



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1407- EGFR mutation testing to determine eligibility for access to PBS subsidised osimertinib second line therapy in patients with locally advanced or metastatic NSCLC

Applicant: AstraZeneca Pty Ltd

Date of MSAC consideration: MSAC 74th Meeting, 22-23 November 2018
MSAC 71st Meeting, 23 November 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

This streamlined codependent application requested:

- Medicare Benefits Schedule (MBS) listing of epidermal growth factor receptor (*EGFR*) *T790M* mutation testing to determine eligibility for treatment with osimertinib in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC); and
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing for treatment with osimertinib for the treatment of Stage IIIB/IV NSCLC who have evidence of a *T790M* mutation of the *EGFR* gene following progression on or after therapy with an EGFR tyrosine kinase inhibitor (TKI).

2. MSAC's advice to the Minister – November 2018 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new MBS item for a test of tumour tissue (derived from a new sample) from a patient with locally advanced (Stage IIIB) or metastatic (Stage IV) NSCLC, who has progressed on or after treatment with an EGFR TKI, to determine if the requirements relating to *EGFR T790M* gene status for access to osimertinib under the PBS are fulfilled. This provides cost-effective access by suitably eligible patients to PBS-subsidised osimertinib.

Summary of consideration and rationale for MSAC's advice – November 2018

MSAC recalled that this application was initially received in July 2017 as an integrated codependent submission also seeking listing of osimertinib on the PBS. In November 2017, MSAC deferred its advice, pending a decision from the Pharmaceutical Benefits Advisory Committee (PBAC). MSAC recalled that it had foreshadowed support, but had recommended testing of tissue rather than circulating tumour DNA in plasma. The PBAC did not

recommend listing of osimertinib at its November 2017 meeting, and in July 2018 received a major resubmission with updated survival data from the AURA3 trial. In November 2018, the PBAC recommended listing on the PBS.

MSAC noted that the applicant had lodged a streamlined codependent reapplication requesting MBS funding of *EGFR* mutation testing to detect *T790M* mutations.

MSAC confirmed that the agreed clinical management algorithm states that a new biopsy is required to determine whether the resistance mutation *T790M* is present and that PBS-subsidised access to osimertinib is limited to patients whose *T790M* mutation has been detected via tumour tissue testing (i.e. not circulating tumour DNA in plasma). If patients are *T790M* negative or unable to be re-biopsied, they would receive platinum-based chemotherapy.

MSAC noted that *EGFR* testing for *T790M* involves the same *EGFR* assay(s) as are currently in routine use in numerous Australian laboratories accredited by the National Association of Testing Authorities (NATA) and that a quality assurance program is already in place.

MSAC noted the estimated cost saving to the MBS of up to \$redacted over 6 years on the basis of a reduced number of patients receiving chemotherapy. However, while osimertinib replaces second-line chemotherapy in 60% of patients, a proportion (estimated to be 48%) would still receive chemotherapy in a third-line setting. In other words, platinum chemotherapy would be displaced rather than replaced.

MSAC noted the proposed item descriptor as:

A test of tumour tissue (derived from a new sample) from a patient with locally advanced (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), who has progressed on or after treatment with an *EGFR* TKI, to determine if the requirements relating to *EGFR* *T790M* gene status for access to osimertinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

Proposed Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75

MSAC noted that, while the item descriptor states the tissue must be from new sample, it does not specify that liquid biopsies should be excluded, so leakage is possible. MSAC also noted that while the item does not specify non-squamous NSCLC, patients with squamous cell NSCLC would not have qualified for treatment with an *EGFR* TKI, so they are effectively excluded.

3. MSAC's advice to the Minister – November 2017 consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC deferred its advice until such time as the Pharmaceutical Benefits Advisory Committee (PBAC) subsequently decides to recommend the PBS listing of osimertinib for the requested population. MSAC foreshadowed its support for a new MBS item for *EGFR* *T790M* mutation testing in tumour tissue obtained after progression on or after therapy with an *EGFR* TKI to help determine eligibility for PBS-subsidised second-line osimertinib for the targeted treatment of patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. This support is subject to a PBAC recommendation to list osimertinib in this patient population, once PBAC's concerns regarding the cost-effectiveness of the medicine are resolved.

