



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1161 – Gefitinib first line testing for mutations of epidermal growth factor receptor (EGFR) in patients with metastatic non-small cell lung cancer (NSCLC)

Sponsor/Applicant/s: AstraZeneca Pty Ltd

Date of MSAC consideration: 1 August 2013

1. Purpose of application

In March 2013, the Department of Health and Ageing received an application from AstraZeneca Pty Ltd requesting a Medicare Benefits Schedule (MBS) listing of epidermal growth factor receptor (EGFR) mutation testing for non-squamous or not otherwise specified non-small-cell lung cancer (NSCLC) to determine eligibility for first-line treatment with gefitinib, through the Pharmaceutical Benefits Schedule (PBS).

The proposed intervention is a genetic pathology test aimed at detecting somatic EGFR mutations in NSCLC tumour tissue. The sub-group of NSCLC tumours that harbour an EGFR “activating” mutation have increased phosphorylation of EGFR and consequently an over-activated intracellular kinase pathway; this increased downstream signalling leads to cell proliferation and contributes to the malignant phenotype in these patients. Most of these mutations occur between exons 18 and 21 of the tyrosine kinase activation domain and result in ligand overexpression. Currently, 80-90% of all mutations identified are either exon 19 in-frame deletion and/or insertion mutations or an exon 21 missense mutation (L858R - causing a leucine to arginine substitution) (Gately et al 2012; Sharma et al 2007).

At the October 2012 MSAC/PBAC Stakeholder Meeting, it was considered that a more appropriate ratio for common to rare mutations was 70%:30% because the accuracy and sensitivity of testing methodologies will most likely improve in the future. As a consequence, a greater proportion of patients with NSCLC tumours containing rare EGFR mutations would be expected to be identified.

EGFR mutation testing of NSCLC tumour cells will enable the identification of patients who may benefit from targeted drug therapy. EGFR tyrosine kinase inhibitors, such as gefitinib, bind at the ATP site of the ligand and inhibit phosphorylation and receptor signalling. This enables restoration of normal downstream cellular processes such as apoptosis (cell death), leading to decreased tumour cell proliferation.

Currently, EGFR mutation testing is available on the MBS to patients with locally advanced or metastatic NSCLC to determine eligibility for access to second-line treatment with gefitinib under the PBS.

MSAC proposed that all patients with NSCLC unequivocally shown not to have squamous cell histology at the time of initial diagnosis should be eligible for EGFR mutation testing (irrespective of disease stage).

2. Background

In July 2004, PBAC recommended PBS listing of gefitinib on the basis of acceptable cost-effectiveness compared with docetaxel and best supportive care as second-line treatment for patients with an activating mutation of the EGFR gene: PBS listing was effective from 1 December 2004. Despite PBS listing of gefitinib for second-line treatment, EGFR testing to determine gefitinib eligibility was not also listed on the MBS at that time.

In December 2010, MSAC recommended public funding for ‘testing in the limited circumstance of determining tumour EGFR activating mutation status to contribute to a determination of eligibility for currently PBS-subsidised gefitinib for a patient with locally advanced or metastatic non-small cell lung cancer’. EGFR testing was MBS listed in May 2012.

In November 2010, PBAC rejected PBS listing of gefitinib for the first-line treatment of patients with locally advanced or metastatic NSCLC (Stage IIIb/IV) who have an activating mutation in the EGFR gene, on the basis of unacceptably high and uncertain cost-effectiveness.

In October 2012, a Stakeholder Meeting was jointly convened by MSAC and PBAC to resolve outstanding issues related to i) EGFR mutation testing, and ii) the clinical place of tyrosine kinase inhibitors (TKIs) in the treatment of locally advanced (Stage IIIb) or metastatic (Stage IV) NSCLC.

In November 2012, MSAC and PBAC reviewed a co-dependent submission for EGFR mutation testing and access to gefitinib for the first-line treatment of locally advanced or metastatic NSCLC patients expressing activating mutations of the EGFR gene. The submission was rejected by PBAC, and MSAC deferred the application for the requested MBS item until such time as PBAC recommended the corresponding PBS listing of gefitinib.

The sponsor lodged a major resubmission to PBAC for the listing of first-line gefitinib on the PBS for consideration at the July 2013 PBAC meeting. The sponsor was advised that a minor resubmission to MSAC was required to address outstanding testing issues raised in the November 2012 gefitinib MSAC minutes.

