



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1173 – Epidermal Growth Factor Receptor (EGFR) gene mutation testing for eligibility for erlotinib treatment as a first line therapy in patients with locally advanced or metastatic non-small cell lung cancer

Applicant: Roche Diagnostics Australia

Date of MSAC consideration: 2 August 2012.

1. Purpose of application

In June 2011, the Department of Health and Ageing received an application from Roche Diagnostics Australia requesting a Medicare Benefits Schedule (MBS) listing for genetic testing for mutations in the epidermal growth factor receptor (EGFR) gene in previously untreated locally advanced (stage IIIB) or metastatic (stage IV) non-small cell lung cancer (NSCLC) patients, to determine eligibility for first-line treatment with erlotinib, including through the Pharmaceutical Benefits Schedule (PBS).

2. Background

MSAC has previously considered an application for public funding for EGFR gene mutation testing as a co-dependent service relating to gefitinib treatment for NSCLC (MSAC Reference 41). In December 2010, MSAC's recommendation to the Minister was as follows: *'MSAC supports 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.'*

There is currently no MBS listing for EGFR gene mutation testing to determine eligibility for treatment with erlotinib in previously untreated locally advanced or metastatic NSCLC patients.

3. Prerequisites to implementation of any funding advice

This application was deemed to propose a co-dependent package of two types of health technology (a pathology test and a medicine) subsidised through two different programs and therefore required advice from MSAC to be coordinated with that of the Pharmaceutical Benefits Advisory Committee (PBAC).

In vitro diagnostic medical devices (IVDs) are, in general, pathology tests and related instrumentation used to carry out testing on human samples, where the results are intended to assist in clinical diagnosis or in making decisions concerning clinical management (Therapeutic Goods Administration 2011).

The TGA regulatory framework for IVDs changed in July 2010, requiring premarket approval for IVDs by the TGA. The new framework also requires all in-house assays (laboratory developed tests) to also be subjected to a review.

Laboratories that manufacture Class 3 in-house IVDs are required to notify the TGA of the types of IVDs manufactured there for inclusion on a register. These laboratories must have National Association of Testing Authorities accreditation, with demonstrated compliance with the suite of standards on the validation of in-house IVDs, as published by the National Pathology Accreditation Advisory Committee (NPAAC), for each test manufactured (Therapeutic Goods Administration 2011).

Roche Products Australia submitted to the TGA for erlotinib use in previously untreated EGFR M+ patients in the third quarter of 2011. Roche Diagnostics Australia also made an application to the TGA for approval of the COBAS EGFR gene mutation test in the fourth quarter of 2011.

4. Proposal for public funding

The application proposed a test of tumour tissue from a patient with non-small cell lung cancer (NSCLC), which is non-squamous or not otherwise classified, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene mutation status for first-line access to erlotinib are fulfilled once the patient is also diagnosed with locally advanced or metastatic disease.

The test was proposed to ordinarily be initiated by a pathologist, medical oncologist or respiratory physician (or occasionally a surgeon). Samples with low quality DNA or low tumour cell content relevant to the sample size available and chosen testing method may require tumour cell enrichment or the use of a method more sensitive than Sanger sequencing.

5. Consumer Impact Statement

Key information from the decision analytic protocol for this assessment was made available to the public for consultation, with one response received and considered by MSAC's Protocol Advisory Sub Committee.

6. Proposed intervention's place in clinical management

Under the proposed scenario, patients diagnosed with NSCLC would be assayed for EGFR gene mutation status either after diagnosis of non-squamous NSCLC or NSCLC NOC (base case) or once their disease reaches Stage IIIB or IV (possible alternative scenario).

In the base case, patient tumour status would be recorded as EGFR M+ if an activating EGFR gene mutation is found or EGFR M- if no activating EGFR gene mutation is found. If diagnosed when the disease is at Stage IIIB or IV, patients would be treated according to their EGFR gene mutation status: erlotinib (or gefitinib if similarly PBS listed) for those who are EGFR M+ and standard platinum-based doublet chemotherapy for those who are EGFR M-. If diagnosed at an earlier stage, once the disease progresses to Stage IIIB or IV, the patient should be assessed for evidence to confirm that the previously detected EGFR gene mutation is stable, ie. the EGFR gene mutation expressing tumour identified has not undergone further mutation. This may require a new biopsy and further EGFR gene mutation testing. In those cases where EGFR gene mutation status is unknown because insufficient tumour tissue has been retrieved for accurate EGFR gene mutation testing, and the decision is made not to re-sample, patients would receive treatment with standard platinum-based doublet chemotherapy.