Summary of consideration and rationale for MSAC's advice – November 2017

MSAC noted that methods used to identify *EGFR T790M* mutation status are well-established in Australia and are identical to those currently in use to determine eligibility for gefitinib and erlotinib (MBS item 73337). MSAC noted the current comparators of no testing for *EGFR T790M* mutation and platinum-based chemotherapy for these codependent technologies, and that these are acceptable.

MSAC noted that, although the proposed MBS item descriptor specifies the use of tumour tissue for testing, the PBS item descriptor for osimertinib does not specify the source of the sample for testing (tissue or plasma) used to determine eligibility, and the MBS item could potentially be used outside the proposed intention if MBS services are claimed on *EGFR T790M* mutation tests conducted using plasma samples.

MSAC advised that the current application was based on tumour tissue testing and not plasma-based testing, and that an application for plasma-based testing would require a full dataset of plasma-based test results which addressed analytical validity, clinical validity and clinical utility (see further details below). On this basis, MSAC foreshadowed that the MBS item descriptor should restrict testing to tumour tissue, and advised PBAC that any PBS restriction should specify that *EGFR T790M* mutation testing be based on tumour tissue.

MSAC noted that the applicant had acknowledged the current status of plasma-based testing technology and accepted the recommendation to specify testing using tumour tissue, and indicated that it was willing to be involved with risk sharing arrangements **redacted**.

MSAC considered that the main adverse event of tumour testing was the risk of pneumothorax. This risk only applied to individuals where lung tissue was the only source of suitable material for biopsy. MSAC noted that the rates of pneumothorax as listed in the AURA clinical trials (1.9% to 5.5%) were lower than the 15% identified in a large USA-based retrospective cohort study (Wiener RS et al 2011). However, MSAC noted that this cohort study had several limitations, including that only CT-guided biopsy of pulmonary nodules was evaluated, and that patients with the disease specified in the descriptor (Stage IIIB and Stage IV NSCLC) were not considered. MSAC noted that the applicant had listed pneumothorax as the only morbidity associated with the rebiopsy procedure, despite the potential for other serious complications such as bleeding (e.g. following transbronchial or other biopsy procedures).

MSAC also noted that the proportion of Australian patients identified as suitable for rebiopsy in the application (82%) had been overestimated, and was more likely to be closer to the approximately 63% based on Japanese and Australian market research data.

Regarding the clinical evidence for *EGFR T790M* mutation testing based on tissue samples, MSAC considered that the prognostic significance of *EGFR T790M* mutation testing had been sufficiently established, and thus the mutation status as a treatment-effect modifier was sufficiently quantified. Being *T790M* mutation positive in tumour tissue is a positive prognostic factor for survival, but it is a negative prognostic factor for survival in plasma.

MSAC noted that no studies were provided comparing osimertinib and chemotherapy in both *T790M* mutation positive and negative subgroups. MSAC noted that evidence for the comparative effectiveness of osimertinib and chemotherapy relied on a direct randomised comparison (AURA3) in patients who were *T790M* mutation positive based on tumour tissue samples. For the outcome of overall survival, the application also presented a naïve indirect comparison of patient subgroups from the pooled single-arm AURA1C and AURA2 studies

and the single chemotherapy-only treatment arm of the IMPRESS trial. However, MSAC noted that the AURA studies and IMPRESS trial had used different sample sources (tumour tissue and plasma, respectively), and that the survival outcomes across these options may therefore reflect the inclusion of patients with different spectrums of disease.

MSAC also noted a comparative study of AURA phase 1 and pooled AURA extension and AURA2 results (Thress KA et al 2015) reported similar overall response rates (ORR) in patients with *T790M*-positive plasma-based tests and *T790M*-positive tissue tests (ORR 60.6% and 61.0%, respectively, in the subgroup of patients who were “evaluable for response”). Additionally, MSAC noted that the progression-free survival (PFS) was 9.7 months for osimertinib treated patients in the group who were *T790M*-positive in plasma and in those who were *T790M*-positive in tissue samples. (Oxnard GR et al 2016). However, MSAC considered that there were too few patients who were both *T790M*-positive plasma and *T790M*-negative tissue to be confident that this apparent similarity would translate into acceptable patient outcomes if reliant on plasma-based testing alone. MSAC noted that, although these studies provided some evidence for plasma-based testing, the high rate of false negative tests meant that patients with *T790M*-negative plasma results would still need a tumour biopsy to determine presence or absence of *T790M*. Given that as many as 35% to 40% of patients were unable to have a biopsy safely (based on AURA 3 data), MSAC considered that testing for plasma-based testing alone may be a reasonable option if supported by additional evidence of adequate test performance.

