.3%)	
<b>Mutant enriched PCR</b>				
Asano et al. 2006	<u>All EGFR mutations</u>			
	100% (95% CI 89.6%, 100%)	94.7% (95% CI 87.0%, 97.9%)	96.3% (95% CI 90.9%, 98.6%)	0.916
	<u>EGFR exon 19 deletions</u>			0.964
	100% (95% CI: 80.6%, 100%)	98.9% (95% CI 94.1%, 99.8%)	99.1% (95% CI 94.9%, 99.8%)	0.902
Otani et al. 2006	<u>EGFR exon 21 L858R</u>			
	100% (95% CI: 81.6%, 100%)	96.7% (95% CI 90.8%, 98.9%)	97.2% (95% CI 92.2%, 99.1%)	0.624
	100% (95% CI 70.0%, 100%)	70.6% (95% CI 46.9%, 86.7%)	80.8% (95% CI 62.1%, 91.5%)	
<b>PCR-Invader</b>				
Goto et al. 2012	100% (95% CI 94.3%, 100%)	97.8% (95% CI 88.7%, 99.6%)	99.1% (95% CI 95.0%, 99.8%)	0.981
<b>PCR fragment analysis (exon 19) plus real-time PCR (exon 21)</b>				
Kamel-Reid et al. 2012	100% (95% CI 86.2%, 100%)	83.3% (95% CI 43.7%, 97.0%)	96.7% (95% CI 83.3%, 99.4%)	0.889
<b>PCR with fragment analysis (exon 19) and restriction fragment length polymorphism (exon 21) plus DNA sequencing verification</b>				
Kamel-Reid et al. 2012	100% (95% CI 86.2%, 100%)	83.3% (95% CI 43.7%, 97.0%)	96.7% (95% CI 83.3%, 99.4%)	0.889

	Positive % agreement	Negative % agreement	Overall % agreement	Kappa
<b>Concordance with real-time PCR amplification for DNA sequencing and PCR fragment analysis (exon 19 deletions) plus Cycleave PCR (L858R and T790M)</b>				
Yatabe et al. 2006	<u>All EGFR mutations</u> 89.7% (95% CI 81.1%, 94.7%)	99.2% (95% CI 95.3%, 99.9%)	95.4% (95% CI 91.5%, 97.6%)	0.902
	<u>EGFR exon 19 deletions</u> 97.4% (95% CI: 86.5%, 99.6%)	100% (95% CI 97.6%, 100%)	99.5% (95% CI 97.2%, 99.9%)	0.984
	<u>EGFR exon 21 L858R</u> 100% (95% CI: 89.3%, 100%)	99.4% (95% CI 96.6%, 99.9%)	99.5% (95% CI 97.2%, 99.9%)	0.982
<b>Concordance with ARMS DxS TheraScreen EGFR29 mutation kit: ARMS TaqMan PCR</b>				
Zhao et al. 2011	100% (95% CI 82.4%, 100%)	100% (95% CI 89.9%, 100%)	100% (95% CI 93.1%, 100%)	0.775
<b>PCR fragment analysis (exon 19) plus real-time PCR (exon 21)</b>				
Kamel-Reid et al. 2012	96.2% (95% CI 81.1%, 99.3%)	100% (95% CI 51.0%, 100%)	96.7% (95% CI 83.3%, 99.4%)	0.870
<b>PCR with fragment analysis (exon 19) and restriction fragment length polymorphism (exon 21) plus DNA sequencing verification</b>				
Kamel-Reid et al. 2012	92.3% (95% CI 75.9%, 97.9%)	75.0% (95% CI 30.1%, 95.4%)	90.0% (95% CI 74.4%, 96.5%)	0.609

The randomised trial which provides the evidentiary standard for this resubmission is the IPASS trial, which relied on Scorpion ARMS technology using the DxS TheraScreen Mutation kit, but did not report any comparative analytical performance data. Two studies (Goto et al. 2012 and Kamel-Reid et al. 2012) provided concordance data for this testing strategy compared with DNA sequencing (with 9/16 laboratories using this testing method in Australia). A breakdown of the concordance between these two methodologies is provided in the Table 5 for the larger study by Goto et al. 2012.

