



Medical Services Advisory Committee

Public Summary Document

Reference No. 41 – Epidermal Growth Factor Receptor Gene Testing and Access to PBS listed Gefitinib

Sponsors: Pathology Services Table Committee
AstraZeneca

Date of MSAC consideration: 51st MSAC meeting, 2 December 2010

1. Purpose of Application

In October 2010, AstraZeneca supplied information to enable the reconsideration of an application requesting Medicare Benefits Schedule (MBS) listing of epidermal growth factor receptor (EGFR) gene mutation testing in patients with locally advanced or metastatic non small cell lung cancer (NSCLC) to identify those patients with an activating mutation (M+) of the tyrosine kinase domain of the EGFR gene, who are most likely to respond to drug therapy with gefitinib (a tyrosine kinase inhibitor - TKI), and those patients without a mutation (M-), who are least likely to respond.

As only NSCLC patients with certain types of EGFR gene mutations have been shown to respond to gefitinib therapy, identification of these mutations in the tumour material is required prior to the initiation of gefitinib therapy.

The indication requested for the proposed service needs to be considered in two contexts:

- 1) the current scenario where gefitinib has been subsidised through the Pharmaceutical Benefits Scheme (PBS) since December 2004 for second-line treatment of locally advanced or metastatic NSCLC in patients with an activating mutation in the EGFR gene; and
- 2) a potential scenario where gefitinib could be PBS listed for first-line treatment of locally advanced or metastatic NSCLC in patients with an activating mutation in the EGFR gene [noting that an application for this listing was considered by PBAC in November 2010].

As testing for EGFR gene mutations is not currently covered under any existing MBS item, the purpose of the current application is to seek public funding of testing for EGFR gene mutations in tumour specimens from patients with NSCLC in each context.

At its 48th meeting in March 2010, MSAC found that consideration of EGFR gene mutation testing should be deferred pending development of a framework which would enable proper consideration of the appropriate basis for appraising such services.

2. Current arrangements for public reimbursement

The proposed service is not covered under any existing MBS item. Currently, patients must either pay for the test themselves or the cost of the test may be covered through the hospital with which their specialist is affiliated.

No MBS item descriptor was proposed in the application.

The following MBS item descriptor was constructed during the evaluation for consideration by MSAC:

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| Category PATHOLOGY P7 - GENETICS |
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| To establish the presence of activating EGFR mutations in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) for consideration of treatment with tyrosine kinase inhibitor (TKI) therapy. |
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An MBS fee range of between \$400 and \$606 has been proposed.

MSAC accepted that the comparator is “no testing”. EGFR gene mutation testing would not replace any other current routine diagnostic service.

3. Background

According to the latest Australian Institute of Health and Welfare (AIHW) data, lung cancer was the fifth most common cancer diagnosis in Australia with 9182 patients diagnosed in 2002 (Australian Institute of Health and Welfare (AIHW) and the Australasian Association of Cancer Registries (AACR) 2008). Lung cancer is responsible for more deaths annually than any other cancer in Australia. There were 7427 deaths in 2005 and for the first time, deaths from lung cancer in females exceeded the number of deaths from breast cancer.

Only 35% of patients diagnosed with lung cancer are expected to survive for more than one year. The five year survival rate is 12%, primarily because lung cancer is most commonly diagnosed in the non-operable Stage IV (metastatic disease - 43%) and Stage III (invasive disease with spread into the regional lymph nodes - 25%).

Improvements in lung cancer staging and diagnosis may lead to better patient management by avoiding invasive diagnostic procedures and by planning more accurate curative and palliative treatment, leading to improved survival and quality of life.

The purpose of EGFR gene testing is to establish the presence of activating mutations in the EGFR gene in tumour samples from patients with locally advanced or metastatic NSCLC to determine their eligibility for:

- 1) PBS-subsidised treatment with gefitinib (Iressa[®]), a tyrosine kinase inhibitor (TKI), after failure of first-line chemotherapy; or
- 2) potential future PBS-subsidised treatment with gefitinib as a first-line treatment option, if recommended by PBAC.