MSAC noted several other issues of concern regarding plasma-based testing, notably that:

- no program for quality assurance of plasma-based testing is currently available and few pathology laboratories can currently perform plasma-based testing;
- although evidence so far was encouraging, there are insufficient data to resolve the discordance between plasma-based and tumour tissue testing, or to determine the equivalent prediction of response on the basis of tumour tissue versus a plasma sample;
- the current reference standard (based on tumour tissue samples) is imperfect because of mutation heterogeneity in tumour tissue, and differs from what would be considered the ‘gold standard’ (measured patient outcomes); and
- the number of false positives for plasma-based testing from trials was small, and may have reflected mutation heterogeneity within tumour tissue, but this required further consideration.

MSAC considered that the potential use of osimertinib as a first-line therapy (compared with erlotinib or gefitinib) in advanced NSCLC with *EGFR* mutations would require a separate application, which should also explore the alternative algorithm of testing plasma samples.

MSAC noted that the fee for the proposed MBS item reflected the fee for the current *EGFR* testing item, and considered this to be reasonable.

MSAC noted the base case scenario of testing on a sample of tumour tissue resulted in an incremental cost effectiveness ratio (ICER) of **\$redacted** per quality adjusted life year (QALY). MSAC noted the alternative testing scenarios modelled, and noted that Scenario 2 in which all patients initially receive testing on a plasma sample, with patients who are plasma *T790M* negative subsequently undergoing rebiopsy and tissue sample testing, raised the incremental cost effectiveness ratio (ICER) only slightly to **\$redacted** per QALY.

MSAC noted that the application estimated annual cost savings to the MBS starting from **\$redacted** and reducing to **\$redacted** over a five year period as numbers of patients undergoing the procedure increase, based on the original estimated number of patients

suitable for biopsy. These estimates assume that chemotherapy-associated cost-offsets would exceed the costs of testing.

MSAC advised that the financial implications of testing plasma-based testing as an alternative or as an additional test to tumour tissue would require revision due to the expansion in the potential pool of patients.

4. Background

Application 1407 was previously considered at the November 2017 MSAC meeting. MSAC deferred its advice until the PBAC subsequently decides to recommend the PBS listing of osimertinib for the requested population.

5. Prerequisites to implementation of any funding advice

A number of different *EGFR* tests are listed on the Australian Register of Therapeutic Goods (ARTG), and are currently in use for determining eligibility for TKIs. They are approved as Class 3 tests.

There is a Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program (QAP) for *EGFR* mutation testing on formalin-fixed, paraffin-embedded (FFPE) tumour tissue from patients with NSCLC.

6. Proposal for public funding

Table 1: Proposed MBS item

Category 6 – PATHOLOGY SERVICES
A test of tumour tissue (derived from a new sample) from a patient with locally advanced (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), who has progressed on or after treatment with an EGFR TKI, to determine if the requirements relating to <i>EGFR T790M</i> gene status for access to osimertinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Proposed Fee: \$397.35 Benefit: 75% = \$298.05 85% = \$337.75

The proposed medical service requires a new tissue sample be collected to determine *EGFR T790M* mutation status, in patients with locally advanced or metastatic NSCLC, who have progressed on or after prior treatment with an EGFR TKI. This sample would then be used for *EGFR T790M* mutation testing, to determine eligibility for osimertinib. Those patients unable to undergo a rebiopsy, or who are *T790M* mutation negative, would receive platinum-based doublet chemotherapy.

The application stated that plasma-based testing would only be available in a limited number of laboratories due to lack of appropriate expertise and quality assurance measures. Hence the main body of the application was restricted to consideration of testing on tumour tissue.

7. Summary of Public Consultation Feedback/Consumer Issues

Public Consultation feedback provided one response from a peak organisation. The organisation raised two questions regarding the protocol in its feedback:

- The Confirmation PICO document mentions that circulating tumour DNA could potentially be tested using the patient’s plasma (not a tumour biopsy). This document states “irrespective of the source of DNA, one extra EGFR mutation test, in addition to the original tests at diagnosis will be conducted per patient” (p7). If the circulating DNA was negative for *T790M* a tumour sample would presumably be required to

ensure the circulating DNA negative result was not a false negative. Would the item be able to be used twice in this situation?