**Table 5: Concordance between the “evidentiary standard” and the most widely used test option in Australia**

		Scorpion ARMS technology using the DxS TheraScreen Mutation kit		
		Yes	No	
DNA sequencing	Yes	A = 63	B = 1	B/(A+B) = 1/64 (1.6%)
	No	C = 1	D = 44	C/(C+D) = 1/45 (2.2%)
		C/(A+C) = 1/64 (1.6%)	B/(B+D) = 1/45 (2.2%)	
		C/(B+C) = 1/2 (50%)	B/(B+C) = 1/2 (50%)	
Overall concordance = 98.2% (95% CI 93.6%, 99.5%); kappa = 0.962				

A high level of agreement between tests in terms of concordance and discordance does not necessarily mean that the identification or absence of a mutation is correct, as both tests may be wrong. The lack of a reference standard precludes certainty regarding test accuracy.

## **Prognostic evidence**

The platinum-based doublet chemotherapy results from the key IPASS trial and the FIRST-SIGNAL trial suggest that EGFR M+ status is not associated with a prognostic effect, if it is accepted that the observed median difference in progression-free survival of less than 1 month (5.5 months for M- versus 6.3 months for M+ in IPASS and 6.4 months for M- versus 6.3 months for M+ in FIRST-SIGNAL) is not a clinically important difference in patients receiving doublet chemotherapy. Overall survival data could not be used from these trials because large proportions of patients on chemotherapy received a TKI upon progression.

The resubmission also identified three cohort studies as providing supportive prognostic evidence. Takano et al found that the OS and response rates to platinum-based doublet chemotherapy were not significantly different between patients with and without EGFR mutations (13.6 v 10.4 months ( $p = 0.12$ ) and 31% v 28% ( $p = 0.50$ ), respectively). Two studies involving patients with operable NSCLC found no evidence of a prognostic effect of the EGFR mutation biomarker.

## **11. Economic evaluation**

The resubmission presented an updated modelled economic evaluation (a cost-utility analysis in terms of cost per quality-adjusted life-year (QALY) gained) based on a superiority claim of the proposed scenario (both first-line EGFR testing and gefitinib are available) over the current scenario (neither first-line EGFR testing nor first-line gefitinib is available) for both comparative benefit and harms. MSAC noted that the Joint ESCs interpreted this comparison as between wider use of earlier EGFR testing and a TKI (in the form of first-line gefitinib) against current use of EGFR testing and later use of a TKI in a subsequent line of treatment.

In the modelled economic evaluation, patients have two options – both first-line EGFR testing and gefitinib are available (proposed scenario, investigation arm) or neither first-line EGFR testing nor first-line gefitinib is available (current scenario, comparator arm). In the proposed scenario, gefitinib is given to EGFR M+ patients and carboplatin + paclitaxel to M– patients. Upon disease progression, 60% of M+ patients switch on to second-line doublet chemotherapy and 60% of M– patients receive second-line docetaxel. In the comparator arm, all patients receive first-line carboplatin+paclitaxel. Upon disease progression, 60% of patients are eligible for active second-line therapy and undergo EGFR testing; patients receive second-line gefitinib if EGFR M+ or second-line docetaxel if M–. Best supportive care is given as second-line therapy for patients who are not eligible for active second-line therapy (40%) and as third-line therapy for all patients alive at second-line disease progression.

MSAC noted that the Joint ESCs considered that the proportion of use of second-line treatment in practice is likely to be lower than 60%, noting the results of an analysis of Medicare Australia data where 45% of patients continued on to second-line therapy. The Joint ESCs noted that assuming a similar percentage of patients receiving crossover second-line treatments between the two intervention arms is inconsistent with the use of second-line treatment in the trial. Notably, a higher proportion of patients in the comparator arm of the model received second-line gefitinib than observed in the IPASS trial. As this leads to a higher drug cost for the comparator arm, this assumption biases the ICER in favour of gefitinib.