3. Prerequisites to implementation of any funding advice

No specific EGFR mutation test was requested in the resubmission for MBS listing. Most EGFR testing is likely to be “in-house” as part of a laboratory network and under the control of an Approved Pathology Authority.

EGFR mutation testing must be performed in National Association of Testing Authorities (NATA) accredited laboratories.

The Royal College of Pathologists of Australasia (RCPA) and Human Genetics Society of Australasia (HGSA) conduct a Molecular Genetics Quality Assurance Program for EGFR mutation screening of human tumours in Australian pathology laboratories.

4. Proposal for public funding

The resubmission requested that the current MBS listing be modified to meet the recent recommendations of MSAC.

Current and proposed MBS item descriptor for EGFR mutation testing

Current MBS item descriptor for second-line EGFR mutation testing	
	Category 6 – Pathology Services Group P7 - Genetics
73328	
A test of tumour cells 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; Benefit: 75% = \$298.05, 85% = \$337.75	
Proposed MBS item descriptor for EGFR mutation testing for access to first-line gefitinib	
73328	
A test of tumour tissue from a patient with diagnosed non-squamous [†] non-small cell lung cancer 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; Benefit: 75% = \$298.05, 85% = \$337.75	

[†] The pathological classification of 'non-squamous' may be expanded to 'non-squamous or not otherwise specified (NOS)' to permit all patients, including those whose tumour is not unequivocally squamous, equitable access to the test under this item. The sponsor defers to MSAC expertise in this matter.

Source: <http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73328&qt=item&criteria=73328>, and Table 1 of minor resubmission to MSAC

Under the proposed MBS item descriptor, EGFR mutation testing would be restricted to patients with non-squamous NSCLC (and possibly also not otherwise specified NSCLC). Patients with squamous NSCLC would not be eligible for testing.

The applicant's proposed PBS restrictions for gefitinib for consideration at the July 2013 PBAC meeting are as follows:

Authority Required

Initial PBS-subsidised treatment, as monotherapy, of locally advanced or metastatic (Stage IIIb/ IV) non-small cell lung cancer (NSCLC) in patients with:

- (1) a WHO performance status of 2 or less and
- (2) a diagnosis of non-squamous NSCLC and
- (3) where there is evidence that tumour material harbours an activating mutation(s) of the epidermal growth factor receptor (EGFR) gene known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs).

Authority Required

Continuing PBS-subsidised treatment of a patient with locally advanced or metastatic NSCLC who has previously received PBS-subsidised treatment with gefitinib and who does not have progressive disease and who remains on first-line therapy.

It is the sponsor's intent that the MBS item descriptor and PBS restriction are aligned, such that the appropriate EGFR gene mutation positive and negative patients are identified and treated expeditiously. The sponsor indicated it is willing to work with MSAC and PBAC to ensure this consistency.

MSAC advice from the November 2012 minutes for Application 1161 suggested that:

- 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 resubmission acknowledged the possible benefits of this recommendation, however, it is sensitive to possible impacts on turnaround times associated with samples that would not be candidates for this treatment, for example those associated with squamous NSCLC.
 - The resubmission stated that: "Channelling of suspected lung cancer biopsy specimens away from localised diagnostic pathology services to the limited number of commercial molecular laboratories may create significant delays in both diagnosis and molecular test reporting. The applicant therefore request MSAC seek guidance via bodies such as the National Pathology Accreditation Advisory Council (NPAAC), the Royal College of Pathologists of Australasia (RCPA), Thoracic Society of Australia and New Zealand and other peak oncology organisations such as the Medical Oncology Group of Australia (MOGA) on the potential service delivery and clinical impacts of a more centralised approach."
- 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 resubmission agreed that the MBS item should be designated a pathology determinable service and states that "associated tissue pathology items should also be included as required".

Changes to pathology services

MSAC advice from the November 2012 minutes for Application 1161 recommended that:

- 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 prevalence 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.

The resubmission:

- supported optimising laboratory practice via the relevant regulatory, accreditation and professional bodies;
- acknowledged the importance of creating uniformity of reporting for molecular test results so that the results and their clinical significance are readily apparent.
 - However, the sponsor also suggested that the Royal College of Pathology Australasia and the National Pathology Accreditation Advisory Council are best placed to manage and develop recommendations for standardisation of molecular laboratory reports.

- stated that clinical practice around optimising sampling techniques is advancing rapidly, as discussed at the Stakeholder Meeting October 2012.