The presence of EGFR gene mutations in NSCLC may also be a prognostic indicator and some clinicians believe that there may be value in knowing the mutation status of a patient even if the test reveals that treatment with a TKI is not an option. MSAC concluded that whilst the test may have a role in prognosis, the prognostic impact of a test result independent of its ability to predict a difference in the treatment effect of gefitinib is not clear from the evidence provided to date.

Several test methods are used to establish the presence of EGFR gene mutations in tumour samples (see Section A (5) of the contracted critique). The test proposed by the drug sponsor (AstraZeneca) is the High Resolution Melt (HRM) method followed by direct DNA sequencing for those samples exhibiting an abnormal HRM trace. The test in the IPASS study, which informs the linkage between test use and drug use, was the amplification refractory mutation system (ARMS), using the DxS EGFR29 mutation detection kit (Qiagen, formerly DxS, Manchester, UK). Patients were deemed EGFR M+ if ARMS detected one of the 29 EGFR gene mutations that the kit was designed to identify, and EGFR M- if none of the 29 EGFR gene mutations was detected.

Currently, this test is required for access to gefitinib on the PBS. However, there are other EGFR targeted therapies that may require this test in the future.

Only four laboratories in Australia are currently offering routine EGFR gene testing and a national quality assurance program does not yet exist.

Medical oncologists are the main professional group who order and use the test results. Respiratory physicians and thoracic surgeons may also carry out the biopsy and thus order the test. Some respiratory physicians will also continue to care for the patient (without a referral to a medical oncologist) and so will also 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.

As part of the usual diagnostic work-up, the lung tumour is biopsied to obtain a tissue sample to determine tumour histology. Currently the amount of tumour material collected from biopsy samples is often insufficient for molecular testing. To avoid the requirement for additional tumour biopsies, clinicians will need to biopsy sufficient tumour material for EGFR gene mutation testing as well as immunohistochemical examination.

MSAC identified there were issues relating to questions of when best to perform EGFR gene testing, 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), and the impact of mutations in other genes.

MSAC therefore considered that all EGFR gene mutation testing should be performed in a NATA-accredited laboratory that has been demonstrated, in a suitable External Quality Assurance Program (QAP), to be proficient in the technique employed. The Department of Health and Ageing would ensure appropriate mechanisms are in place before any MBS listing of the test.

MSAC also noted there are interpretative challenges in the laboratory, such as whether mutations in EGFR gene testing may be activating, neutral or resistant; a gene may have multiple mutations requiring a determination as to which one would take precedence biologically. MSAC noted that knowledge in this area was evolving as more data accumulate.

The test is to identify those patients with a mutation of the EGFR gene who are likely to respond to gefitinib. Since December 2004, the detection of an activating EGFR gene mutation in tumour samples has been a prerequisite for patient eligibility for PBS-subsidised gefitinib as second-line therapy for locally advanced or metastatic NSCLC. To date there has been no MBS funding for such testing, creating potential barriers for treatment with gefitinib.

Pathology laboratories would perform EGFR gene mutation testing if they have the necessary expertise/technology available. EGFR gene mutation testing is currently performed in four laboratories in Australia and either the patient is charged or the laboratory bears the cost; or patients 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.

As EGFR testing relates to the current use of gefitinib as second or later line treatment, MSAC formed the view that its use is reserved for a small group of patients. These patients must meet certain clinical criteria, have exhausted all other therapeutic options including erlotinib, but still have health status sufficient to justify the use of an active treatment.

MSAC noted the potential for wider use of EGFR gene testing to support a possible future expansion of the PBS listing of gefitinib into first-line treatment of locally advanced or metastatic NSCLC and decided to consider this potential separately.

Firstly the patient is referred to a respiratory physician / medical oncologist, based on symptoms. Following a diagnostic CT scan, a biopsy of relevant site (bronchoscopy with fine needle aspiration is considered adequate) is followed by completion of tumour staging (including imaging with PET or MRI in some cases). Lastly the EGFR gene status and/or other tissue markers may be identified. Patients who fit the clinical criteria for the use of gefitinib would have a tumour sample tested (paraffin block) at a laboratory able to perform the test and if positive for a relevant EGFR genetic mutation, would be eligible for gefitinib.