There are four health states in the model: progression-free, first-line progression, second-line progression and death. All patients enter the model in the progression-free health state. The

base case of the economic evaluation did not compare gefitinib with carboplatin + gemcitabine, the most commonly used first-line chemotherapy in the Australian clinical practice. MSAC noted that the Joint ESCs considered that the resubmission's nominated comparator of carboplatin and paclitaxel was reasonably representative of the more common platinum-based doublet therapies used in Australian clinical practice.

The resubmission predicted an incremental cost-effectiveness ratio (ICER) in the range of \$15,000-\$45,00 (Redacted Information)/QALY based on the observed PFS benefit of first-line gefitinib over carboplatin + paclitaxel from the IPASS trial, extrapolated to 5 years (from a median follow-up of 17 months in the trial). Utility values were applied from QoL scores reported in the IPASS trial that had been converted using an algorithm derived from another TKI (second-line) clinical trial (ZODIAC) as well as utility decrements associated with disease progression reported in one published study (Nafees et al. 2008).

<b>Redacted Information</b>	<b>Redacted Information</b>		
<b>Redacted Information</b>	<b>Redacted Information</b>	<b>Redacted Information</b>	<b>Redacted Information</b>
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consider other costs which may be associated with EGFR mutation testing, e.g. patient episode initiation and specimen referral fees. The test cost/treated patient exceeds \$2000.

## 12. Financial/budgetary impacts

Likely number of patients tested and treated: **(Redacted Information)**

Number of patients likely to be tested: **(Redacted Information)** **(Redacted Information)**

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5. The number of patients likely to be tested is a key area of uncertainty in the resubmission, as it is based on a number of inadequately supported assumptions. The resubmission also used 2014 as a proxy for the first year of gefitinib listing, and this may overestimate the financial implications should the listing occur earlier.

Number of patients likely to be treated: **(Redacted Information)** The likely number of patients likely to be treated per year was estimated in the submission to be less than 10,000 in Year 5. This estimate was very uncertain due to a paucity of reliable data on the prevalence of the EGFR mutation in Australian NSCLC patients. As the proportion of patients with EGFR M+ NSCLC had a considerable impact on the estimated costs to the health budget, this becomes a key issue for the financial estimates provided in the resubmission.

**(Redacted Information)**

[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

Financial cost to the MBS/PBS

**(Redacted Information)** **(Redacted Information)**

[Redacted]					
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]
[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]	[Redacted]

The MBS cost was calculated from the cost of EGFR mutation testing and cost offsets resulting from a decrease in administration and monitoring of chemotherapy. The net cost to the MBS was estimated in the submission to be less than \$5 million in Year 5.

**(Redacted Information)**

The resubmission considered the costs of re-biopsy and re-testing for patients who initially did not have an adequate tissue sample. The MBS cost offsets relating to the reduction in the number of patients receiving chemotherapy were also considered. Patient co-payments had not been subtracted from the MBS costs due to difficulties in determining the treatment settings. Overall, due to uncertainties surrounding multiple assumptions in the resubmission it was difficult to determine whether the cost to the MBS had been under- or over-estimated.

### 13. Key issues for MSAC from ESC

#### Main issues around the proposed eligible population for public funding and/or the proposed main comparator?

The current clinical management algorithm, reflected the MBS listing for EGFR mutation testing to access the current PBS listing of gefitinib for second-line treatment. In this algorithm it was 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 indicated that adenocarcinoma was not an appropriate determination of patient eligibility, 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.

PASC 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.

#### Main issues around the evidence and conclusions for safety?

It is expected that some patients would require another biopsy due to an inadequate amount of tumour tissue or poor quality of the first sample. There also is a risk of biopsy-related adverse events that will vary according to site of the primary tumour or metastasis and the biopsy method used, which had not been addressed in the resubmission. Computed tomography guided percutaneous fine needle aspiration (used in the economic model) carries a greater risk of complications for patients than the more commonly performed bronchoscopy (with or without endobronchial ultrasound-guidance). Bronchoscopy and needle biopsy is safer, whereas video-assisted thorascopic surgery yields better samples which would tend to reduce re-biopsy rates and so benefit some patients.