5. Consumer Impact Statement

PASC received six responses during the public consultation period for the DAP from three medical specialists and three stakeholders. The concerns raised included: when to test, reflex testing, whom to test (squamous versus non-squamous NSCLC) and what to test (common or uncommon mutations). These issues were raised at the October 2012 MSAC/PBAC Stakeholder Meeting on EGFR mutation testing, and at the November 2012 MSAC meeting discussion of Application 1161 (EGFR mutation testing for first-line treatment with gefitinib). Concerns were also raised about the need for duplicate testing of specimens and the true cost of EGFR mutation testing being in excess of \$400 per test.

6. Proposed intervention's place in clinical management

EGFR mutation testing would be used to identify a subgroup of patients with locally advanced or metastatic non-squamous NSCLC who would likely benefit from first-line treatment with gefitinib.

EGFR mutation testing for access to first-line TKIs will result in some additional testing because currently testing should only occur in patients who have stage IIIb/IV NSCLC so that they can access gefitinib as a second-line treatment option. However, as most people progress to advanced disease within 2 years, the number of additional tests performed will be small. Thus, the proposed intervention will mostly change the timing of the test (relative to treatment) for those patients diagnosed with an earlier stage of disease.

All patients diagnosed with, or progressed to, stage IIIb/IV NSCLC would then be treated according to the results of the EGFR mutation test. Those with an activating mutation of the EGFR gene would be eligible to receive gefitinib, while those who do not have an EGFR mutation would receive platinum doublet chemotherapy.

Prevalence of EGFR mutations in NSCLC

The economic evaluation and financial estimates in the resubmission to PBAC used a 15% EGFR mutation prevalence as the base case and a range of 10-20% in sensitivity analyses. This is consistent with the November 2012 MSAC advice for Application 1161.

7. Other options for MSAC consideration

Whom to test

The November 2012 MSAC advice for Application 1161 suggested that the proposed MBS item descriptor should exclude EGFR testing from patients with NSCLC tumours shown unequivocally to have squamous cell histology.

- The resubmission agreed with MSAC and reworded the MBS item descriptor to allow testing of patients with diagnosed non-squamous NSCLC. The sponsor deferred to MSAC expertise as to whether the pathological classification of 'non-squamous' may be expanded to 'non-squamous or not otherwise specified (NOS)' to permit all patients whose tumour is not unequivocally squamous, equitable access to the test under this item.

What to test

Taking into account the October 2012 Stakeholder Meeting advice, 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).

- The resubmission disagreed with MSAC with respect to the definition of an EGFR test positive:
 - commenting that the proposed population in the PBS listing and economic evaluation presented in the resubmission to PBAC is patients with tumours expressing activating EGFR mutations known to be associated with increased sensitivity to treatment with gefitinib (EGFR TKIs) and
 - stating that “It is inappropriate for AstraZeneca to request a PBS listing in a population broader than the supportive clinical evidence” (Summary of November 2012 MSAC Advice for EGFR Testing Table).

The November 2012 MSAC advice for Application 1161 advised that the corresponding economic evaluation presented to PBAC should reflect the fact that the common mutations (exon 19 deletions and exon 21 L858R point mutations) comprise only 70% of all activating mutations and that the effectiveness of gefitinib has only been demonstrated in randomised trial evidence for these mutations.

- The resubmission did not address this issue and all EGFR mutation positive patients treated with gefitinib were assumed to be equally responsive to TKIs in the economic evaluation presented in the resubmission to PBAC.

When to test

The November 2012 MSAC advice for Application 1161 suggested that the descriptor should allow NSCLC patients to have EGFR testing from the point of initial diagnosis of NSCLC.

- This advice was based on the following:
 - only a minority of early stage non-squamous NSCLC cases will not eventually relapse, consequently there would be no unnecessary EGFR testing following this approach and
 - Application 1161 showed a small but favourable advantage in cost/QALY can be gained for testing at diagnosis, mainly by avoiding costs of retrieving FFPE tissue blocks from archive in approximately 40% of patients diagnosed prior to development of Stage IIIb/IV NSCLC.
- The resubmission agreed with MSAC and the MBS item descriptor was reworded to remove reference to disease stage at time of testing.