Alternatively, if an EGFR gene mutation is found which renders the patient insensitive to erlotinib (ie. T790), the patient may be ineligible to receive erlotinib. Patients who harbour these mutations and those who have squamous cell NSCLC would be eligible for platinum-based chemotherapy. If a patient receives erlotinib as a first-line treatment and is found not to respond to erlotinib treatment, they would not be given the drug in subsequent lines of treatment.

7. Other options for MSAC consideration

An alternative scenario proposed for MSAC consideration was that patients would not be tested for EGFR gene mutation status until their disease has progressed to Stage IIIB or IV cancer, although many patients will be first diagnosed having already reached this stage. For those diagnosed at earlier stages, their biopsy sample would be retrieved and processed for EGFR gene mutation testing when Stage IIIB or IV is reached, again on the basis that the mutation is stable. Patients would then be treated according to their EGFR status: erlotinib (or gefitinib if PBS listed) for those who are EGFR M+ and standard platinum-based doublet chemotherapy for those who are EGFR M-.

An additional scenario (submission base case) was proposed by the Applicant in their submission based assessment which was not presented in the Final Decision Analytical Protocol for Application 1173. The population included all NSCLC patients, which is also aligned with the proposed TGA population for whom TGA approval was sought.

8. Comparator to the proposed intervention

The comparator considered by MSAC for this intervention was no EGFR gene mutation testing and the use of platinum-based doublet chemotherapy after a patient presents with locally advanced or metastatic disease.

9. Comparative safety

MSAC had agreed in 2010 that there are no safety issues for the patient from the application of the test to tissue samples already obtained for diagnosis. Safety concerns directly related to the process of EGFR gene testing arise when additional biopsies are required from some patients where sample DNA quality/quantity is inadequate.

The current submission addressed this concern that EGFR testing that requires a re-biopsy may be a significant imposition to a person with advanced lung cancer. It identified a re-test rate of 10%. The Decision Analytical Protocol (DAP) assumed a re-biopsy rate of 10% where there is an unsuitable sample from archived tissue. It is not clear whether re-testing is on existing biopsy material or re-biopsy.

MSAC noted that there were questions about whether it was currently routine to take a tumour biopsy in all NSCLC patients for other purposes (e.g. to guide diagnosis or staging), or whether the availability of first-line erlotinib would increase the rate of biopsies. The rate of tumour biopsy is likely to be high, but it is also unlikely to be 100%.

MSAC considered that the risk of harm is likely to increase with the progression of a patient's disease or deterioration of a patient's health status, the method (or invasiveness) of the tissue sampling technique and the size of the sample needed. Thus, in the event that a patient is diagnosed before reaching locally advanced or metastatic disease, the patient may be harder to biopsy later when the disease progresses and breathing problems become more severe. More invasive biopsy techniques, such as open biopsy or video-assisted thorascopic surgery (which both require general anaesthesia) may provide a more adequate sample, but

are associated with greater harms than bronchoscopic or needle biopsies, presenting a difficult trade-off for the clinician obtaining the biopsy sample. Adverse events related to lung biopsy include haemorrhage, infection, dyspnoea, pneumothorax, bronchial spasm, arrhythmia and in some cases death.

10. Comparative effectiveness

There is no agreed ‘gold standard’ EGFR mutation test currently available. As such, the final DAP recommended that comparisons should be made against the specific tests used to generate the evidence to support the effectiveness of first-line erlotinib (the “evidentiary” standard). These tests were:

- polymerase chain reaction (PCR) followed by length analysis in an ABI Prism 3130 DNA analyser for exon 19 deletions and a 5’ nuclease PCR (Taqman) assay for exon 21 point mutations (EURTAC trial), and
- PCR-based direct sequencing (OPTIMAL trial).

DNA sequencing is currently the most commonly used method for detecting EGFR mutations in Australian clinical practice and is regarded as the most optimal method for determining EGFR status when the tumour being analysed is an adequate sample (>20% tumour cell content). In the EURTAC and OPTIMAL trials, this limitation of Sanger sequencing was overcome by tumour-cell enrichment using laser capture microdissection (LCM), which the submission notes is expensive and unlikely to be implemented in Australian clinical practice. However the pre sub-committee response (PSCR) (p2) states “It is common practice in Australia, even when using Sanger alone, to assess tumour content and if it is less than 50% to either macrodissect or laser microdissect. Similarly DNA enrichment is commonly done prior to testing. This is considered to be part of the test process and is used by laboratories as needed.” In the absence of a reference standard, the submission presents concordance data. This was presented from the EURTAC trial clinical study report and the cobas® EGFR mutation test Product Information. Concordance results studies retrieved from the literature search are also presented below.

