



Australian Government

Department of Health

MEDICAL SERVICES ADVISORY COMMITTEE

**EGFR mutation testing to determine eligibility for
access to PBS subsidised AZD9291 therapy in
patients with locally advanced or metastatic
EGFRm NSCLC**

Final Protocol

MSAC Application 1407

November 2015

Title of Application

Epidermal Growth Factor Receptor (EGFR) mutation testing to determine eligibility for access to Pharmaceutical Benefits Scheme (PBS) subsidised AZD9291 therapy in patients with locally advanced (Stage IIIb) or metastatic (Stage IV) non-squamous or not otherwise specified (NOS) EGFR sensitising mutation positive (EGFRm) non-small cell lung cancer (NSCLC) who have previously received treatment with an EGFR Tyrosine Kinase Inhibitor (TKI) (gefitinib, erlotinib, afatinib), have a World Health Organisation (WHO) Performance Status (PS) of 0 or 1 and have progressive disease.

Purpose of application

The purpose of this application is to request the addition of a new MBS item code with the proposed item descriptor:

'A test of tumour DNA, derived from a new tissue sample, from a patient with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous or not otherwise specified (NOS) non-small cell lung cancer (NSCLC), with a sensitising EGFR mutation (EGFRm) who has previously received treatment with an EGFR TKI (gefitinib, erlotinib, afatinib) and have progressive disease, requested by a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor (EGFR) gene status for access to AZD9291 under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.'

PBS listing for AZD9291 will be sought for treatment of patients with locally advanced (Stage IIIb) or metastatic (Stage IV) non-squamous or NOS EGFR mutation positive NSCLC who have previously received EGFR TKI therapy (gefitinib, erlotinib, afatinib), who have progressive disease, PS 0-1, and whose tumour(s) harbour a T790M resistance mutation within the EGFR gene.

The consequence of a new MBS item would be a requirement for an additional tumour DNA sample and an additional EGFR mutation test (currently MBS item 73337) for eligible patients.

The rationale for this application is the current limited number of effective treatment options for patients with EGFRm advanced NSCLC with progressive disease.

Australian clinical treatment guidelines [1] recommend that *'Patients with known activating gene mutations (exon-19 deletions or exon-21 point mutations) to EGFR should be treated with an EGFR TKI.'* The availability of EGFR mutation testing of non-squamous or not otherwise specified (NOS) NSCLC at diagnosis ('reflex') on the MBS means most frequently an EGFR TKI is commenced as first-line treatment in the advanced setting. In some cases,

platinum based doublet chemotherapy may be commenced if there is a delay in testing, or to relieve symptoms prior to initiation of the TKI.

Despite the initial efficacy of the first-generation (gefitinib or erlotinib) and second-generation (afatinib) EGFR-TKIs, most, if not all, patients treated with these agents will eventually progress such that median progression-free survival (PFS) is often reported to be less than 12 months [2-5]. Jackman and colleagues [6] proposed a clinical definition for this 'acquired resistance' to EGFR TKIs in tumours for which several mechanisms have been identified. The most common is the presence of a secondary mutation, T790M, which is detected in up to 60% of patients [7-13].

This point mutation occurs in exon 20 of EGFR and leads to substitution of methionine for threonine at position 790 in the kinase domain of the receptor [14, 15]. In the absence of competitive pressure from the driver sensitising mutation(s) being suppressed by an EGFR TKI, T790M clones proliferate in the tumour environment.

In the advanced NSCLC post-EGFR TKI treatment failure setting, no approved therapy is currently available for patients with T790M mutation positive tumours that have acquired EGFR TKI resistance or are refractory to EGFR TKI treatment. Subsequent treatment of EGFRm NSCLC includes using platinum-based chemotherapy doublet treatment [16-18] with the associated toxicity burden that may include nausea, vomiting, bone marrow suppression, alopecia, fatigue, and peripheral neuropathy.

The only way to confirm if the tumour growth in a patient receiving EGFR TKI is being driven by the secondary mutation, T790M, is to obtain a tumour DNA sample, and conduct an EGFR mutation test at the time of disease progression.

Note: The EGFR T790M mutation is rarely (<1%) identified in EGFR TKI-naïve tumours. These "de novo" T790M mutations have been identified in EGFR mutation testing for first-line EGFR TKI access. These generally occur concurrently with an EGFR sensitizing mutation and have been found to be associated with decreased sensitivity to the first and second generation EGFR TKIs. Clinical treatment in these cases, may be to commence EGFR TKI treatment, however research suggests that these subset of patients have a distinct clinical course and further data is required to determine the optimum clinical management for these patients [19, 20]. A study of AZD9291 in the treatment of first-line locally advanced or metastatic EGFRm NSCLC is currently recruiting participants (FLAURA, NCT02296125) and may provide further data on the most appropriate clinical management. Nevertheless, if such patients did receive prior EGFR TKI treatment and fulfil other eligibility criteria this should not preclude them from further EGFR mutation testing and potential treatment with AZD9291.