Prevalence of EGFR mutations in early versus late stage NSCLC

MSAC noted several studies which compared the prevalence of EGFR mutations in early versus late stage NSCLC disease at diagnosis. Overall, there was very little difference in the prevalence of EGFR mutations at diagnosis of early and late stage disease with a median 17.8% in early stage (I-IIIa) and 15.4% in late stage (IIIb-IV) NSCLC.

The October 2012 Stakeholder Meeting minutes stated that repeat testing for EGFR mutations would not be required for checking multiple sites to confirm concordance of EGFR status or for assessing mutation stability over time.

8. Comparator to the proposed intervention

The comparator to EGFR mutation testing in the current treatment pathway for locally advanced or metastatic non-squamous NSCLC is ‘no testing’ in both the Final DAP and the submission.

The November 2012 MSAC advice for Application 1161 agreed that the nominated comparator of no EGFR testing for first-line therapy was appropriate.

EGFR mutation testing for second-line therapy with gefitinib was included as part of the current treatment algorithm in both the Final DAP and the resubmission. In line with MSAC advice, the proposed management algorithm allowed for EGFR mutation testing of all patients with non-squamous NSCLC at initial diagnosis.

In the current scenario of ‘no testing’, platinum-based doublet chemotherapy (mostly carboplatin + gemcitabine) was the preferred treatment offered to patients with locally advanced and metastatic NSCLC as a first-line therapy. Under the proposed intervention, EGFR mutation testing of patients with non-squamous NSCLC will enable the use of gefitinib as a first-line therapy for those who are EGFR mutation positive on diagnosis of, or progression to, stage IIIb or stage IV disease.

9. Comparative safety

The main safety concern with EGFR testing is the need to re-biopsy as this can result in complications such as pneumothorax and haemorrhage, which were considered to occur in 14% of re-biopsy cases.

The October 2012 Stakeholder Meeting minutes considered that repeat testing for EGFR mutations would only occur in unusual and specific circumstances, as 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. However, there is some evidence to suggest that repeat testing after exposure to cancer therapies may be beneficial for those patients whose EGFR mutation status changes.

Some patients would need to be re-biopsied and retested due to either an insufficient tumour sample or an inconclusive EGFR mutation test result. This was accounted for in the economic evaluation presented in the resubmission to PBAC; the base-case assumed a 12% re-biopsy rate and explored a range of costs in the sensitivity analyses. It is acknowledged that with increasing experience and knowledge of sampling requirements, the re-biopsy rate may decrease over time.

10. Comparative effectiveness

There is no accepted ‘reference standard’ against which the performance of EGFR mutation testing methods can be compared. The evidentiary standard used in the key IPASS trial was the DxS TheraScreen[®] EGFR 29 Mutation Detection Kit, which uses Scorpion-ARMS technology. This EGFR testing technology is used in several Australian diagnostic laboratories.

A summary of the EGFR mutation testing methods used in the main clinical trials and in Australian laboratories are shown in the table below.

Summary of EGFR mutation testing methods used in clinical trials and Australian pathology laboratories

Drug	Clinical trial	EGFR mutation testing method
Afatinib	LUX Lung 3	DxS TheraScreen [®] EGFR 29 Mutation Detection Kit (uses Scorpion-ARMS technology)
Erlotinib	EURTAC	DNA sequencing, fragment length analysis (exon 19), TaqMan assay (exon 21)
Erlotinib	OPTIMAL	DNA sequencing, fragment length analysis (exon 19), Cycleave assay (exon 21)
Gefitinib	IPASS	DxS TheraScreen [®] EGFR 29 Mutation Detection Kit (uses Scorpion-ARMS technology)
Gefitinib	First-SIGNAL	DNA sequencing of exons 19, 20 and 21 (repeated to confirm)

Drug	Clinical trial	EGFR mutation testing method
Gefitinib	NEJ002	PNA-LNA PCR clamp
Gefitinib	WJOTG3405	Fragment length analysis (exon 19), Cycleave assay (exon 21) confirmed by DNA sequencing

Australian pathology laboratories	Direct DNA sequencing
	Mass Spectrometry Sequenom
	Scorpion ARMS technology (including DxS TheraScreen® Kit)
	TaqMan® Mutation Detection Assays
	Cobas® EGFR Mutation Test

ARMS = Amplified Refractory Mutation System; EGFR = epidermal growth factor receptor; PCR = polymerase chain reaction; PNA-LNA = peptide nucleic acid-locked nucleic acid.