MSAC noted that the number of patients tested might increase with MBS funding of EGFR gene testing, but was confident that this expansion of use would be limited by the current PBS restrictions for gefitinib. The subsequent PBS listing of erlotinib, another tyrosine kinase inhibitor, as second-line therapy for locally advanced or metastatic NSCLC without the requirement for EGFR gene testing, has reduced the need for gefitinib.

4. Clinical need

The current clinical need is to optimise treatment of patients with advanced/metastatic (Stage IIIb/ Stage IV) NSCLC who have failed chemotherapy.

Currently, the recommended course of treatment for these patients is intravenous doublet chemotherapy with platinum-based drugs (either carboplatin or cisplatin). Following progression during or after first-line therapy, single agent chemotherapy, usually docetaxel or pemetrexed, is recommended for patients well enough to tolerate intravenous chemotherapy. Erlotinib, another TKI, is available on the PBS for use in patients who have failed second-line chemotherapy. It can also be used to treat patients unable to tolerate single agent intravenous chemotherapy.

Gefitinib has been available on the PBS since December 2004 to treat EGFR M+ patients with locally advanced or metastatic NSCLC who have failed previous chemotherapy. The current use on the PBS is well below initial predictions, at approximately only 20 scripts a month (Medicare Australia data, August 2009). The low use of gefitinib on the PBS has been attributed to the requirement for EGFR gene mutation testing for this medication, which is currently not MBS reimbursed, and the availability of other therapies.

Only a small number of patients are currently eligible for gefitinib under the current PBS listing: based on incidence data presented in the application it is estimated that up to 250 patients/year would be tested in this setting. The target patient population is also likely to have higher proportions of women, non-smokers and patients with non-squamous cell cancer than the unselected NSCLC population. These subgroups of patients have a higher prevalence of activating mutations of the EGFR gene and so the “number needed to test” to find patients eligible for gefitinib therapy would be lower than in an unselected NSCLC population.

However, reliable estimates of the prevalence of the particular mutations of interest in the tested population will be important if the population covered were to be extended. Prevalence is also likely to vary with any proposal to pre-select the population for testing based on clinical or histological criteria, such as patients with non-squamous tumours only. Although this would be intended to improve EGFR gene test performance by increasing the likelihood of the selected population testing positive for activating mutations of the EGFR gene, this pre-selection would also be associated with false positive and false negative results, the consequences of which should also be assessed.

Limiting the eligibility of MBS funding of EGFR gene testing for NSCLC patients to those with “locally advanced or metastatic” disease was supported by MSAC as being consistent with the current PBS listing. MSAC did not support MBS subsidy for wider EGFR gene testing at the time of diagnosis of NSCLC or for any other purpose. If PBAC were to reconsider PBS subsidy of gefitinib for any other clinical setting, MSAC anticipated that it would be closely involved.

5. Comparator

MSAC noted that PBAC had resolved issues around the appropriate test comparator:

- Gefitinib is only beneficial and cost-effective in patients with responsive tumours;
- An assay for activating mutations in EGFR is a marker of gefitinib responsiveness;
- The drug is approved only on basis of EGFR gene mutation status.

Accordingly, the comparator for the test is not testing. EGFR gene mutation testing would not replace any other current routine diagnostic service.

6. Scientific basis of comparison

MSAC noted that DNA sequencing of adequate sample (>20% tumour load) is proposed by some experts as the ‘gold standard’ against which the analytical validity of other tests should be compared, because it potentially detects all mutations.

MSAC noted there is no direct evidence available comparing the health outcomes of patients for whom EGFR gene mutation testing is used to target TKI therapy, compared to those for whom targeted TKI therapy is not available.

MSAC also noted that no specific analyses of test performance were presented in the application for EGFR gene mutation testing. There is no systematic assessment of EGFR gene testing methods presented and thus reliable relative measures of diagnostic accuracy or safety are not available. However, specification of a particular test was not in scope for MSAC as RCPA/NATA are responsible for benchmarks, quality assurance, and quality control of testing.

Issues of safety are largely mediated through false test results subsequently resulting in sub-optimal treatment decisions.