- The Confirmation PICO document mentions patients with *T790M* who have received prior EGFR TKIs would not be excluded. Would they need repeat biopsy and *EGFR* testing or would the presence of *T790M* at baseline biopsy be considered sufficient to receive osimertinib?

The ESCs advised that patients would likely prefer to avoid a rebiopsy, if there is an accurate non-invasive alternative test available.

8. Proposed intervention's place in clinical management

The population proposed for testing comprises patients with locally advanced (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), which has progressed on or after treatment with an EGFR TKI.

The biomarker is the *EGFR T790M* mutation, which increases the binding affinity of EGFR for adenosine triphosphate (ATP), which reduces the binding rate of ATP competitive TKIs and restores enzymatic activity. In the target population, the biomarker is present in approximately 60% of patients.

The *EGFR T790M* mutation test would be an additional test for patients who have progressed on or after EGFR TKIs.

As proposed, patients would be required to undergo a rebiopsy to retrieve a tumour tissue sample at the point of progression on or after EGFR TKI treatment. This sample is then used for *EGFR T790M* mutation testing, and those with a *T790M* mutation would be eligible to receive osimertinib. Those unable to undergo a rebiopsy, or who are *T790M* mutation negative, would receive platinum-based doublet chemotherapy.

Testing of circulating tumour DNA from a plasma sample is possible, but was reasonably not proposed as an option within the application.

9. Comparator

The application nominated no testing for *EGFR T790M* mutation and all patients treated with platinum-based doublet chemotherapy as the main comparator for the codependent technologies.

10. Comparative safety

Adverse events from testing

The main adverse event related to testing is the risk of pneumothorax from CT-guided lung rebiopsy requiring treatment. The rates of pneumothorax reported in the AURA clinical trials (1.9 to 5.5%) were lower than identified in a large retrospective cohort of patients undergoing CT-guided biopsies of pulmonary nodules in the United States (15%).

Adverse events from changes in management

The change in management expected to arise due to *EGFR T790M* mutation testing, is the use of osimertinib, rather than chemotherapy, in those who have mutations in their tumour tissue. The safety profile of osimertinib differs from chemotherapy and both are well-established,

with skin, nail and gastrointestinal effects more prominent with osimertinib, and more haematological events associated with platinum-based chemotherapy.

Osimertinib, if listed, would not substitute for chemotherapy, but rather displace it to a later treatment line. It would therefore be expected that chemotherapy-related AEs would be delayed rather than totally avoided.

11. Comparative effectiveness

Overview of the evidence base

The application presented a linked evidence approach (see table below) to support the contention that targeting patients with the *T790M* mutation with osimertinib will improve their overall survival, compared to no testing and treatment with platinum-based doublet chemotherapy.

Data from the AURA1B study, a dose ranging study investigating efficacy and safety of osimertinib in patients with advanced NSCLC following prior therapy with an EGFR TKI and data from the chemotherapy arm of the IMPRESS trial were used to identify the prognostic and predictive impact of *EGFR T790M* mutation status.

Table 2: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	Concordance studies between evidentiary standard and other forms of <i>EGFR</i> mutation testing ^a	☒ k=3 n=833	Low to moderate risk of bias
Prognostic evidence	Comparison of outcomes in patients with and without <i>T790M</i> mutations (based on plasma) who receive the chemotherapy + placebo	☒ k=1 n=120	High risk of bias due to use of plasma-based rather than tumour tissue-based test
Predictive evidence	Comparison of outcomes in patients with and without <i>T790M</i> mutations (based on tumour tissue) who receive osimertinib	☒ k=1 n=244	High risk of bias for interpretation of predictive validity, as this is based on a naïve indirect comparison with the prognostic evidence
Change in patient management	Not supplied	☐ k=0 ^a n=NA	
Treatment effectiveness Treatment effect (enriched)	AURA3 ^b was a head-to-head trial comparing osimertinib with platinum-based chemotherapy in tumour <i>T790M</i> positive patients. However, due to treatment switching in AURA3, the application used a naïve indirect comparison ^c between 2 single arm osimertinib studies and a single platinum-based chemotherapy arm from the IMPRESS trial.	☒ k ^b =1 n= 419 ☒ k ^c =3 n= 190	^b Direct comparison at low risk of bias for PFS, although high risk of bias for OS ^c Naïve indirect comparison at high risk of bias

^a reference standard not available; ^b direct comparison; ^c indirect naïve comparison; k=number of studies, n=number of patients.
Source: Compiled during the evaluation.