AZD9291 is an oral, mutant-selective, irreversible third-generation EGFR TKI with activity against tumours harbouring sensitising mutations (EGFRm) including the resistance conferring T790M mutation (EGFRm/T790M) of the EGFR gene in NSCLC. AZD9291 has been shown in a Phase I and II studies to be clinically active and well tolerated as monotherapy [21-25]. The targeting of EGFR mutations of the tyrosine kinase domain including the T790M mutation leads to attenuation of uncontrolled cell survival and proliferation.

Population and medical condition eligible for the proposed medical services

Disease Description:

Lung cancer is the fourth most commonly diagnosed cancer in Australian men and women, with an expected 12,180 new cases in 2016 [26]. The disease is the most common cause of death from cancers. Prognosis is poor with a 5-year survival rate of approximately 14% [27]. This is due in part to late presentation and detection, with over 50% of patients with lung cancer being diagnosed when the disease is already at an advanced and inoperable stage [28].

In Australia, approximately 80% of lung cancers are classified histologically as non-small cell lung cancer (NSCLC), and of these 84% are further classified as non-squamous / NOS [29].

As noted above, 'reflex' EGFR mutation testing at diagnosis, irrespective of disease stage, of NSCLC non-squamous / not otherwise specified histology, has been MBS subsidised since 2014 [30]. For patients with EGFRm NSCLC, the EGFR TKIs, gefitinib and erlotinib, are available on the PBS for any line of treatment in the locally advanced or metastatic stage [31, 32]. Afatinib is TGA registered and has a PBAC positive recommendation but is not yet PBS reimbursed [33]. The EGFR TKI treatment is not curative and, in the majority of cases, the disease will ultimately progress.

Proposed patient population:

This service would apply to patients with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous or NOS EGFRm NSCLC who have previously received treatment with an EGFR TKI (gefitinib, erlotinib, afatinib), PS 0-1, and have progressive disease. Conducting an additional EGFR mutation test at this time point will identify those patients whose tumour(s) harbour the T790M mutation and thus are most likely to benefit from treatment with AZD9291. It is expected that a T790M mutation will be present, as the mechanism of acquired resistance, in approximately 60% of these patients [6]. Prevalence of T790M in the Australian EGFRm advanced NSCLC post EGFR TKI population at this time point is not known.

Three clinical studies for this indication (Table 1) are in progress. The completed AURAEX and AURA2 studies will form the pivotal evidence base for regulatory and reimbursement dossiers. The randomised controlled study, AURA3 may not have reached the primary endpoint at the expected times of submission. PASC noted that from these studies the evidence to be submitted should enable MSAC to assess both the clinical validity of the T790M test to inform prognosis and the clinical utility of the T790M test to predict variation in the effectiveness of AZ9291.

Table 1 Clinical studies of AZD9291 in ≥2nd-line treatment of T790M+ EGFRm locally advanced or metastatic NSCLC

Criteria(Protocol date)	STUDY	AURAEX [†] (Feb 2014)	AURA2 (Sep 2014)	AURA3 (Dec 2014)	#1407 proposed population
AZ Study code		D5160C00001	D5160C00002	D5160C00003	-
NCT number (www.clinicaltrials.gov)		NCT01802632	NCT02094261	NCT02151981	-
Study design		Single-arm Open-label	Single-arm Open-label	Randomised Double-blind	-
Study drug dose and frequency		80mg tablet once daily oral			80mg daily
Subject numbers (n)		201	210 [2 nd -line (n=70); >2 nd -line (n=140)]	410 [study drug (n~270); doublet chemo (n~140)]	-
Australian study sites (n)		3	0	5	-
Inclusion					
Male or female, ≥18yrs		✓	✓	✓	✓
Histological or cytological confirmation of NSCLC		✓	✓	✓	✓
Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy		✓	✓	✓	✓
Radiological documentation of disease progression. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study. Either - following 1 st -line EGFR TKI treatment but who have not received further treatment OR		✓	✓	✓	✓ or clinical progression as determined by clinician
- following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy. Patients may have also received additional lines of treatment.		Second-line	Second-line	Second-line	Second-line
		>Second-line	> Second-line	x	✓ > Second-line
Subjects must have a diagnosis of 'non-squamous NSCLC' to be eligible to receive treatment with pemetrexed platinum-based doublet chemotherapy		NA	NA	✓	✓ Non-squamous / NOS
Confirmation that the tumour harbours an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q) OR		✓	✓	✓	✓ From diagnostic EGFR mutation test