MSAC considered that the available test options and any strategies to combine test options (e.g. DNA sequencing with or without high resolution melt polymerase chain reaction pre-screening) need to be identified in any consideration of wider use of EGFR gene testing. A comparative assessment of their analytical performance based on empirical data is also needed. This comparative assessment should refer to the testing approach used in the clinical trial evidence provided to support the co-dependency between EGFR gene testing and the proposed wider use of gefitinib, including the type, collection and handling of samples. This comparative assessment should also refer to the reference or gold standard test if one can be identified. The collection and handling of samples should also be considered to assess the

impact on test performance of inadequate samples.

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

7. Safety

MSAC agreed that there are no safety issues for the patient from the application of the test to tissue samples already obtained for the diagnosis. Safety concerns directly related to the process of EGFR gene testing are unlikely as testing would generally be performed on biopsy samples taken for diagnostic work-up. However, additional biopsies may be required from some patients where sample DNA quality/quantity is inadequate.

8. Clinical effectiveness

Data concerning the accuracy of different EGFR gene mutation tests or combinations of tests indicate that sample preparation is key and that the goal of test sensitivity must be balanced against retaining test specificity, particularly as noted already for the potential extension to include treatment in the first-line setting which would involve replacing known efficacious chemotherapy with a targeted TKI therapy.

MSAC considered that multiple conditions are necessary to achieve optimal test performance, namely adequate sample size/quality, adequate proportion of tumour DNA in the sample, an accurate tumour identification and removal process, and lack of potential modification of DNA by formalin fixation processing of the sample. These are primarily quality assurance issues associated with sample removal, preparation and testing.

MSAC also considered that EGFR results may change with exposure to radiotherapy and other therapies and thus the results of testing the primary tumour may not be representative of EGFR gene mutation status in non-small cell lung cancer metastases in some patients.

MSAC noted that any errors in the EGFR gene mutation test result would have consequential impacts for the patient:

- False positive results would expose the patient to the adverse effects of gefitinib without any benefit and, if gefitinib were to be used in the first line setting, would deny the patient other effective treatment;
- False negative results would deny the patient access to the potential benefits of gefitinib.

These consequential impacts are less serious for the current use of gefitinib as last-line therapy in eligible patients. However, a major concern was the potential harm of extending treatment with any TKI therapy to include previously untreated metastatic NSCLC patients, who are either identified as having mutations but do not (false positives) or have mutations which are resistant to TKIs or not predictive of benefit from TKI therapy. Although the

likelihood of a false positive is low, knowledge of the clinical implications of different EGFR gene mutations is important when using targeted therapy where there are alternatives with proven positive net clinical benefit. The implications of a false negative should also be recognised as the possibility of forgoing the potential for the claimed incremental benefit with gefitinib.

Whilst the drug sponsor proposed that the use of HRM followed by direct DNA sequencing of samples with an identified mutation – with adequate tumour material – is 100% sensitive and specific, no comparative data versus direct DNA sequencing alone were available for this test combination or any other testing methodologies.

Where EGFR gene mutation testing is not performed at initial diagnosis, consequential issues are the need for a repeat biopsy to obtain a new sample or the retrieval of a stored sample if available (which may be assisted by appropriate attention to managing cell blocks). These are important issues for any expansion of the use of EGFR gene mutation testing given the comparatively small tumour samples which are retrieved in NSCLC through standard techniques such as fine needle aspiration biopsy. Obtaining multiple samples and performing multiple tests over time would have consequences for the patient and the healthcare system which would need to be assessed.

Issues related to the question of when best to perform EGFR gene mutation testing should it be proposed for wider use include the amount of tumour tissue in a biopsy sample (tumour load), stability of the mutation over time in a patient and between primary and secondary tumours (mutation frequency), and the impact of mutations in other genes.

In order to address the concerns of possible false negative results of the limited use of EGFR gene mutation testing as currently proposed, MSAC considered that the test should be supported by a suitable quality standards and a quality assurance program specific to EGFR gene testing developed by RCPA and should be performed in a NATA accredited laboratory, and be ordered by an oncologist.

MSAC also noted that uncertainties remain around the causes of resistance to gefitinib, 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 the EGFR gene mutation status.