Data for the linked evidence components are outlined in the table below. The critique noted that gaps in the evidence include comparative treatment effectiveness in patients who are *T790M* mutation negative. The benefit of selective osimertinib treatment, i.e., treatment based

on *EGFR* mutation testing, rather than non-selective treatment, has not been assessed. The submitted evidence does not allow a distinction between prognostic and predictive effects.

Table 3: Data availability to inform comparisons

Proposed test vs no test	-	
Proposed test vs alternative test	AURA1A/1B, AURA2, Hor et al (2016)	
	Osimertinib	Platinum-based doublet chemotherapy
Biomarker test positive	AURA1B (<i>T790M</i> mutation status based on tumour tissue) AURA3 (<i>T790M</i> mutation status based on tumour tissue) AURA1C and AURA2 (<i>T790M</i> mutation status based on tumour tissue)	IMPRESS (<i>T790M</i> mutation status based on plasma) AURA3 (<i>T790M</i> mutation status based on tumour tissue)
Biomarker test negative	AURA1B (<i>T790M</i> mutation status based on tumour tissue)	IMPRESS (<i>T790M</i> mutation status based on plasma)

Source: Compiled during the evaluation.

The critique noted that populations selected by plasma-based versus tumour tissue-based testing are likely to have different spectrums of disease and considered that the findings from different components of the linked evidence approach are therefore not transferrable. The critique also stated that there is a high risk of bias associated with the included evidence.

Prognostic evidence

A systematic review and meta-analysis was identified, which assessed the prognostic impact of acquired *T790M* mutation status on post-progression survival. Four studies showed that a *T790M* mutation in tumour tissue was a positive prognostic factor for survival (HR = 0.57, 95% CI 0.44, 0.73). One study showed that a *T790M* mutation in circulating tumour DNA (ctDNA) in plasma was negatively associated with survival (HR = 1.87, 95% CI 1.42, 2.47).

Predictive evidence

No studies were provided comparing osimertinib and chemotherapy in both *T790M* mutation positive and negative subgroups. The application reported that patients with *T790M* mutations in their tumour tissue in AURA1B who received osimertinib had superior objective response rates (ORR) and progression-free survival (PFS) compared to those without *T790M* mutations. However, it is unclear whether these differences were due to the prognostic effect of *T790M* mutation status, a differential treatment effect, or due to both factors with the influence of each unable to be quantified.

Comparative analytical performance

The evidentiary standard, as ratified by PASC, was the Cobas® *EGFR* mutation test version 1. Concordance between the Cobas® *EGFR* mutation test (the evidentiary standard) and other forms of *EGFR* mutation tests likely to be applicable in Australia, and performed on tumour tissue, was moderately high. The critique noted that acquired *EGFR* mutations are more likely to have a heterogeneous distribution in tumour tissue than *de novo* mutations. Some patients will therefore have false negative results, if the biopsy samples the tumour in a location without *T790M* mutations. These patients will therefore forego the benefit of osimertinib, and receive chemotherapy, which is current standard practice. False positive results are likely to be rare.

Table 4: Comparative analytical validity of available *EGFR* tests for *T790M* mutations compared with the Cobas® *EGFR* test (tumour tissue)

Study ID	Evidentiary standard	Test	Estimated sensitivity [95%CI]	Estimated specificity [95%CI]	Estimated PPV [95%CI]	Estimated NPV [95%CI]
Dearden et al (2017)	Cobas® testing	Local testing (Cobas®, Sanger sequencing, Therascreen, PNA-Clamp, Sequenom, and SNaPSHot)	93.9 [88.4, 97.4]	85.9 [76.2, 92.7]	91.9 [86.7, 95.1]	89.3 [81.0, 94.3]
Hor et al (2016)	Cobas® <i>EGFR</i> test	Sanger sequencing	95.7 [95.5, 99.5]	100 [92.6, 100]	100 [not reported]	96 [86.1, 98.9]
COB- <i>EGFR</i> -341	Cobas® <i>EGFR</i> test v1	Cobas® <i>EGFR</i> test v2	with invalid results: 93.0 [89.0, 95.6]	with invalid results: 87.3 [81.1, 91.7]	97.8 [95.0, 99.1]	94.2 [89.2, 97.0]

Source: Compiled during the evaluation from Section 2B.5.1 of the application.