Criteria(Protocol date)	STUDY	AURAE [†] (Feb 2014)	AURA2 (Sep 2014)	AURA3 (Dec 2014)	#1407 proposed population
Must have experienced clinical benefit from EGFR TKI, according to Jackman criteria followed by systemic objective progression while on continuous treatment with EGFR TKI		✓ Escalation [^] × Expansion Extension	×	×	×
Patients must have central confirmation of tumour T790M mutation positive status from a biopsy sample taken after documented disease progression on the most recent treatment regimen.		✓	✓ Plasma ctDNA samples were also taken	✓ First-line treatment with an approved EGFR TKI	✓ Approved local laboratory
World Health Organisation (WHO) performance status 0-1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.		✓	✓	✓	✓
At least one lesion, not previously irradiated and not chosen for biopsy during the study screening period, that can be accurately measured at baseline as ≥ 10mm in the longest diameter (except lymph nodes which must have short axis ≥ 15mm) with computerised tomography (CT) or magnetic resonance imaging (MRI) which is suitable for accurate repeated measurements.		✓	✓	✓	In clinical practice, a combination of imaging and symptomatology
Participants should be using adequate contraceptive measures		✓	✓	✓	Discussion with clinician
Exclusion					
Treatment with more than one prior line of treatment for advanced NSCLC		×	×	✓ Second-line AZD9291 only	×
Treatment with an EGFR-TKI (e.g., erlotinib, gefitinib, or afatinib) within 8 days or approximately 5x half-life, whichever is the longer, of the first dose of study treatment.		✓	✓	✓	Clinical practice
Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment.		✓	✓	✓	✓

† AURAE is the Extension Phase of the AURA Study commenced following completion of the Escalation and Expansion Phases. ^Escalation phase did not preselect by T790M status.

Details of expected utilisation, if service is to be publically funded:

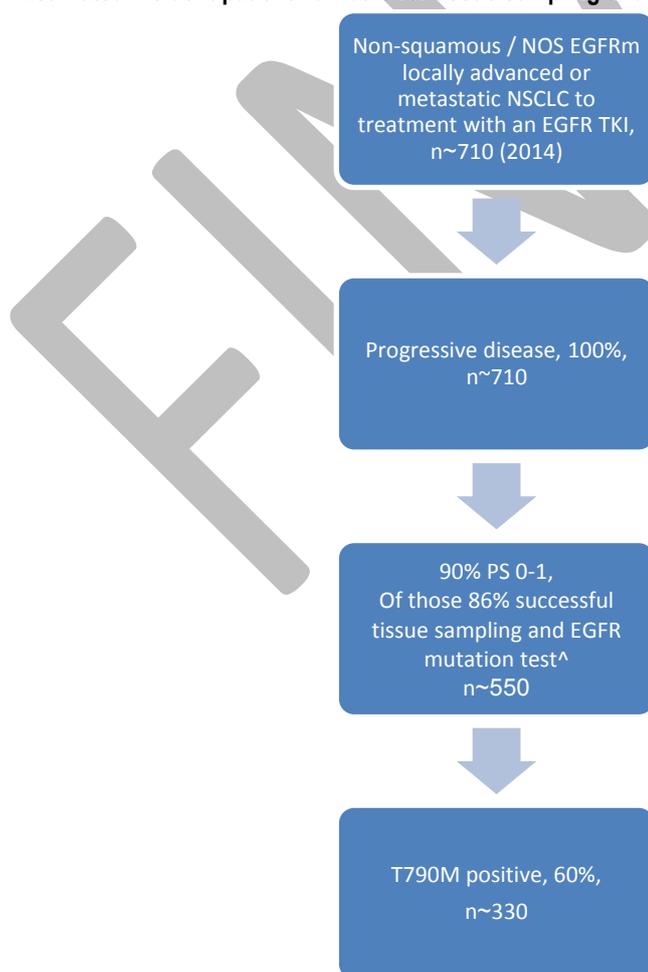
The infrastructure required for a biopsy and EGFR mutation test is already in place in the Australian health system. Prior to reimbursement of EGFR mutation testing and EGFR TKIs in 2014, it was estimated that approximately 710 Australian EGFRm NSCLC patients would be eligible to be treated with an EGFR TKI in the first-line setting. It is this EGFR TKI pre-treated population who may receive the proposed additional EGFR mutation testing service, with the assumption that locally advanced or metastatic disease eventually will progress. Additionally, in the initial years of the proposed listing, there will be a pool of prevalent patients, who have previously received and progressed on an EGFR TKI and may be eligible

for this service. This prevalent population will be estimated in the submission. Estimated numbers of incident patients in the first year are shown in Figure 1.