Table 1: Concordance data for various EGFR mutation testing methodologies using NSCLC tumour samples

Study	Positive % agreement	Negative % agreement	Overall % agreement
Comparisons with DNA sequencing and a tumour cell enrichment process			
GeneScan (Exon 19 deletions) and Taqman (L858R point mutations) versus DNA sequencing (<i>with laser capture microdissection [LCM] tumour enrichment</i>)			
EURTAC clinical trial	100% (95% CI 90.4, 100)	100% (95% CI 97.2, 100)	100% (95% CI 97.8, 100)
HRM analysis versus DNA sequencing (<i>with LCM tumour enrichment</i>)			
Fukui et al. 2008	100% (95% CI 82.4, 100)	100% (95% CI 89.9, 100)	100% (95% CI 93.1, 100)
Comparisons with DNA sequencing alone			
Cobas® EGFR Mutation Test versus DNA sequencing			
cobas® EGFR Test product information	95.8% (95% CI 88.3, 99.1)	97.5% (95% CI 91.3, 99.7)	96.7% (95% CI 92.5, 98.9)
Angulo et al. 2011	93.8% (95% CI 71.7, 98.9)	100% (95% CI 95.9, 100)	99.1% (95% CI 94.8, 99.8)
ARMS EGFR Mutation Test versus DNA sequencing			
Ellison et al. 2010	47.1% (95% CI 26.2, 69.0)	94.9% (95% CI 90.9, 97.2)	91.1% (95% CI 86.5, 94.2)
Morinaga et al. 2008	75.0% (95% CI 40.9, 92.9)	89.1% (95% CI 81.1, 94.0)	88.0% (95% CI 80.2, 93.0)
RT-PCR versus DNA sequencing			
Gombos et al. 2010	0% (95% CI 0, 79.4)	77.8% (95% CI 45.3, 93.7)	70.0% (95% CI 39.7, 89.2)

Study	Positive % agreement	Negative % agreement	Overall % agreement
PCR-CE plus RFLP versus DNA sequencing Gombos et al. 2010	100% (95% CI 20.7, 100)	66.7% (95% CI 35.4, 87.9)	70.0% (95% CI 39.7, 89.2)
MEL versus DNA sequencing Lu et al. 2009	100% (95% CI 77.2, 100)	55.6% (95% CI 39.6, 70.5)	67.4% (95% CI 53.4, 78.8)
HRM analysis versus DNA sequencing Nomoto et al. 2006	86.4% (95% CI 66.7, 95.3)	100% (95% CI 79.6, 100)	91.9% (95% CI 78.7, 97.2)
Takano et al. 2007 (methanol-fixed)	96.4% (95% CI 82.3, 99.4)	76.3% (95% CI 60.8, 87.0)	84.9% (95% CI 74.3, 91.6)
Takano et al. 2007 (FFPE-fixed)	89.3% (95% CI 72.8, 96.3)	74.3% (95% CI 57.9, 85.8)	81.0% (95% CI 69.6, 88.8)
IHC analysis with mutation specific antibodies versus DNA mutation testing methods Kawahara et al. 2010	75.0% (95% CI 60.6, 85.4)	100% (95% CI 80.6, 100)	81.7% (95% CI 70.1, 89.4)
Simonetti et al 2010	80.4% (95% CI 68.2, 88.7)	100% (95% CI 85.1, 100)	85.9% (95% CI 76.5, 91.9)
TheraScreen EGFR Mutation Test versus GeneScan and Taqman EURTAC and Thera Screen EGFR assays	100% (95% CI 93.0, 100)	100% (95% CI 91.0, 100)	100% (95% CI 95.9, 100)
PCR-CE versus RT-PCR Gombos et al. 2010	100% (95% CI 34.2, 69.0)	75.0% (95% CI 40.9, 92.9)	80.0% (95% CI 49.0, 94.3)

ARMS = Amplification Refractory Mutation System; HRM = high-resolution melt; IHC = immunohistochemical; LCM = laser capture microscopy; MEL = mutant-enriched liquid chip suspension array; PCR = polymerase chain reaction; PCR-CE = capillary electrophoresis PCR; RT-PCR = real time PCR