The critique stated that, by contrast with the data above, concordance between the Cobas® *EGFR* testing of plasma or tumour tissue was low (57%). A negative plasma-based result is uninformative, with a negative predictive value of 57.5%. However, the positive predictive value was 81.1%. That is, in those patients who had *T790M* mutations identified in their plasma, over 80% also had mutations identified in tumour tissue. The remainder of plasma-based positive cases should not be classified as being “false positives” because of the use of an evidentiary standard rather than an accepted reference standard. There may have been cases where the mutation was present in the bloodstream, but not in the single tumour slice tested, due to a heterogeneous distribution of mutation-bearing cancer cells within the tumour. The health impact of osimertinib in “false positive” patients is unknown.

Prevalence

The prevalence of the biomarker assumed in the application was 60%. There were no clear differences found in biomarker prevalence between ethnicities.

Change in management in practice

No data were presented in the application that demonstrated the way in which *EGFR T790M* mutation testing would change management compared to no testing. However, the critique stated that it was reasonable to conclude that test results would be trusted, and that those who have a *T790M* mutation identified in tumour tissue would receive osimertinib.

Clinical claim

The overall clinical claim is that the proposed codependent technologies (*EGFR T790M* mutation testing and osimertinib) are superior in terms of clinical effectiveness, patient safety and quality of life versus the main comparator (i.e. no testing and platinum-based doublet chemotherapy).

12. Economic evaluation

A modelled economic evaluation, in terms of incremental cost per life year gained and incremental cost per quality-adjusted life year (QALY) gained, was presented based on the claim of superior effectiveness and safety of osimertinib compared to platinum-doublet chemotherapy in patients who had progressed following prior *EGFR* TKI treatment.

The application presented an ICER of **\$redacted** per QALY, based on PFS outcomes from the AURA3 trial, and overall survival (OS) outcomes from a naïve indirect comparison of results from two cohorts: a pooled analysis of single arm studies (AURA1C and AURA 2) for osimertinib and the platinum-based chemotherapy arm from IMPRESS. Outcomes were extrapolated to 10 years' duration from a median duration of follow-up across the osimertinib studies of approximately 13 months, with utility weights from AURA3 and IMPRESS applied.

During the evaluation, an alternative scenario was modelled to explore the cost-effectiveness of osimertinib without *EGFR T790M* testing.

The base case economic analysis assumed that the test used in the AURA3 trial (the Cobas *EGFR* Mutation Test) would be used in Australian clinical practice, and so assumed 100% sensitivity and 100% specificity in the model. Sensitivity analyses were additionally presented using concordance data between the Cobas test and other *EGFR* tests in tumour tissue.

13. Financial/budgetary impacts

The application used an epidemiological approach to estimate the numbers of patients eligible for, and the uptake of, *EGFR T790M* testing and osimertinib treatment, over a six year period.

The application estimated cost savings to the MBS of up to **\$redacted** per year (revised: **\$redacted**) over the first 6 years. Net cost savings to the MBS were claimed on the basis of a reduced number of patients being treated with chemotherapy (and so a reduced number of chemotherapy services). While osimertinib is expected to replace chemotherapy as second-line treatment, the application assumed that some patients (48%) would still receive chemotherapy in the third-line setting (i.e. that osimertinib would displace, rather than replace, services associated with chemotherapy and pemetrexed maintenance administration).

The critique noted that there is potential for use outside of the proposed MBS item descriptor if services are claimed on tests conducted on plasma samples. Also, the net cost savings to the MBS due to the listing of *EGFR T790M* testing and osimertinib treatment may have been overestimated, as only patients with Stage IIIB/IV disease at diagnosis were considered, i.e. not those who have progressed to Stage IIIB/IV from an earlier stage, and there is the potential for broader use outside of the proposed listings.

The ESCs noted that the Pre-Sub-Committee Response presented a combined sensitivity analysis of the financial estimates (incorporating an initial plasma-based pre-test and tissue testing in 50% of patients, a 20% recurrence rate in early stage NSCLC, and an average treatment duration of **redacted** months with osimertinib). These combined changes increased the projected net savings to the MBS to **\$redacted** in the first year of listing.