Methodologies to obtain circulating-tumour (ct) DNA from plasma samples to use to determinate T790M status and appropriateness for treatment with AZD9291 are in development. Plasma sampling will overcome the potential impact of tumour heterogeneity, where acquired resistance may not develop equally, and be missed by tissue biopsy of one tumour at one location only.

The MBS item statistics presented in the protocol critique are less than anticipated based on an expected 15% prevalence (n = 710 EGFRm patients, total tests >4,000 per year). Potential reasons include claiming using the MBS item code 73328, also for EGFR mutation testing, until it was deleted in October 2014; private testing via access programs; preselection based on phenotype; public laboratories are funded via State Health Departments and do not claim rebates via Commonwealth schemes; pathologists and medical oncologists not being aware of the 'pathologist determinable' designation of the item.

Figure 1: Estimated incident patient numbers for tissue sampling and EGFR mutation testing



^ A 2011 study demonstrated that post-progression tissue sampling of NSCLC patients was feasible and provided sufficient material for mutation analysis in 104 (86%) of 121 patients. Most failures were related to low tumour content. [11]

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Intervention – proposed medical service

Description of the proposed medical service:

The proposed medical service is an additional EGFR mutation test to determine the presence of the T790M mutation in patients with locally advanced (Stage IIIB) or metastatic (Stage IV), non-squamous or not otherwise specified EGFR mutation positive NSCLC, PS 0-1, who have previously received EGFR TKI treatment, and whose disease has subsequently progressed. PASC advised that it does not support reflex testing for the new MBS item proposed for T790M gene testing.

As the aim of this additional mutation test is to identify changes in the tumour environment following exposure to an EGFR TKI, a further tumour sample is required at this time point. In order to perform a successful molecular mutation test, a sufficient quantity of tumour cells is required to ensure that an adequate amount of tumour DNA is extracted for analysis; thus, tumour biopsy samples have been the most suitable, commonly available and preferred sample type. There are a number of Guidelines with recommendations regarding tumour tissue sampling for lung cancer management and subsequent molecular testing [34-37]. PASC noted that as the trial data for the intervention is based on tumour biopsy samples, so the possible use of cytology samples will be excluded from the base case.

This protocol is neither specifying nor sponsoring any specific methodology for EGFR mutation testing. As per MBS item 73337, any appropriately accredited and validated EGFR mutation test methodology is within the scope of this application. The submission will provide details of the tests available commercially in Australia and required concordance and quality assurance data (as per MSAC Application 1611 [38]).

Please note that there are no EGFR test methodologies available that only test for the presence of T790M on exon 20. AZD9291 has activity against the known sensitising mutations of the EGFR gene as well as T790M [21].

Technical specification and any reference or “evidentiary” standard that has been established.

There is no established reference standard for EGFR mutation testing.

The AURA studies use the cobas[®] EGFR Mutation Test (Roche Molecular Diagnostics) to determine eligibility of patients. This is a real-time polymerase chain reaction (PCR) test [39]. The test kit was registered on the Australian Register of Therapeutic Goods (ARTG)

#194319, effective 3rd February 2012 [40] and is the proposed 'evidentiary' standard for this evaluation.

The cobas[®] EGFR Mutation Test consists of two major steps: (1) a manual DNA isolation step and (2) PCR amplification and detection of target DNA using complementary primer pairs and oligonucleotide probes labelled with fluorescent dyes. The test kit:

- Identifies 41 mutation in exons 18, 19, 20 and 21 of the EGFR gene. The test is designed to detect G719X (G719A, G719C and G719S) in exon 18; deletions and complex mutations in exon 19; S768I, **T790M mutation** and insertions in exon 20; and L858R in exon 21. A mutant control and a negative control are included in each run to confirm the validity of the run.
- Detects <5% mutant sequence copies in a background of wild-type DNA.
- Can be performed on a single, 5 µm formalin-fixed paraffin-embedded (FFPE) section with >10% tumour. Macrodissection of the tissue section is only required if the estimated tumour content is <10% by pathological assessment.

PASC advised that more details of the testing process would be needed (e.g. tumour sample size and tissue heterogeneity) to specify the evidentiary standard adequately. If alternative methods of collection, for example cytology samples, are proposed, these will also be required to be assessed against the evidentiary standard.

In the AURA studies, biopsy is the source of tumour tissue for mutation testing.

As per MSAC Application 1161 for the reimbursement of EGFR mutation testing to determine eligibility for access to gefitinib [38], no specific test methodology to determine EGFR T790M status is proposed for this service.

Does the service include a registered trademark?

No registered trademark is proposed to be associated with this service. AstraZeneca is not a sponsor of any EGFR mutation testing methodologies.