9. Economic evaluation

Limited data were provided to enable an assessment of cost-effectiveness, in terms of an estimated incremental cost effectiveness ration (ICER), to address the question of MBS funding of EGFR gene mutation testing in the current scenario where gefitinib is only available as a second-line treatment. Estimates of test volumes were available but no data on the outcomes associated with second-line gefitinib were available.

Limited information was presented in the MSAC application of the economic evaluation of EGFR gene mutation testing supporting the cost-effectiveness of the extended use of gefitinib as presented in the submission considered by PBAC in November 2010.

MSAC noted that the economic evaluation did not address the impact of test performance and sample adequacy on overall safety, efficacy and cost-effectiveness.

From the economic data available, MSAC identified that the ICER of this co-dependent ‘test plus drug’ combination in its potential extended use is sensitive to the unit cost of the test. Therefore the determination of an appropriate fee for the service is an important consideration in a potential listing of the test.

The economic evaluation of this potential extended use is also sensitive to the prevalence of EGFR M+ status in the tested population. The unselected NSCLC population in Australia has a lower EGFR M+ prevalence compared to the trial populations, all of which recruited NSCLC patients from subgroup types known to have higher prevalences.

Also, but to a lesser extent, the determination of the patient population for this potential extended use will have some impact on cost-effectiveness, but this might need to be considered in the context of tissue retrieval and storage practicalities, as well as treatment planning timelines.

MSAC further noted that the proposed fee for the tests to determine EGFR gene status did not appear to have a strong rationale. There was also no basis in an economic evaluation to determine a fee which could be defined as being acceptably cost-effective. The Department advised MSAC that a fee for any new MBS service would be determined in the implementation phase, should the Minister approve MBS listing.

The economic assessment did not address the cost of the test to the Australian Government, to State and Territory Governments, or for individual patient co-payments.

The economic assessment did not address the impact on the Medicare Safety Net, although MSAC considered that a significant impact was unlikely.

MSAC noted that PBAC had concluded that the ICER for potential extended use of gefitinib was unacceptably high and uncertain. MSAC further noted that the ICER is very sensitive to test performance, test cost, and mutation frequency – which are all poorly defined in the Australian setting. There are no prevalence data and hence MSAC could not accurately estimate costs for testing prevalent cases.

10. Financial/budgetary impacts

MSAC noted that the estimates of utilisation and budgetary impacts provided for the potential extended use of gefitinib were all based on incidence data. However, there were no data provided in the application on the prevalence of advanced/metastatic NSCLC in the Australian community, hence no ability to accurately estimate costs or benefits of testing the initial prevalent population. However, given the natural history of this disease, with a high mortality rate, MSAC accepted that the prevalent population is unlikely to be large.

MSAC estimated that the cost to the MBS in Year 1 for all new patients (7720) with advanced/metastatic NSCLC would range between approximately \$2.32 million and \$3.09 million, depending on sample retrieval costs. This estimate is more directly relevant to the potential extended use of gefitinib. It overestimates the impact of MBS funding for EGFR gene mutation testing to support the current use of gefitinib which should reflect a lower estimate of testing of approximately 250 patients/year who have received earlier lines of therapy.

11. Other significant factors

MSAC noted that gefitinib is publicly funded through the PBS, and its use is dependent on a test that is not publicly funded.

MSAC noted that this application has assisted in the development of methodologies for the assessment of co-dependent technologies.

MSAC noted there are similar drugs in the pipeline which will require patient selection through molecular testing.

MSAC also noted that another targeted therapy funded through the PBS (trastuzumab) is dependent on a specific test for HER2 (EGFR2) and that, through an arrangement with the Australian Government, the test is currently funded by the drug sponsor in selected laboratories.

MSAC noted that quality assurance programs will be developed by the RCPA if the test is approved for public funding.

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

MSAC noted the evidence provided was insufficient for a full appraisal of the safety, performance and cost of the options available for epidermal growth factor receptor (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 gene testing. It considered the application in two parts: a limited use to support the current Pharmaceutical Benefits Scheme (PBS) listing of gefitinib (Iressa[®]) and a possible future expansion of use to support an extension of this PBS listing.

