



**57th MSAC Meeting
29-30 November 2012**

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

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 (κ 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.

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.