Indicate the proposed setting in which the proposed medical service will be delivered:

The EGFR mutation test is proposed to be conducted in Australian molecular laboratories with EGFR mutation testing as part of their National Association of Testing Authorities, Australia (NATA; National Association of Testing Authorities) approved scope.

Describe how the service is delivered in the clinical setting.

It is expected that locally advanced or metastatic NSCLC patients will be the population to whom this service will apply. In the Australian clinical setting, the majority of such patients will be under the care of a Medical Oncologist, and those whose tumours are of non-squamous or NOS histology, will undergo mutation testing (at diagnosis) for the presence of an EGFR sensitising mutation. In clinical practice, for patients who are eligible for, and receive an EGFR TKI, disease progression is generally detected following regular investigations (e.g. CT scan), and/or symptom return. The medical oncologist and patient will decide whether a subsequent active treatment and a biopsy procedure to obtain tumour tissue at this time point in the disease is a possibility. If yes, a referral to a Respiratory Physician or Interventional Radiologist for the biopsy will be made. The specimen collected will be forwarded to an approved molecular pathology laboratory for conduct of the EGFR mutation test. Decisions on subsequent treatment will depend upon the presence or absence of the T790M mutation.

Plasma ctDNA [41]:

To avoid the costs, discomfort and possible complications of an invasive procedure, and permit as many patients as possible to be tested for mutations following EGFR TKI treatment, in July 2014 AstraZeneca announced a collaboration with Roche to develop a plasma-based companion diagnostic test, cobas™, to support AZD9291. cobas™ based on ctDNA is being designed to identify EGFR mutations in both tumour tissue and plasma derived from patients with NSCLC.

AstraZeneca Australia is investigating the feasibility of a sequential approach where EGFR T790M mutation status may be first assessed using a plasma-based ctDNA test, and if the result is negative then sampling of tumour tissue by biopsy and a subsequent test. In this scenario, a positive determination of T790M mutation status by either a plasma-based or tissue-based EGFR mutation test would indicate suitability for treatment with AZD9291

[Co-dependent information \(if not a co-dependent application go to Section 6\)](#)

MSAC Application #1407 includes co-dependent technologies. The requested service (EGFR mutation test) is required to identify patients who have a specific mechanism of acquired

resistance (T790M point mutation) driving disease progression. The drug, AZD9291, selectively and irreversibly binds to the tyrosine kinase domain of exon 20 mutation T790M (as well as sensitising mutations of the EGFR gene) and inhibits tumour growth. AZD9291 has not been studied as a treatment option for other mechanisms of acquired resistance.

The service is required at this time point in the course of the disease as it is only during treatment with an EGFR TKI, and suppression of sensitising mutations of the EGFR gene that the resistance mutation, T790M clones flourish and contribute to disease progression. It is only with confirmation of the presence of T790M at the time of progression, that AZD9291 becomes the treatment of choice.

It is intended that MBS listing of the EGFR mutation test to determine T790M mutation and PBS listing of AZD9291 for eligible patients will occur simultaneously.

Comparator – clinical claim for the proposed medical service

The comparator for this application is the current standard of care. That is, at progression on treatment with an EGFR TKI or subsequent therapy, no biopsy will be performed and all patients able to continue with active therapy (PS 0-1), will receive either a platinum-based doublet chemotherapy for 4-6 cycles, with or without maintenance treatment; or single agent chemotherapy [1]. Data will be collected and presented in the submission to provide further details regarding local clinical practice and specific comparators. The proposed intervention requires a biopsy to obtain tumour tissue for the EGFR mutation test (no established reference standard; evidentiary standard is cobas EGFR mutation test, no preferred testing methodology specified) to determine the presence of T790M. In patients with T790M positive tumour(s), treat with AZD9291 80 mg daily oral. For patients who are T790M mutation negative or status unknown, treatment is per standard of care.

Clinical claim

For patients with locally advanced (Stage IIIb) or metastatic (Stage IV) NSCLC of non-squamous or NOS histology harbouring a sensitising mutation of the EGFR gene, who have progressed after previous treatment with an EGFR TKI (gefitinib, erlotinib, afatinib), PS 0-1, EGFR mutation testing followed by treatment with AZD9291 for those with an identified T790M mutation, and platinum-based doublet chemotherapy or mono-chemotherapy for those without a T790M mutation, is superior, in terms of both comparative effectiveness and safety, to no test and treatment with platinum-based doublet chemotherapy or mono-chemotherapy for all patients.

Expected health outcomes relating to the medical service

Health outcomes relating to the proposed indications include overall survival, progression free survival, objective response rate, disease control rate, tumour shrinkage, duration of response, quality of life measures, safety and tolerability, the diagnostic accuracy of the EGFR mutation test and comparison of performance between test methodologies.