The results of GeneScan and Taqman testing (to identify specific EGFR mutations/deletions) and HRM testing (to identify EGFR mutations) were perfectly concordant with DNA sequencing that included tumour cell enrichment. In turn, the TheraScreen EGFR mutation test had results that were concordant with GeneScan and Taqman testing. Of the remaining tests that were compared to DNA sequencing alone (and, thus, potentially affected by false negatives due to samples with a low level of tumour cells), results from the Cobas® EGFR Mutation Test had the highest level of agreement with DNA sequencing. In this comparison, approximately 25% of the results were invalid, the majority of which were related to DNA sequencing. The reasons for the invalid results are not clear from the available data.

MSAC had identified issues previously 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 had previously 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 noted the overall integrated submission addressed comparative effectiveness as mediated through erlotinib in patients testing positive for EGFR, and that this was the subject of PBAC consideration.

11. Economic evaluation

The MSAC noted that the submission did not consider potential out-of-pocket costs from charging higher fees and other relevant costs associated with EGFR testing, e.g. a patient episode initiation fee (ranging from \$2.40 to \$17.70) and a specimen referral fee of \$10.30. In addition, costs for re-testing and/or re-biopsy, IHC testing and sample enrichment were not taken into account.

MSAC noted the overall integrated submission addressed comparative cost-effectiveness as mediated through erlotinib in patients testing positive for EGFR, and that this was the subject of PBAC consideration.

12. Financial/budgetary impacts

MSAC noted joint advice from its Evaluation Sub-Committee and the Economics Sub-Committee of PBAC regarding uncertainties of the net MBS costs. As, with the economic evaluation, the submission did not consider other relevant costs associated with EGFR testing, e.g. a patient episode initiation fee and a specimen referral fee. In addition, costs for re-testing and/or re-biopsy, IHC testing and sample enrichment were not taken into account.

13. Key Issues for MSAC

MSAC noted that the following matters were referred by the July 2012 PBAC meeting:

- the disease stage at which subsidised testing should occur
- the total number of tests
- the number of tests per patient reflecting the frequency of repeat testing
- the costs of testing per patient treated with first-line erlotinib
- and the overall increase in the cost of testing to support first-line use compared to current testing for the existing PBS listing of gefitinib effectively as third-line therapy and
- the extent of discordance across the various EGFR test options.

PBAC noted that information on the extent of discordance would be important to reduce overall uncertainty in the comparative effectiveness and cost-effectiveness of erlotinib. In addition, the prevalence of EGFR mutations in Australian patients with NSCLC for both a pre-selected “enriched” population excluding squamous cell NSCLC and an unselected population may be particularly important given the consequences for both the cost-effectiveness and the financial implications of the proposal to PBAC for the extended listing of erlotinib on the PBS.

14. Other significant factors

MSAC noted advice that on 1 May 2012, a new item (73328) for EGFR testing became available under MBS arrangements for access to gefitinib in its current second-line Pharmaceutical Benefits Schedule listing. MSAC considered an amendment to this item to include erlotinib would be a suitable means of achieving the proposed listing should it wish to support the proposal of the application.

MSAC noted that this integrated application had been processed under pilot arrangements for co-dependent health technologies involving testing strategies to be considered for MBS listing by MSAC and medicines to be considered for PBS listing by PBAC. The committee acknowledged the efforts undertaken to date to assist it and PBAC undertake a coordinated assessment of this particular co-dependent package. As prior experience has been limited, MSAC considered that its adoption of a structured approach to considering the test component of the co-dependent package would be useful for future applicants

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

MSAC noted that the submission defined a different population of patients with non-small cell lung cancer (NSCLC) for EGFR testing than the base case defined in the Decision Analytic Protocol (DAP) finalised by Protocol Advisory Sub Committee (PASC), by including patients with squamous NSCLC and by proposing to confine testing to patients with Stage III C or Stage IV NSCLC. The submission's proposed definition more closely reflected the characteristics of the participants in the key randomised trial for the co-dependent first-line erlotinib therapy (EURTAC).

MSAC considered that enriching the tested population by excluding patients with squamous NSCLC (who have a reported prevalence of EGFR activating mutations of 0% to 1.1%) 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. However, MSAC also noted that morphological diagnosis of squamous NSCLC is itself associated with false positives and false negatives (even allowing for interpretation of the histology results by expert pathologists using multiple rather than single sections). The consequences of diagnostic disagreement on morphology would mean that some patients would be wrongly included or excluded from EGFR mutation testing.