Test accuracy

The November 2012 MSAC advice for Application 1161 considered that an assumption for modelling purposes of 100% sensitivity and 100% specificity for the test forming the evidentiary standard used in the key gefitinib trial (IPASS) overestimated the likely test performance across test options and pathology laboratories in Australia. MSAC recommended that the sensitivity analyses of the economic evaluations presented to PBAC should appropriately examine the likely extent of proportions of false positive 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.

The Final DAP noted that the evidentiary standard would be used to determine false positive and negative values for the current and proposed decision analysis. The resubmission to PBAC used 100% sensitivity and specificity in the base case, as this reflects the use of the evidentiary standard in the key trial, but the resubmission also presented results for a range of EGFR testing sensitivity and specificity values between 80% and 98%.

In the Australian clinical setting, the impact of test accuracy is more likely to relate to sensitivity rather than specificity. The inclusion of poor samples with too few tumour cells may lead to a false negative report, but is unlikely to result in a false positive report. False positives would most likely result from human error; e.g. cross contamination of samples or the reporting of mutations with unknown effects on EGFR TKI activity.

The potential for false negative or false positive reporting by Australian laboratories is very low based on the results of the RCPA Molecular Genetics Quality Assurance Program (QAP) Generic Report on EGFR, KRAS and BRAF mutation screening of human tumours, which became available on 5th September 2012 (RCPA 2008).

However, the QAP report does not provide any data on the accuracy of test results obtained in Australian diagnostic laboratories from poor quality samples containing less than 25% tumour tissue. The likelihood of a false negative result increases dramatically as the proportion of tumour material in a sample decreases below 20%. This can be overcome with the use of tumour enrichment techniques, such as Laser Capture Microdissection, which are utilised in some Australian laboratories.

11. Economic evaluation

The proposed MBS fee

November 2012 MSAC advice for Application 1161 suggested 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.

The resubmission suggested that the current MBS fee associated with item 73328 is reasonable and did not request any changes to the current fee.

Cost-effectiveness analysis

The November 2012 MSAC advice for Application 1161 recommended the following.

1. The 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 resubmission did not agree with this advice and argued that the proposed PBS listing and associated economic evaluation for gefitinib as first-line treatment requests access for patients with tumours expressing activating EGFR mutations known to be associated with increased sensitivity to treatment with gefitinib. The resubmission to PBAC presented a cost-effectiveness analysis assuming all EGFR mutation positive patients are equally responsive to gefitinib treatment. There was no further analysis of the effect of treating patients with uncommon EGFR mutations that may be less responsive to treatment.
2. 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 resubmission to PBAC conducted a cost-effectiveness analysis and used a prevalence of 15% for the base-case economic model:
 - the base case (without pemetrexed maintenance) with a 15% EGFR mutation prevalence was estimated to be dominant for gefitinib (estimated cost saving of \$(redacted information) per patient with (redacted information) QALYs gained per patient)
 - when a 10% prevalence was used in sensitivity analysis, the incremental cost increased to be less than \$15,000/QALY
 - when a 20% prevalence was used in sensitivity analysis, gefitinib remained dominant (cost saving of \$(redacted information) and an additional (redacted information) QALYs gained).
3. The economic evaluations and financial analyses presented to PBAC should include:
 - i. a 12% re-biopsy rate
 - ii. a 14% complication rate per biopsy
 - iii. the costs of patient retrieval for re-biopsy, such as professional attendance fees, medical imaging or use of bronchoscopy.
 - The base case economic analysis in the resubmission to PBAC assumed a 12% invalid test rate and assumed all invalid tests lead to a re-biopsy with a 14% complication rate and all samples were retested. However, the resubmission to PBAC failed to consider the MBS costs for EGFR retesting when calculating the financial implications to the MBS.
 - In calculating the cost of re-biopsy and the associated complications, the following estimates were used in resubmission to PBAC:

- the cost of bronchoscopy as an outpatient (\$**(redacted information)**) was used for **(redacted information)**% of patients
 - the cost of bronchoscopy as an inpatient (\$**(redacted information)**) was used for **(redacted information)**% of patients
 - the average weighted cost per bronchoscopy was \$**(redacted information)**
 - the average weighted cost per bronchoscopy for the 14% with complications was \$**(redacted information)** (\$**(redacted information)** for complications requiring hospitalisation and \$**(redacted information)** for those not requiring hospital admission)
 - sensitivity analyses were conducted varying the costs for re-biopsy (**(redacted information)**), from **(redacted information)** for complications requiring hospitalisation, and up to \$**(redacted information)** for complications not requiring hospitalisation.
4. The economic evaluations and financial analyses presented to PBAC and MSAC need not include any other repeat testing.
 5. The economic evaluations and financial analyses presented to PBAC and MSAC should include the full costs of testing, such as patient episode initiation fees and any extra specimen enrichment.
 - In the economic model, the resubmission to PBAC used a cost of \$397.35 plus a patient episode initiation fee of \$**(redacted information)** and a specimen referred fee of \$**(redacted information)** per EGFR test, for a total cost of \$**(redacted information)**. A cost for specimen enrichment was not taken into account in the economic model. The resubmission argued that with sample enrichment, eg micro- or macro-dissection, when required, the associated costs are considered as part of the conduct of the mutation test and not coded separately.

12. Financial/budgetary impacts

The listing of gefitinib for first-line therapy would have an impact on the MBS as patients with non-squamous or not otherwise specified NSCLC would undergo MBS-funded EGFR testing to determine their EGFR mutation status at the time of diagnosis, as opposed to only after first line treatment has failed. However, as most patients would have disease progression once diagnosed with NSCLC, it is likely that the increase in testing would be small. The costs to the MBS of the proposed MBS and PBS listings associated with gefitinib were presented in the resubmission to PBAC.

The projected number of patients that would require an EGFR mutation test was derived from the incidence of lung cancer as extracted from the Australian Cancer Incidence and Prevalence statistics (AIHW, 2011). Literature searches were conducted to provide information to determine the proportion of lung cancer patients with non-squamous or not otherwise specified NSCLC.

The number of patients eligible for EGFR testing was assumed to be in the range 10,000 – 50,000 in the fifth year.

The net cost to the MBS was estimated to be less than \$5 million in the fifth year. The costs to the MBS could be either higher or lower than these estimates, as the resubmission did not consider the costs for re-testing, costs for EGFR testing before second-line gefitinib (in the comparator arm only), the associated MBS fees for re-biopsy and complications for patients treated in a public hospital as private patients or in a private hospital, and the savings from avoiding side-effects associated with chemotherapy (eg. blood transfusion).

13. Key issues for MSAC

Uncertainty remains regarding the test performance of the EGFR testing methods used in Australian laboratories relative to that in the IPASS trial. The economic model is sensitive to the EGFR mutation test specificity.

14. Other significant factors

Nil.

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

MSAC noted that the July 2013 PBAC meeting had deferred its decision in relation to extending the listing of gefitinib on the PBS, but had reaffirmed its intention to restrict such a listing to locally advanced (stage IIIB) or metastatic (stage IV) non-squamous or not otherwise specified (NOS) non-small-cell lung cancer (NSCLC) in patients with evidence that the tumour harbours an activating mutation(s) of the EGFR gene known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors (TKIs). MSAC reaffirmed the importance of aligning the population of patients eligible for testing with this restriction, although also allowing for EGFR mutation testing in non-squamous or NOS NSCLC at initial diagnosis rather than necessarily requiring that a patient waits until progression to locally advanced or metastatic disease before testing.

MSAC foreshadowed it would advise that the medication names “gefitinib or erlotinib or afatinib”, or any appropriate sub-set thereof, would be used in the revised wording of an MBS item for EGFR mutation testing in the event of a PBAC recommendation to list any one or more of these medicines. MSAC did not prefer the alternative of “EGFR tyrosine kinase inhibitor” because it wanted to be able to review each new co-dependent linkage at this early stage of considering co-dependent test and medicine technologies. For example, it would want to consider the “evidentiary standard” test for each subsequent new treatment option (the test used to identify the EGFR mutation status in the key trials supporting the new treatment option) and to consider the means through which the treatment option achieves its effect.

MSAC rejected any proposal to include “tumour cells” rather than “tumour tissue” to define the source of the specimen for EGFR mutation testing. In particular, MSAC advised that EGFR mutation testing should not be subsidised when the source of the specimen is circulating tumour cells. Suitable specimens include a tissue biopsy of the lung cancer which would include cytology blocks.