PASC suggested that genetic heterogeneity be considered in the modelling of the intervention and comparator arm (which is based on tumour biopsy).

Describe any potential risks to the patient. From the biopsy:

The invasive nature of tissue sampling procedures (described in Gefitinib Protocol, [42]) means that there is an associated risk of complications. Jekunen [43] conducted a systematic literature review in 2015, using search terms *rebiopsy* and *lung cancer*, and concludes that rebiopsy is feasible in NSCLC provided careful site selection and adequate evaluation of risks for complications are performed prior. Articles identified reported one serious complication among 155 rebiopsies patients [10] and 13 minor complications in 94 patients [44]. In addition, no complications in 47 biopsied patients were reported by Bepler et al. in their repeated biopsy article [45].

Potential problems associated with rebiopsy reported during clinical studies may be exacerbated by the need for larger solid tissue samples to satisfy protocol inclusion requirements for slide numbers. Further information on local clinical practice outside of clinical trials and potential additional costs incurred with rebiopsy in this population will be sought and included in the co-dependent submission.

From EGFR mutation testing:

There is a potential risk of a false positive or a false negative result. This will be explored in the submission based on the cobas test specifications as the evidentiary standard.

From AZD9291 treatment:

Based upon 90 NSCLC patients receiving the recommended 80mg daily dose of AZD9291 in a Phase I study [23], the most commonly reported adverse events were diarrhoea; rashes and acne; nausea; decreased appetite; constipation; pruritus.

Specify the type of economic evaluation.

A cost-utility analysis is proposed to be based on the superior efficacy, safety and quality of life of AZD9291 versus platinum-based doublet chemotherapy or monotherapy in locally advanced (Stage IIIb) or metastatic (Stage IV) EGFRm and T790M mutation positive NSCLC patients.

Fee for the proposed medical service

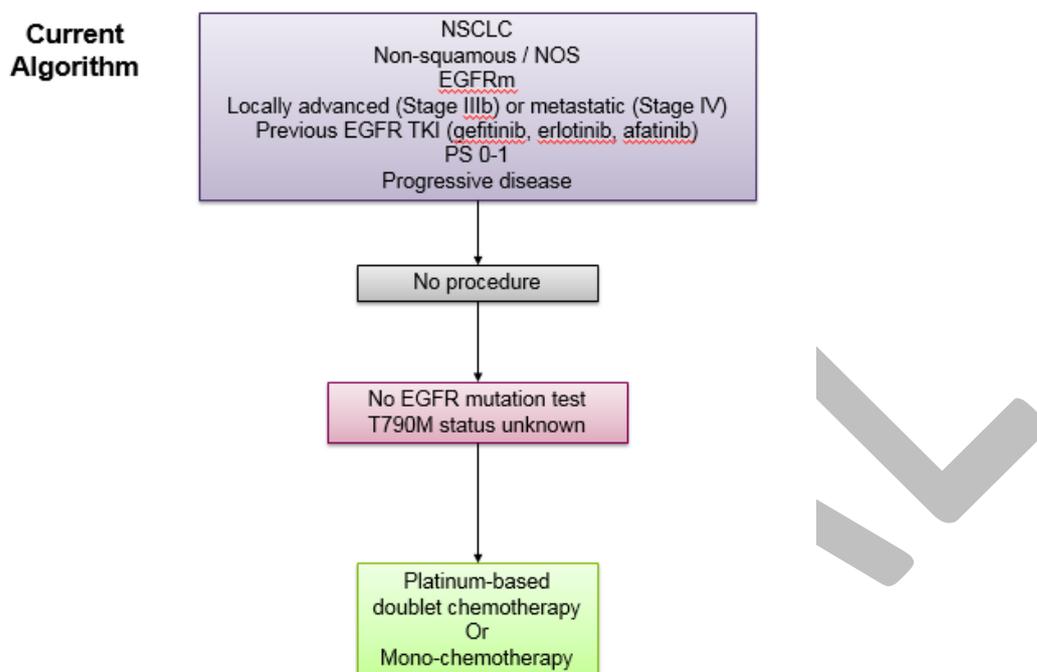
The current fee for MBS item 73337 (EGFR mutation test) is \$397.35 per service. As the requested MBS item will be for the same service (EGFR mutation test) the fee is proposed to remain at \$397.35 per service. The cost of a biopsy to obtain a tumour tissue sample will be as per the relevant MBS item code fees (e.g. 41892 Bronchoscopy, \$235.05; 30710 EBUS procedure, \$536.30). [46].