EGFR gene testing to support current PBS listing of gefitinib

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 non-small cell lung cancer (NSCLC). To date there has been no MBS funding for such testing, creating potential barriers for treatment with gefitinib.

Although small numbers of patients are eligible for PBS-subsidised gefitinib, larger numbers of patients would require testing to determine the proportion who test positive for the EGFR activating mutation.

MSAC noted that the number of patients tested might increase with MBS funding of EGFR gene testing, but was confident that this expansion of use would be limited. The subsequent PBS listing of erlotinib, another tyrosine kinase inhibitor, as second-line therapy for locally advanced or metastatic NSCLC without the requirement for EGFR gene testing, has reduced the need for gefitinib. MSAC formed the view that the use of gefitinib is reserved for a small group of patients who meet certain clinical criteria: have exhausted all other therapeutic options including erlotinib, but still have good health status.

Currently such patients either have to pay for the EGFR gene test 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.

For these reasons, and despite the lack of adequate evidence provided on the safety, performance and cost of the test options available, MSAC agreed to advise the Minister that public funding should be made available in this limited and clinically well-defined setting.

MSAC was concerned to ensure that public funding should not be extended to allow use of EGFR gene testing for other purposes, and advised that an item descriptor for the MBS service should reflect the current PBS conditions for use of gefitinib. The following wording was therefore proposed for the item descriptor:

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.

The criteria of “locally advanced or metastatic” were included to support the current PBS listing. MSAC did not support MBS subsidy for wholesale EGFR gene testing at the time of diagnosis of NSCLC or for any other purpose. If the Pharmaceutical Benefits Advisory Committee (PBAC) were to reconsider PBS subsidy of gefitinib for any other clinical setting, it is anticipated that MSAC would be closely involved.

MSAC further noted that the proposed fee for the tests to determine EGFR gene status did not appear to have a strong rationale. There was also no basis in an economic evaluation to determine a fee which could be defined as being acceptably cost-effective. The Department advised MSAC that a fee for any new MBS service would be determined in the implementation phase, should the Minister approve MBS listing.

The increase in volume of EGFR gene testing as a result of MBS funding is difficult to forecast. MSAC expected that the patients being considered for last-line gefitinib would be selected based on their health status at the time. Numbers are likely to be small: based on incidence data presented in the application it is estimated that up to 250 patients/year would be tested in this setting. The target patient population is also likely to have higher proportions of women, non-smokers and patients with non-squamous cell cancer than the unselected NSCLC population. These subgroups of patients have a higher prevalence of activating mutations of the EGFR and so the “number needed to test” to find patients eligible for gefitinib therapy would be lower than in an unselected NSCLC population.

Consistent with the introduction of other tests of tumour material, MSAC noted the importance of an appropriate quality assurance and laboratory accreditation program to accompany any MBS listing to support optimal practice by oncologists, laboratories and pathologists.

Possible future expansion of EGFR gene testing

MSAC noted that the November 2010 PBAC meeting had declined a submission to extend the PBS listing for gefitinib to include first-line monotherapy for locally advanced or metastatic NSCLC in patients with an activating mutation of the EGFR gene. The committee indicated that an integrated submission would be needed across the co-dependent EGFR gene testing and gefitinib in any future re-consideration of this request.

The consequences of such an extension beyond the current PBS listing would be a large increase in the number of patients who would require EGFR gene testing to determine eligibility for gefitinib.

In the first-line setting, the adverse consequences of a false positive test resulting in terms of inappropriate exposure to gefitinib are more serious than in the last-line setting where no other treatment options are available. First-line treatment of NSCLC typically includes doublet chemotherapy and hence patients with a false positive EGFR gene mutation result would receive an ineffective therapy (gefitinib) rather than active treatment.

MSAC suggested that future consideration of co-dependent tests and drugs should ideally be coordinated across PBAC, the Pathology Services Table Committee (PSTC), the National Pathology Accreditation Advisory Council (NPAAC) and the Royal College of Pathologists of Australasia (RCPA).