#### Main issues around the evidence and conclusions for clinical effectiveness?

Consistent with the August 2012 MSAC meeting, the Joint ESCs advised that despite the apparently high concordance, the impact of false negative test results and false positive test results remained a matter of concern. Particularly because of the serious adverse consequences for false positive tests, the lack of a clear reference standard and doubts that the comparative analytical concordance data adequately reflected the range of variation expected across laboratories in regular practice or that these data adequately accounted for the full range of threats to optimal analytical performance. The Joint ESCs advised that the resubmission's modelled assumption of 100% sensitivity and 100% specificity unacceptably overestimated test performance and thus overestimated the effectiveness and cost-effectiveness of the co-dependent package.

#### Other important clinical issues and areas of clinical uncertainty?

##### **Biomarker**

- EGFR mutation positive status is likely to be a statistically significant positive predictor for overall survival, which should be considered alongside the request to restrict gefitinib to patients testing positive for EGFR mutations.
- Little information was provided to examine the consequences of distinguishing exon

- 19 deletions or L858R point deletions from other EGFR activating mutations that are known to be sensitive to TKIs, such as exon 18 G719X and exon 21 L861Q;
- More information was required about the prevalence of EGFR resistance mutations, such as exon 20 insertions and T790M point mutations, in patients with locally advanced or metastatic non-squamous EGFR M+ NSCLC to aid patient management:
- These patients should not be treated with TKIs such as gefitinib.
- Due to variability of results from existing studies and the uncertain implications of changing the definition of the biomarker (eg including or excluding EGFR resistance mutations) or the definition of the tested population (eg excluding patients with squamous cell or poor performance status), relevant EGFR mutation prevalence rates in NSCLC for the target Australian population are uncertain.

### Testing

- There is some evidence to suggest that there was discordance between EGFR mutation status in the primary tumour and metastases:
- This may mean that additional biopsies are required to determine eligibility for treatment with TKIs;
- This provides a strong rationale for determining current EGFR status when deciding eligibility for treatment with TKIs;
- Re-biopsy may also be required due to an inadequate amount of tumour cells in a sample which could potentially cause harm to the patient;
- The resubmission noted that DNA sequencing is currently the most commonly used method for detecting EGFR mutations in Australian clinical practice:
- This test is imperfect when used as a stand-alone test with no form of tumour enrichment (eg using laser capture microdissection) on poor samples;
- Using more expensive tumour cell enrichment techniques or more expensive tests than direct DNA sequencing would also increase costs.
- Despite the apparently high concordance, the impact of false negative test results and false positive test results remained a matter of concern.
- The resubmission's modelled assumption of 100% sensitivity and 100% specificity unacceptably overestimated test performance and thus overestimated the effectiveness and cost-effectiveness of the co-dependent package.

### Main economic issues and areas of uncertainty?

There are serious uncertainties regarding:

- The prevalence of EGFR mutation in the Australian NSCLC patients;
- The EGFR test performance in Australian laboratories relative to that in the IPASS trial;
- The use of parametric models for survival curves; and
- The utility values/decrements applied to the economic model.

### *Economic issues*

- The applicability of the IPASS trial was problematic due to differences in patient demographics, particularly smoking status, ethnicity and gender, between the trial population and the relevant Australian population;
- There were a number of inconsistencies between the economic model, the results of the premodelling studies, the financial analysis, the IPASS trial data and the clinical management algorithms.