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Clinical Management Algorithm - clinical place for the proposed intervention

Current Treatment Algorithm

Figure 2 - Flowchart of current clinical algorithm



The current approach to management in Australian clinical practice of locally advanced or metastatic NSCLC of non-squamous or not otherwise specified histology and known EGFR mutation positive status, is to treat with one of the available and indicated EGFR TKIs (gefitinib, erlotinib, afatinib). Gefitinib and erlotinib are PBS reimbursed for one line of therapy. Hence, at progression, the TKI is ceased and further active treatment initiated dependent upon patients Performance Status (PS) and preferences.

A number of clinical practice guidelines, including Australian ones [1, 47, 48] contain no specific recommendation regarding treatment following progression on a TKI in EGFRm patients. NCCN Guidelines [17] suggest in the event of symptomatic, systemic progression with multiple lesions in EGFRm NSCLC, doublet chemotherapy (\pm bevacizumab) for patients with a PS 0-1.

In 2014, the Italian Association of Thoracic Oncology held an International Expert Panel Meeting on the role for chemotherapy in EGFR mutation positive advanced NSCLC [16] which recommended:

'Panelists agreed that in patients with EGFR mutation+ advanced NSCLC, chemotherapy should be used after EGFR TKI failure. ...

There is no evidence to recommend a preferred chemotherapy regimen in EGFR mutation+ patients. Panelists agreed that platinum-based regimens should always be considered after EGFR TKI failure in eligible EGFR mutation+ patients.'

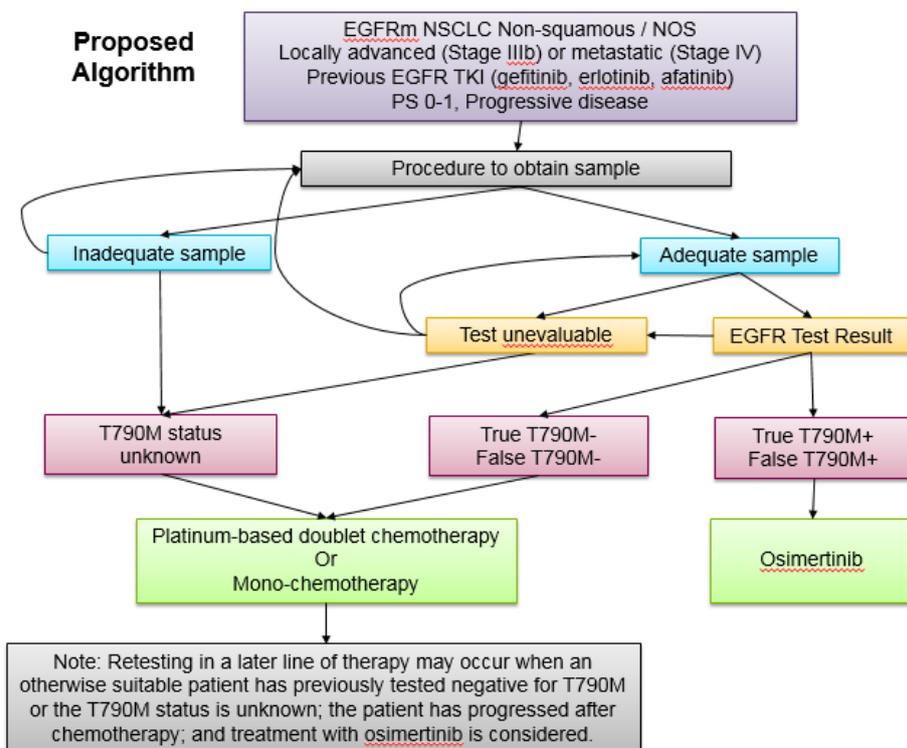
Currently available reimbursed therapy options for this patient population in Australia are platinum-based doublet chemotherapies or a single agent chemotherapy, such as pemetrexed or docetaxel. Data will be collected and presented in the submission to provide further details regarding local clinical practices.

Current clinical practice is no routine EGFR mutation testing in this population. The T790M mutation status of all patients is unknown and treatment decisions are made on this basis.

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Proposed Treatment Algorithm

Figure 3 - Flowchart of Proposed Treatment Algorithm



Note: if sampling issue, resample or treat as unknown status; if testing issue, retest or resample or treat as unknown status. The algorithm includes all possible options in the event of a sampling or testing issue. The proportions for each pathway will be provided in the submission.

The availability of AZD9291 will alter patient management. At progression, patients whose performance status is 0-1 may elect, in discussion with their clinician, to undergo another biopsy to collect tumour tissue. Already having experienced the benefits from TKI therapy due to their EGFRm status, patients are likely to understand the necessity for the procedure. EGFR mutation testing will determine T790M status. Those patients who are T790M mutation positive will be eligible to commence treatment with AZD9291. Those who elect not to undergo biopsy, or T790M status is negative or unknown, will receive current standard of care.