In general terms, MSAC considered that some of the issues to be considered when judging the value of adopting any enrichment or triaging strategy would be:

- (a) the quantified effect on the Australian prevalence of being test positive (and hence on the number of patients who would need to be tested per patient treated);
- (b) the confidence in the enrichment diagnosis being able to minimise erroneous inclusions and exclusions from the more definitive testing strategy;
- (c) the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive or false negative results based on these erroneous inclusions and exclusions (which can vary across clinical settings, e.g., between first-line therapy where there are effective alternative treatments and last-line therapy where there are not);
- (d) the amount of tissue required to make multiple types of diagnosis when tumour tissue is limited (e.g. via fine needle aspirate biopsy) and so the need for larger tumour samples or re-sampling has implications for harm to patients and costs to the health care system; and
- (e) whether the enrichment diagnosis itself might have an effect on predicting treatment effect variation independent of the testing strategy (e.g., the effect of erlotinib might also vary according to histology type).

For this submission, MSAC advised that patients with squamous cell NSCLC should be excluded from EGFR testing with two provisos. Firstly, that a histological diagnosis could be made with confidence and secondly that targeting testing to non-squamous cancers was material to the overall decision to support funding for the co-dependent test and drug package. The latter was noted to be influenced by the Australian prevalence rates of EGFR activating mutations and the number needed to test per patient treated.

Similarly, MSAC considered that associated investigations (e.g., to exclude small cell lung cancer to leave only NSCLC and to ascertain the presence of locally advanced or metastatic disease) are also sources of diagnostic uncertainty which can reduce confidence in the results of EGFR testing. In turn, this can reduce confidence in correctly identifying patients who are suitable for erlotinib as proposed in the integrated submission. The overall performance across all investigations affects the overall effectiveness and cost-effectiveness of the proposed clinical management.

MSAC considered that only testing patients with Stage IIIB or Stage IV disease 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, because some patients tested at an earlier stage may not progress to more advanced disease (e.g., if surgical treatment is successful). However, MSAC noted that this approach would have practical consequences for the minority of NSCLC patients who initially present with less advanced disease and then later progress to more advanced disease. They would either have to provide a new biopsy sample, or their previous sample would have to be provided via block retrieval. The optimal chance to obtain the best tumour sample in NSCLC is usually at initial diagnosis, when histology and staging are also being determined. MSAC considered that EGFR testing when treatment with erlotinib was being considered for NSCLC compared with consideration of EGFR testing at earlier stages of the disease may be associated with increased pressure for shorter turnaround times, and increased rates of retesting where retrieved samples prove inadequate for later EGFR testing. The latter could result in increased costs per EGFR test conducted if testing was confined to the point of treatment. In general terms, MSAC considered that some of the issues to be considered when judging the value of testing earlier would be:

- (a) the urgency of knowing the test result (e.g., in terms of any extra time taken up between when the patient presents with for example, Stage -IIIB or Stage IV NSCLC and the start of drug treatment);
- (b) the costs of block retrieval and costs or (and patient harms) obtaining new tumour samples;
- (c) the confidence that the test result or tumour sample previously obtained represents the mutation status of the patient at the time of deciding which treatment to start (e.g., the stability of the mutation over time or in response to prior treatment or between the primary tumour and metastatic disease); and
- (d) the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive or false negative conclusions based on changes in mutation status.

For this particular submission, MSAC advised that there was not sufficient quantified information upon which to base a preference for either option, but that a pragmatic option might be to consider EGFR testing for patients who are not suitable for surgical treatment (because of tumour stage or other factors). MSAC noted that for those patients who had undergone surgery the resected tissue would be stored and available for testing if the patient developed recurrent disease.

MSAC discussed whether the definition of the biomarker should be limited to exon 19 deletions and L858R point deletions only (as defined for EURTAC and suggested by PBAC in the context of its November 2010 consideration of first-line gefitinib in the same patient population and which together account for some 99% of EGFR mutations) or extended more broadly to include any EGFR activating mutation.

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 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 amount, and this is currently being exacerbated because the tumour samples will need to be used for an increasing number of purposes. Thus Sanger sequencing, which typically requires more tumour tissue than more targeted test options,

would not be preferred because it would increase the need for larger tumour samples and increase the re-biopsy rate beyond the 10% estimated in the submission.