For these reasons, MSAC decided to further clarify what information it would need in a re-consideration and to coordinate any such re-consideration of these co-dependent technologies with PBAC. MSAC identified the following issues:

Options need to be developed and compared to assess when in the clinical pathway of managing a patient it would be best to perform EGFR gene testing to determine eligibility for gefitinib in a wider PBS listing. This might be at initial diagnosis of all cases of NSCLC or only at diagnosis of locally advanced or metastatic disease. The rationale for selecting patients for mutation testing on the basis of tumour stage relates to the probability that a patient will develop metastatic disease and hence be potentially eligible for gefitinib treatment. For example, patients with early stage resected lung cancer are less likely to require future systemic cancer therapy than patients with more advanced disease at presentation.

Also the possibility of preselecting patients for mutation testing on the basis of the likelihood of harbouring an activating mutation in the EGFR gene should be considered. It was noted that pre-selection criteria had been applied in the randomised studies of gefitinib. Selection of patients could be based on clinical or histological criteria known to be prognostic of progression. If proposed, these options should be assessed according to the confidence of unequivocally differentiating between factors at diagnosis with different prognostic impact.

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

Issues related to these questions of when best to perform EGFR gene testing include the amount of tumour tissue in a biopsy sample (tumour load), stability of the mutation over time in a patient and between primary and secondary tumours (mutation frequency), and the impact of mutations in other genes.

MSAC noted that PBAC had proposed limiting any extension of the PBS listing for gefitinib to particular exon 19 deletions and exon 21 L858R point mutations, so this might obviate the need to obtain larger samples with minimum thresholds of tumour volume in order to test for all possible mutations, for example by DNA sequence analysis.

Reliable estimates of the prevalence of the particular mutations of interest in the tested population will be important. Prevalence is also likely to vary with any proposal to pre-select the population for testing based on clinical or histological criteria, such as patients with non-squamous tumours only. Although this would be intended to improve EGFR gene test performance by increasing the likelihood of the selected population testing positive for activating mutations of the EGFR gene, this pre-selection would also be associated with false positive and false negative results, the consequences of which should also be assessed.

Resolving the question of the timing of ordering the EGFR gene test in the context of the overall clinical pathway would help determine the wording of any MBS item descriptor, and whether the test should be ordered by a surgeon, pathologist or oncologist. Any proposal to further confine EGFR gene testing to any pre-selected group based on clinical or histological criteria would also need to be communicated in any MBS item descriptor.

Any quality assurance program developed by the Royal College of Pathologists of Australasia that is suitable for implementation by the National Association of Testing Authorities, Australia (NATA) should encompass any extension of the proposed MBS listing of EGFR gene testing.

The available test options and any strategies to combine test options (e.g., DNA sequencing with or without high resolution melt polymerase chain reaction pre-screening) need to be identified. A comparative assessment of their analytical performance based on empirical data is also needed. This comparative assessment should refer to the testing approach used in the clinical trial evidence provided to support the co-dependency between EGFR gene testing and the proposed wider use of gefitinib, including the type, collection and handling of samples. This comparative assessment should also refer to the reference or gold standard test if one can be identified. The collection and handling of samples should also be considered to assess the impact on test performance of inadequate samples.

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

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

Any reconsideration of EGFR gene testing would need to consider whether it might have other uses, noting that none have been identified to date in establishing a diagnosis, making a prognosis or monitoring therapy.

13. MSAC's advice to the Minister

MSAC supports public funding for testing in the limited circumstance of determining tumour EGFR activating mutation status to contribute to the determination of eligibility for currently PBS-subsidised gefitinib for a patient with locally advanced or metastatic non-small cell lung cancer.

Testing should be performed in a NATA accredited laboratory, and be ordered by an oncologist. It should also be supported by suitable quality standards and a quality assurance (QA) program specific to EGFR gene testing developed by the Royal College of Pathologists of Australasia (RCPA).

Draft item descriptor:

A test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer to determine if requirements relating to epidermal growth factor receptor (EGFR) gene status for access to gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

14. 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 including those 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 Minister’s 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 such sub-committees.”

15. Linkages to Other Documents

MSAC’s processes are detailed on the MSAC Website at: www.msac.gov.au.

More information is available on the home page for Reference 41:

<http://www.msac.gov.au/internet/msac/publishing.nsf/Content/ref41-1>