14. Key issues from ESC for MSAC

The ESCs noted that no studies were provided comparing osimertinib and chemotherapy in both *T790M* mutation positive and negative subgroups. The application provided evidence from the AURA1B study, a single-arm non-comparator trial, where patients with *T790M* mutations in their tumour tissue who received osimertinib had superior objective response rates (ORR) and progression-free survival (PFS) compared to those without *T790M* mutations. The ESCs noted that, due to this lack of direct evidence for both subgroups, it is unclear whether these differences were due to a prognostic effect of *T790M* mutation status, a

differential treatment effect due to osimertinib, or due to both factors with the influence of each unable to be quantified.

The ESCs noted that the application relied on a naïve indirect comparison to assess the comparative effectiveness of the osimertinib relative to chemotherapy. The comparison between osimertinib and chemotherapy involved a subgroup of second-line patients from the pooled single-arm AURA1C and AURA2 studies and a subgroup from the single chemotherapy-only treatment arm of the IMPRESS trial (IRESSA Mutation Positive Multicentre Treatment Beyond ProGRESsion Study). The ESCs noted that the studies used different sources of test sample. The osimertinib AURA trials involved a total of 411 pre-treated *EGFR T790M* mutation positive patients. In these trials, the *T790M* mutation was identified using tumour samples, while the IMPRESS study identified the mutation using plasma samples. The ESCs noted that this may introduce problems as the spectrum of disease may have differed, depending on whether a tumour sample (as per the AURA trials) or a plasma sample (as per the IMPRESS study) was used. The IMPRESS study found that when patients with non-small cell lung cancer (NSCLC) provided plasma samples, those with the *T790M* mutation had poorer overall survival (OS) than those without the mutation. However, in contrast, the critique identified a meta-analysis (k = 4) (Liu Y et al 2017) which assessed the prognostic impact of acquired *T790M* mutation status on post-progression survival, finding that a *T790M* mutation in tumour tissue was a positive prognostic factor for survival.

The ESCs noted that these differences are consistent with the likely different spectrum of disease in those supplying a plasma sample, usually because a rebiopsy of the primary tumour is not possible because of risks to the patient. These patients are more likely to have a high tumour burden and distant metastases (“shedders”) and consequently, poorer prognosis. The ESCs considered that, due to the likely different spectrum of patients classified as *T790M* mutation positive in the IMPRESS versus the AURA trials, the indirect comparison provided in the application is biased, favouring osimertinib. The ESCs noted that, although the applicant attempted to address this by re-presenting the PFS curves for *T790M* positive patients, this argument assumes that PFS is a surrogate for OS, and that this has not been accepted in the literature or by the PBAC.

The ESCs noted that it was claimed in the application that, due to the substantial cross-over in AURA3 (a randomised study comparing the efficacy of osimertinib with platinum-based chemotherapy), data from second-line patients in “AURA Pooled” (combined data from the single-arm non-comparative AURA1C and AURA2 trials) were used to inform the OS for patients treated with osimertinib. The preferred method would have been the direct AURA3 intention-to-treat analysis, with or without adjustment for treatment switching. The ESCs noted that, as the OS event rates for the AURA Pooled and the AURA3 were similar (**redacted**% versus **redacted**%, respectively), the argument for use of the pooled data to inform the effectiveness component of the model could not be justified.

The ESCs noted that the proposed PBS restriction does not specify the basis of testing (tissue or plasma). The current ARTG listing for the Cobas *EGFR* mutation test version 2 test (the evidentiary standard) allows testing on either plasma or tumour tissue samples. The ESCs also considered that there was potential for the test to be used outside the proposed MBS item descriptor if services are claimed on tests conducted using plasma samples. The ESCs also considered that plasma-based testing could be used in patients unwilling or unable to undergo a rebiopsy of tumour tissue, which would expand the patient group to be broader than that of the AURA trials.

The ESCs noted that concordance is moderately high between the Cobas *EGFR* mutation test (the evidentiary standard) and other forms of *EGFR* mutation tests likely to be applicable in Australia performed on tumour tissue. However, the ESCs noted that false negative results

may arise due to the likelihood of heterogeneity in acquired *EGFR* mutations in tumour tissue. The ESCs noted the implications of this are that some patients may consequently receive chemotherapy (standard practice) in place of osimertinib. The ESCs also noted contrasting evidence around concordance between the Cobas *EGFR* plasma-based testing and tumour-based testing (57%; Thress KS et al 2015). The ESCs noted that the negative predictive value (57.5%) of plasma-based testing is too low to be informative. However, it was also noted that the positive predictive value (81.1%) of plasma-based testing is high; that is, more than 80% of patients with *T790M* mutations detected in plasma will also have the mutation in tumour tissue.