**(Redacted Information)** The ICER associated with the use of first-line EGFR testing and gefitinib in Australian settings is likely to be greater than the resubmission's estimate, given that the economic model:

- Used a maximum of six cycles for platinum-based doublet chemotherapy, which is longer than the duration of doublet chemotherapy recommended by Australian guidelines (four cycles);
- Failed to consider the most commonly used chemotherapy regimen in the Australian target population in current clinical practice, namely carboplatin + gemcitabine, as the comparator; and
- Assumed a higher proportion of patients receiving second-line gefitinib in the comparator arm;

Uncertainties remain regarding:

- The background EGFR mutation rate in the proposed MBS population;
- The test performance of the EGFR testing methods used in Australian laboratories relative to that in the IPASS trial;
- The appropriateness of the parametric models applied to extrapolate PFS, overall survival and time to second-line progression in the economic evaluation; and
- The validity of the utility values/decrements applied to the economic model.

Financial issues

- There was considerable uncertainty in the resubmission's estimate of the number of patients who are eligible to receive gefitinib in the first-line setting hence the costs to the MBS is unknown, given that:
- The resubmission did not fully justify the methodologies used in estimating the number of patients; and
- There were limited data on the prevalence of EGFR positive mutations in the Australian setting.

The Joint ESCs also advised that:

- The number of patients likely to be tested (and treated) excluded patients who do not have a WHO performance status of 0-2 or squamous cell cancer when these restrictions are not proposed for inclusion in the item descriptor;
- The proportion of re-biopsied patients is likely to be underestimated at 1.2% (although the costs of testing re-biopsied tissue may be double-counted for the 70% of patients who are assumed to be re-biopsied in the community);
- Costs of re-biopsy were an underestimate as they do not include professional attendance fees, medical imaging or procedural use (eg bronchoscopy /percutaneous fine needles aspiration);
- The projected MBS financial costs were inappropriately based on MBS fees rather than MBS rebates net of patient co-payments and do not include any MBS-eligible costs for patient episode initiation, specimen retrieval, storage or enrichment; and
- Any acceptance of the claimed financial cost offsets should be consistent with any acceptance of these offsets in the economic evaluation.

#### **14. Other significant factors**

Not applicable.

## **15. Summary of consideration and rationale for MSAC's advice**

### *Whom to test?*

Based on the advice of the October 2012 Stakeholder Meeting on EGFR testing and tyrosine kinase inhibitor (TKI) therapy co-sponsored by MSAC and Pharmaceutical Benefits Advisory Committee (PBAC), MSAC considered that enriching the tested population by excluding patients with a clear morphological diagnosis of squamous non-small cell lung cancer (NSCLC) would have the advantage of lowering the number and costs of patients who would need to be tested per patient treated and the total number and costs of extra tests. Given that the prevalence of EGFR activating mutations in patients with squamous NSCLC is only 0% to 1.1% confining testing to non-squamous cancers would have negligible effect on the total number of patients who would receive a positive test result. However, MSAC also noted that morphological diagnosis of squamous NSCLC is itself associated with false positives and false negatives, and so only a confident diagnosis of squamous NSCLC should serve as an exclusion from subsequent epidermal growth factor receptor (EGFR) mutation testing.

### *When to test?*

Based also on the advice of the October 2012 Stakeholder Meeting, MSAC considered that all patients, irrespective of disease stage, with NSCLC, which is clearly not squamous cell carcinoma should be considered eligible to proceed to EGFR testing at initial diagnosis. Although this approach would increase the number of patients who would need to be tested and the total number and costs of extra tests, only a minority of early non-squamous NSCLC cases will not relapse. Further, this approach would have practical advantages for the minority of NSCLC patients who initially present with less advanced disease and then later progress to more advanced disease. If not tested at diagnosis, such patients would either have to provide a new biopsy sample, or their previous sample would have to be provided via block retrieval. Further, the optimal time to obtain the best tumour sample in NSCLC is usually at initial diagnosis, when histology and staging are also being determined. MSAC accepted that waiting to conduct EGFR testing when treatment with a TKI is being considered for NSCLC compared with conducting EGFR testing at earlier stages of the disease would reduce pressure on short turnaround times, and reduce rates and costs of retesting where retrieved samples prove inadequate for later EGFR testing. The minutes from the Stakeholder Meeting provided reassuring advice that repeat testing for EGFR mutations would only occur in unusual and specific circumstances, and so once per lifetime testing for EGFR would be acceptable in general circumstances. For example, MSAC considered that repeat testing was not needed for monitoring purposes; assessing the development of resistance; checking multiple sites to confirm concordance of EGFR status; assessing mutation stability over time or in response to various treatments; or re-establishing eligibility for another TKI.