The test concordance data provided in the submission focussing on the applicant's proprietary test (the Cobas EGFR Mutation Test), and supplemented by a wider assessment of test options in the evaluation report, provided some reassurance that, under optimal circumstances, different test options would not produce widely different test results. 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 was 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).

In general terms, MSAC considered that some of the issues to be considered when judging the optimal definition of the biomarker would be:

- (a) the patient and cost consequences of different sampling needs to support different test options when it is difficult to obtain sufficient tumour samples
- (b) the prevalence of the different types of EGFR mutations in NSCLC, noting that the evidence is likely to be greater for common mutations compared to rare EGFR mutations
- (c) the frequency and predictive consequences of multiple EGFR mutations in a single tumour (i.e. tumour heterogeneity and mosaicism) or indeed the impact of mutations in genes other than EGFR which may influence sensitivity to EGFR inhibitors
- (d) the evidence of clinical utility for each type of EGFR mutation, either directly (e.g., if it is included in the evidentiary standard definition and ideally shows a material difference in the biomarker's ability to predict treatment effect variation), or evidence from in vitro studies, or by inference (e.g., there is a biologically plausible basis to differentiate between mutations that are activating or not, between mutations that predict resistance to the drug effect or sensitivity to the drug effect or neutrality to the drug effect, and between mutations that persist or not)
- (e) the clinical and cost-effectiveness consequences of misallocation of treatment due to false positive or false negative results based on these clinical utility conclusions.

For this particular submission, MSAC signalled a likely preference for EGFR activating mutations which are associated with sensitivity to erlotinib. However MSAC would prefer data on the issues raised above so that a more confident basis for a recommendation could be made. MSAC considered that it did not have a sufficient basis to advise on the likely rate of retesting, or to advise on whether there is sufficient concern about test performance. Therefore, important information necessary for the construction of the item descriptor was not available.

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 considered that EGFR testing was not proposed for prognostic use and that repeated EGFR testing was not required because it had no role in monitoring disease or treatment.

MSAC noted that the submission did not present data on the relationship between mutant load of EGFR in a tumour sample and the treatment effect of erlotinib. MSAC noted that this

remains an area of uncertainty and is the subject of ongoing research. In the meantime, the detectable mutant load of the “evidentiary standard” test used in EURTAC should be ascertained to define a benchmark against which to assess the consequences of using other test options which are able to detect greater or lesser loads. Given the rate of technological advances in gene testing methodologies, MSAC advised that, in the event that EGFR testing is listed on the MBS, this and other aspects of comparative test performance should be reviewed after two years to assess whether subsequently introduced test options are likely to materially affect the clinical and cost-effectiveness basis for supporting the listing.

MSAC noted that the studies of prognosis demonstrated overall that EGFR mutation positive status is a statistically significant positive predictive factor for overall survival. This means that, compared to the ideal evidentiary basis, the alignment of this prognostic conclusion with treatment effect in EURTAC of only patients who test positive according to the test strategy in the trial (the “evidentiary standard”) leaves a residual uncertainty in quantifying the true co-dependent effect.

MSAC was unable to quantify the extent of this uncertainty for regular practice in Australia, but also noted that the submitted modelled economic evaluation was not designed to examine this source of uncertainty.

MSAC noted that the considerations above addressed the matters referred to it by the July 2012 PBAC meeting. There was not enough information in the submission to quantify the consequences of the different options considered, and the modelled economic evaluation was not structured to examine how these consequences would vary the results of the incremental cost per extra quality-adjusted life-year (QALY) gained. In particular, variations in the proportions of false positive test results and false negative test results from those of the evidentiary standard will have clinical and cost-effectiveness consequences of the resulting misallocation of treatment, and the model needs to be able to examine these.

MSAC also advised that the PASC process would not need to be re-visited before lodging any resubmission addressing the matters outlined above.

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 EGFR testing to help determine eligibility for proposed PBS-subsidised first-line erlotinib in locally advanced or metastatic non-small cell lung cancer, MSAC advised the Minister that it does not support public funding for this indication on the basis of insufficient evidence to determine the comparative performance and costs across the testing options and their consequences for the comparative effectiveness and cost-effectiveness of erlotinib.

17. Applicant’s Response to Public Summary Document

Roche will be addressing the EGFR testing issues identified in the advice from MSAC in the form of a Resubmission.

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

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

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