The ESCs noted a number of alternative testing scenarios were presented in the critique, two of which included the use of the plasma-based test. Of these scenarios, the greatest impact on the incremental cost effectiveness ratio (ICER; increase from ~\$redacted per QALY to ~\$redacted per QALY) occurred if there were no *EGFR T790M* testing prior to undertaking osimertinib therapy. The ESCs noted that the scenario in which all patients receive initial testing of a plasma sample, with *T790M* negative patients undergoing tissue biopsy and testing to identify any plasma-based false negatives, resulted in only a modest increase to the base case ICER (by ~\$redacted per QALY).

The ESCs noted that a fourth testing scenario, which was not presented in the application, was possible. This involved using the existing MBS item (item 73337) to test for the *T790M* mutation at the time of diagnosis of locally advanced or metastatic NSCLC as the methods for *EGFR* testing for the proposed MBS item are identical to the methods currently used under this item. The ESCs noted that this scenario has clinical, economic and financial implications:

- patients with *T790M* at diagnosis who subsequently receive first-line treatment with gefitinib, erlotinib (or afatinib if it is PBS-listed) may not require testing via the new proposed MBS item at the time of progression on or after an EGFR TKI to determine eligibility for osimertinib if not thought to have an alternative acquired resistance mechanism, and could hence avoid an unnecessary biopsy at the time of progression. This would result in a small reduction in costs to the MBS; and
- knowledge of *T790M* at the time of diagnosis may lead to first-line use of osimertinib (noting that such use would be within the TGA-approved indication, but not within the proposed PBS restriction), especially given the results of the FLAURA trial (see below) of osimertinib in this setting.

Regarding the possible exploration of alternative testing scenarios that include the use of the plasma-based test for *T790M*, the ESCs considered that, as there is a lack of evidence regarding the comparative effectiveness of osimertinib in patients with the *T790M* mutation in plasma, a new application would be required to determine the eligibility for treatment with osimertinib on this basis.

The ESCs noted the results of the Phase III FLAURA study (AZD9291 Versus Gefitinib or Erlotinib in Patients With Locally Advanced or Metastatic Non-small Cell Lung Cancer), which is assessing the efficacy of osimertinib as a first line treatment in patients with *EGFR* mutation positive NSCLC, reported that the median PFS for osimertinib was 18.9 months compared with 10.2 months for standard care. The ESCs advised that this had the potential to push osimertinib to first line use rather than use following progression on or after EGFR TKI therapy.

The ESCs noted that testing for *T790M* status upon disease progression would introduce a key additional step, which is rebiopsy of lung tissue and that rebiopsy would introduce an additional risk of adverse events, particularly pneumothorax. The ESCs queried the rates of

pneumothorax as listed in the application (3.5%), and consequent cost of two specialist attendances (MBS item 116) related to adverse events that was modelled and considered that the rates may have been underestimated. The ESCs noted that the critique had explored a rate of 14% based on the literature and MSAC advice ([MSAC Application 1161 Public Summary Document, November 2012](#)) and unit costs based on AR-DRG amounts (for bronchoscopy and associated multi-day hospital stay), resulting in a 5% increase in the ICER. The ESCs noted the claim in the application that 82% of patients would be suitable for rebiopsy, whereas Japanese and Australian market research data presented in the application both reported 63%. The ESCs also noted that the impact of biopsy on patients (in terms of utility decrement) had not been captured in the model, which assumes no impact on subjects (no reduction in quality of life), potentially affecting the ICER.

The ESCs noted that, in the Pre-Sub-Committee Response, costs based on the observed mean duration of treatment with osimertinib had been revised **redacted**. This increased the ICER from ~\$**redacted** per QALY to ~\$**redacted** per QALY. The ESCs also noted that the Pre-Sub-Committee Response assumed a treatment duration of **redacted** months in revisions to the sponsor's estimations of financial impact.

The ESCs noted that patients would likely prefer to avoid a rebiopsy, if there is an accurate non-invasive alternative test available.

15. Other significant factors

Nil

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

The applicant had no comment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)