### *What to test?*

Taking into account the advice of the October 2012 Stakeholder Meeting, MSAC considered that the definition of the biomarker in a PBS restriction should be any EGFR activating mutation, rather than being limited to exon 19 deletions and exon 21 L858R point deletions only (as suggested by PBAC in the context of its November 2010 consideration of first-line

gefitinib in the same patient population). MSAC accepted advice from the Stakeholder Meeting that, as wider EGFR testing is being performed, these two types of mutation now account for some 70% of EGFR activating mutations rather than the 99% estimate available from the early trials. MSAC also accepted advice from the Stakeholder Meeting that the key randomised trials of the TKIs focussed on these two limited types of mutations, and so a broader biomarker definition would encourage broader reporting of mutations and broader access for patients, but would not be based on strong evidence.

MSAC noted that the choice of definition of the biomarker would affect the preference across test options because restricted allele specific PCR tests were used in the randomised trials of some TKIs for the narrower definition, and more broadly targeted test options (such as Sanger sequencing or a broader array of allele specific PCR tests) would be needed to encompass a broader definition. These differing test options would also have consequences for the amount of tumour tissue required from the biopsy sample and for their comparative analytical performance against different biomarker definitions. The amount of tumour tissue is important in NSCLC because of the difficulty in getting a sufficient sample, and this is currently being exacerbated because the tumour samples will need to be used for an increasing number of purposes. Thus Sanger (DNA) sequencing, which typically requires more tumour tissue than more targeted test options, would increase the need for larger tumour samples and thus the re-biopsy rate would be expected to be about 12%.

MSAC considered that the submission's assumption for modelling purposes of 100% sensitivity and 100% specificity for the test forming the evidentiary standard used in the key trial (the Scorpion amplification refractory mutation system) overestimated the likely test performance across test options and pathology laboratories in Australia. In the absence of an agreed reference standard, the best available concordance data comparing this test with Sanger sequencing (kappa 0.962), which was supplemented by a wider assessment of test options in the evaluation report, did provide some reassurance that these different test options would not produce widely different test results under optimal circumstances. However, these data were not conclusive because they did not involve a clear reference standard and they did not examine all threats to this optimal analytical performance. Consideration is also needed of the procedural steps from obtaining sufficient tumour sample from the patient to its examination in the diagnostic test apparatus (such as the adequacy of tumour sample from core biopsy, bronchoscopy, fine needle aspirate biopsy or pleural effusions; the method of fixation; the use of laser capture microdissection tumour enrichment before sequencing; and other quality control practices in relation to intra- and inter-laboratory variation in methods and interpretation of results). Overall, MSAC advised that the impact of test uncertainty on overall clinical effectiveness and cost-effectiveness needed to be incorporated in the economic evaluation presented for PBAC consideration. The sensitivity analyses provided in the submission and the unevaluated sensitivity analyses provided in response to the Joint ESC Report both generated some implausible results because the consequences of worsening sensitivity or specificity should be an increase in incremental costs, a decrease in incremental QALYs gained, and an increase in incremental cost per extra QALY gained.

MSAC considered that the range of uncertainty in the estimate of prevalence was sufficiently great as to not be able to discern the effect of excluding patients with clearly squamous

NSCLC from testing, or the effect of using different test options with different test performances. The range in the estimates of prevalence of 5% to 36% across the studies presented was affected by small studies with outlier estimates, and MSAC advised that the base case estimate of 15% should be examined in the sensitivity analyses by a range of 10% to 20%.