MSAC reaffirmed its November 2012 advice that the proposed MBS item should be made a pathology determinable service so that the pathologist can perform EGFR mutation testing on samples which meet the requisite histological criteria. This process ensures that the diagnostic process is not interrupted by the need to get a referral from a clinician for mutation testing. This supports MSAC's preference that EGFR mutation 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. It is also consistent with MSAC's previous advice that pathology practice should be optimised through a more centralised approach to ensure EGFR mutation testing is limited to laboratories with appropriate expertise and back-up. However, MSAC did not change its advice on the text for the proposed MBS item descriptor to require that the one laboratory performs both the histology and genetic testing on the specimen. Similarly, MSAC reaffirmed its November 2012 advice that biopsy sampling practice should also be optimised to obtain sufficient tumour tissue of adequate quality to obtain high rates of satisfactory specimens.

MSAC noted that the economic evaluations and financial analyses presented to the July 2013 PBAC meeting generally followed its November 2012 advice including on the prevalence of activating EGFR mutations (15%), re-biopsy rate (12%), costs for re-biopsy, complication rate for re-biopsy (14%), costs for testing, and the need for sensitivity analyses of the likely extent of proportions of false positive test results and false negative test results in Australia.

MSAC reaffirmed its November 2012 advice 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 mutation testing. MSAC noted the applicant's estimates of financial implications to the MBS were less than \$5 million per year.

MSAC recalled its November 2012 advice to collect data on the prevalence of various types of detected EGFR mutations and to support the clinical basis for determining whether they predict sensitivity or resistance to subsequent TKI therapy. MSAC noted that representatives of the National Health and Medical Research Council, MSAC, PBAC and the Department had met to discuss targeted data collection relating to BRAF mutation testing and BRAF inhibitor treatment as proposed by PBAC in March 2013 and supported by MSAC in April 2013.

MSAC reaffirmed its advice that such data collection be also applied to EGFR mutation testing and EGFR TKI treatment, noting that the proportion of EGFR mutations which had not been included in the evidentiary EGFR TKI trials was likely to be significant (e.g if benchmarked against BRAF mutations, the proportion predicted is likely to be greater than the proportion of BRAF V600 mutations which had not been included in the BRAF inhibitor trials).

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) mutation testing to help determine eligibility for proposed PBS-subsidised first-line gefitinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC again deferred the application for the requested MBS item until such time as PBAC makes a decision regarding the corresponding PBS listing of gefitinib. MSAC reiterated that, if PBAC subsequently decides to recommend to the Minister that gefitinib be listed on the PBS for the first-line treatment of advanced NSCLC, it would support an expedited process for reconsideration to align MSAC support for public funding of EGFR testing according to the circumstances recommended by PBAC. MSAC foreshadowed its support for public funding to be achieved by modifying MBS item 73328. The MBS fee of \$397.35 would be retained, but the item descriptor would be amended to:

A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, 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.

MSAC reiterated that it would support an expedited MSAC process of re-consideration if PBAC subsequently recommends PBS listing. MSAC also reaffirmed its November 2012 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively to be reviewed two years after listing.

Out-of-Session MSAC Consideration – October 2013

Application 1161 - Gefitinib first line testing for mutations of epidermal growth factor receptor (EGFR) in patients with metastatic non-small cell lung cancer (NSCLC)

Summary of consideration and rationale for MSAC's advice

MSAC deferred this application at its meetings on 29-30 November 2012 and 1 August 2013. MSAC's considerations were coordinated with PBAC considerations of gefitinib on 7-9 November 2012 and 9-12 July 2013. On both occasions, MSAC indicated support for the proposal to modify the existing MBS item for EGFR mutation testing, but deferred provision of formal advice to the Minister until such time as MSAC advice could be coordinated with a PBAC recommendation to modify the existing PBS items for gefitinib.

The MSAC Chair and Secretariat were advised that, on 1 October 2013, PBAC recommended that the PBS listing for gefitinib be modified to include subsidy for its use for EGFR mutation positive advanced NSCLC.

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) mutation testing to help determine eligibility for proposed PBS-subsidised first-line gefitinib in locally advanced or metastatic non-small cell lung cancer (NSCLC), MSAC advised that the item descriptor for MBS item 73328 be amended to read as below:

*A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, 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 erlotinib **or gefitinib** under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.*

MSAC reaffirmed its November 2012 and August 2013 advice that the proposed MBS item should be made a pathologist determinable service.

MSAC advised that the MBS fee of \$397.35 should be retained.

MSAC reaffirmed its November 2012 and August 2013 advice that, as part of implementing coordinated MBS and PBS listing of these co-dependent health technologies, appropriate data be collected prospectively.

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

No comment.

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.