Regulatory Information

The proposed medical service involves the use of an in-vitro diagnostic (IVD) test to detect EGFR mutations in patients with NSCLC, in order to determine eligibility for AZD9291 treatment. As this is a human genetic test intended to identify patients who may benefit from treatment with AZD9291, per current EGFR mutation testing it is classified as 'Medical

Device Included – IVD Class 3 [49]. The cobas[®] EGFR Mutation Test is listed on the ARTG (number: 194319), effective date 03-02-2012.

AZD9291 is currently not registered for marketing in any jurisdiction. AZD9291 has been granted Breakthrough Therapy designation, Orphan Drug and Fast Track status by the US FDA [50].

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Decision analytic

Table 2 - Summary of PICO to define research question

PICO	Comments
Patients to test	Patients with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous or NOS EGFRm NSCLC previously treated with an EGFR TKI (gefitinib, erlotinib, afatinib), PS 0-1, and who has progressive disease.
Intervention	Biopsy to obtain tumour DNA EGFR mutation test to determine T790M status If T790M positive, receive AZD9291 80mg tablet once daily oral If T790M negative or status unknown, receive platinum-based doublet chemotherapy or mono-chemotherapy
Comparator	No biopsy No EGFR mutation test Platinum-based doublet chemotherapy or mono-chemotherapy
Outcomes#	Diagnostic accuracy of T790M testing (sensitivity, specificity, negative predictive value, positive predictive value, likelihood ratios) dependent upon available data; Comparison of test performance between T790M testing methodologies against the evidentiary standard Objective Response Rate (ORR) Disease Control Rate (DCR) Tumour shrinkage Duration of Response (DoR) Progression Free Survival (PFS; investigator assessments and central review) Overall Survival (OS) Quality of Life (QoL) (EORTC QLQ-C30; EQ-5D-5L, EORTC QLQ LC13) Safety and tolerability (adverse events graded by CTCAE v4; clinical chemistry, haematology, urinalysis; vital signs, physical examination, weight; digital ECG including QTc interval; WHO performance status; echocardiogram) Cost and cost-effectiveness

Definitions of Complete Response (CR), Partial Response (PR), Stable Disease (SD) and Progressive Disease (PD), tumour shrinkage using RECIST version 1.1 [51].

Objective Response Rate (ORR) is defined as the number of subjects with measurable disease with at least one visit response of CR or PR that is confirmed at least 4 weeks later.

Duration of response (DoR) defined as the time from the date of first documented response until date of documented progression or death.

Disease control rate (DCR) is defined as the percentage of subjects who have a best overall response of CR or PR or SD.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)

EuroQol (EQ-5D-5L) [52]

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ LC13)

Common Terminology Criteria for Adverse Event (CTCAE)

Electrocardiogram (ECG)

Table 3 - For investigative services

Prior tests	EGFR mutation test at time of diagnostic biopsy, irrespective of disease stage
Reference standard	There is no established reference standard. The evidentiary standard used in the AZD9291 clinical development program is cobas® EGFR Mutation Test (Roche Molecular Diagnostics)

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Healthcare resources

Table 2 (List of resources to be considered in the economic analysis) has been completed with category descriptions for the comparator and proposed intervention of the likely resource utilisation that will be relevant to the economic evaluation. Further details will be included in the co-dependent submission. The model is in development and Table 3 is unable to be completed (and not included) at this time.

Questions for public funding

Please list questions relating to the safety, effectiveness and cost-effectiveness of the service / intervention relevant to this application, for example:

- Which health / medical professionals provide the service
- Are there training and qualification requirements
- Are there accreditation requirements

Table 2: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Resources provided to identify eligible population										
Specialist consultation	Medical Oncologist									
Biopsy	Respiratory Physician or Interventional Radiologist									
Resources to monitor and manage any side effects associated with biopsy										
Preparation of tissue sample	Pathologist									
EGFR mutation test for T790M status	Molecular Pathologist									
If EGFRm/T790M positive, patient is eligible for treatment with AZD9291										
Specialist consultation	Medical Oncologist									

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other government budget	Private health insurer	Patient	Total cost
Cost of AZD9291										
Resources associated with management of side effects associated with AZD9291										
If EGFRm/T790M negative or status unknown, patient receives platinum-based doublet chemotherapy										
Specialist consultation	Medical Oncologist									
Cost of chemotherapy										
Drug Administration in various clinical settings	Day patient Outpatient	Public Private								
Pre-treatments and co-administered interventions										
Monitoring and follow-up										
Resources to manage side effects of chemotherapy										

* Include costs relating to both the standard and extended safety net.

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