#### *Other considerations*

MSAC agreed that the nominated comparator of no EGFR testing was appropriate, and that a comparison of analytical performance of the alternative test options was also appropriate. MSAC concluded that the primary co-dependency claim had been established, namely that EGFR testing is important to avoid the hazards of exposing patients with advanced NSCLC to inferior first-line gefitinib when they do not have an EGFR activating mutation because more effective alternative treatments are available in this situation. Given that between 80% and 90% of patients with advanced NSCLC do not have an EGFR activating mutation; it is important that they do not receive first-line gefitinib because they would experience an inferior outcome. From the post hoc subgroup analyses of the supporting IPASS randomised trial, there is evidence of a qualitative interaction between EGFR status and treatment outcome, with first-line gefitinib patients experiencing a statistically significantly inferior progression-free survival compared with doublet chemotherapy when EGFR mutation negative and a statistically significantly superior progression-free survival compared with doublet chemotherapy when EGFR mutation positive. The corresponding results of the smaller First SIGNAL randomised trial are qualitatively similar, albeit not statistically significant. MSAC also concluded that this co-dependency claim could be distinguished from the slightly better prognosis for patients who have an EGFR activating mutation.

Based also on the advice of the October 2012 Stakeholder Meeting, MSAC considered that, from a testing perspective, there was no basis to differentiate between the proposed first-line TKIs in advanced NSCLC, and that any differentiation from a treatment perspective was a matter for PBAC.

Based also on the advice of the October 2012 Stakeholder Meeting, MSAC advised that, in relation to EGFR testing, a shift in pathology practice towards a more centralised approach would increase confidence in the results of these tests by ensuring appropriate expertise and back-up and achieving most parsimonious use of the specimen. This would also facilitate the collation of data on the prevalences of various types of detected EGFR mutations and the clinical basis for determining whether they predict sensitivity or resistance to subsequent TKI therapy, which MSAC considered to be a desirable development. However, by way of some moderation of this proposed shift, MSAC advised that it should not inhibit a more localised approach to conducting a triage test of the specimen when the diagnostic question is still at the stage of differentiating between lung cancer and other pathologies such as an infection. Roughly one third of patients with a lung biopsy are diagnosed not to have lung cancer and these patients should not be disadvantaged unnecessarily. MSAC also noted that poor pathology practice in relation to EGFR testing is likely to reduce the rate of test positive results. Given that this also likely means a reduction in the rate of false positive results, this provides some reassurance that an inability to optimise pathology performance should not

expose patients to inferior use of first-line gefitinib in advanced NSCLC following a false EGFR test positive result because there are more effective alternative treatments available.

Similarly, based also on the advice of the October 2012 Stakeholder Meeting, MSAC advised that a preferred practice model should be promoted to support the integrity of the NSCLC specimens obtained for testing via biopsy. This includes trends by clinicians to obtaining more material at the time of biopsy and thus to using more invasive techniques such as core biopsy rather than fine needle aspiration biopsy. This has consequences for both harms to patients and overall costs of sampling.

MSAC noted that the considerations above and advice below addressed the matters referred to it by the November 2012 PBAC meeting.

MSAC advised that, in the absence of any reason not to do so, the current MBS fee should apply to any expansion of eligibility for MBS funding of EGFR testing.

## **16. MSAC's advice to the Minister**

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness of epidermal growth factor receptor (EGFR) testing to help determine eligibility for proposed PBS-subsidised first-line gefitinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC deferred the application for the requested MBS item until such time as PBAC makes a decision regarding the corresponding PBS listing of gefitinib. MSAC's responses to questions from PBAC are addressed in the following advice:

- the proposed MBS item descriptor should allow NSCLC patients to have EGFR testing from the point of initial diagnosis of NSCLC
- the proposed MBS item descriptor should exclude EGFR testing from patients with NSCLC tumours shown unequivocally to have squamous cell histology
- the proposed MBS item descriptor should require that EGFR testing be performed on the same specimen in the same laboratory as the prerequisite histology testing because this would optimise both confidence in pathology results and parsimonious use of the specimen
- the proposed MBS item should therefore be made a pathology determinable service so that the pathologist can proceed to the second EGFR testing step as indicated by the prerequisite histology step without being interrupted to get a referral from a clinician to do so
- the definition of EGFR test positive in a PBS restriction for a first-line listing of a tyrosine kinase inhibitor (TKI) should be any activating EGFR mutation, but the corresponding economic evaluation presented to PBAC should reflect the fact that the effectiveness of gefitinib has only been demonstrated in randomised trial evidence for up to 70% of the prevalent EGFR activating mutations (that is, for exon 19 deletions and exon 21 L858R point mutations)
- the base case of the economic evaluations and financial analyses presented to PBAC should use 15% for the prevalence of activating EGFR mutations and the corresponding sensitivity analyses should examine a range of 10% to 20%

- the economic evaluations and financial analyses presented to PBAC should include a re-biopsy rate of 12% to reflect the rate of indeterminate results from the initial biopsy, for example, due to not enough tumour tissue being obtained
- the economic evaluations and financial analyses presented to PBAC should include the costs of patient retrieval for re-biopsy, such as professional attendance fees, medical imaging or use of bronchoscopy
- the economic evaluations and financial analyses presented to PBAC should include a 14% complication rate per biopsy
- the economic evaluations and financial analyses presented to PBAC need not include any other repeat testing
- the economic evaluations and financial analyses presented to PBAC should include the full costs of testing, such as patient episode initiation and any extra specimen enrichment
- the sensitivity analyses of the economic evaluations presented to PBAC should appropriately examine the likely extent of proportions of false positive test results and false negative test results in Australia compared with those of the evidentiary standard because these proportions will have clinical and cost-effectiveness consequences due to the resulting misallocation of treatment
- pathology practice should be optimised to ensure EGFR testing is limited to laboratories with appropriate expertise and back-up through a more centralised approach by requiring that the one laboratory performs both the histology and genetic testing on the specimen
- this centralised approach should also be developed to facilitate the collation of data across standardised reports to the requesting oncologists on the prevalences of various types of detected EGFR mutations and the clinical basis for determining whether they predict sensitivity or resistance to subsequent TKI therapy
- biopsy sampling practice should also be optimised to obtain sufficient tumour tissue of adequate quality to obtain high rates of satisfactory specimens.

If further relevant matters require reconsideration, MSAC will expedite this process. If PBAC subsequently decides to recommend to the Minister that gefitinib be listed on the PBS for the first-line treatment of advanced NSCLC, MSAC will support an expedited process for reconsideration to align MSAC support for public funding of EGFR testing according to the circumstances recommended by PBAC. The purposes of the reconsideration would be to review the wording of the proposed MBS item descriptor, and consider changes in the estimates of costs to the MBS.

## **17. Applicant's comments on MSAC's Public Summary Document**

Nil.

## **18. Context for decision**

This advice was made under the MSAC Terms of Reference.

MSAC is to:

Advise the Minister for Health and Ageing on medical services that involve new or emerging technologies and procedures and, where relevant, amendment to existing MBS items, in relation to:

- the strength of evidence in relation to the comparative safety, effectiveness, cost-effectiveness and total cost of the medical service;

- whether public funding should be supported for the medical service and, if so, the circumstances under which public funding should be supported;
- the proposed Medicare Benefits Schedule (MBS) item descriptor and fee for the service where funding through the MBS is supported;
- the circumstances, where there is uncertainty in relation to the clinical or cost-effectiveness of a service, under which interim public funding of a service should be supported for a specified period, during which defined data collections under agreed clinical protocols would be collected to inform a re-assessment of the service by MSAC at the conclusion of that period;
- other matters related to the public funding of health services referred by the Minister.

Advise the Australian Health Ministers' Advisory Council (AHMAC) on health technology assessments referred under AHMAC arrangements.

MSAC may also establish sub-committees to assist MSAC to effectively undertake its role. MSAC may delegate some of its functions to its Executive sub-committee.

## **19. Linkages to other documents**

MSAC's processes are detailed on the MSAC Website at: [www.msac.gov.au](http://www.msac.gov.au).