

# **MSAC application 1811**

**Testing for MET overexpression & amplification in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) to determine eligibility for treatment with PBS subsidised savolitinib in combination with osimertinib**

## **Application for MBS eligible service or health technology**

### **HPP Application number:**

HPP200328

### **Application title:**

Genetic testing for MET overexpression and amplification (IHC/FISH) in patients with locally advanced or metastatic NSCLC who have progressed post osimertinib to determine eligibility for savolitinib in combination with osimertinib through the PBS

### **Submitting organisation:**

ASTRAZENECA PTY LTD

### **Submitting organisation ABN:**

54009682311

## **Application description**

### **Succinct description of the medical condition/s:**

Non-Small Cell Lung Cancer (NSCLC) with EGFR mutations who are initially treated with the EGFR-targeted medicine Tagrisso (osimertinib) are a specific subtype of lung cancer patients. Most patients on this treatment will eventually have their cancer progress due to resistance mechanisms developing in response to treatment. The most common cause of resistance to Tagrisso treatment are changes to the MET receptor protein which can lead to tumour cell growth and metastases.

### **Succinct description of the service or health technology:**

For this MSAC application, changes in the MET receptor protein are detected in two main ways. Immunohistochemistry (IHC) uses a special stain that can be applied to tumor cells that allows the pathologists to visualize the concentration of the MET receptor on the tumor cell wall. Changes can also be detected using fluorescent in situ hybridization (FISH), which binds a fluorescent marker to the MET gene, allowing pathologists to count the number of MET gene copies in each cell. Several MBS items are currently on the MBS that utilize these technologies, with three specifically for non-small cell lung cancer (NSCLC) patients.

Detecting MET changes with IHC and FISH can help identify which NSCLC patients might benefit from specific treatments, but these tests are not done routinely at present. New targeted therapies for patients with EGFR mutations that develop MET-related resistance are expected to become available in Australia soon.

## **Application contact details**

**Are you the applicant, or are you a consultant or lobbyist acting on behalf of the applicant?**

Applicant

**Are you applying on behalf of an organisation, or as an individual?**

Organisation

**Applicant organisation name:**

ASTRAZENECA PTY LTD

## **Application details**

**Does the implementation of your service or health technology rely on a new listing on the Pharmaceutical Benefits Scheme (PBS) and/or the Prescribed List?**

Yes

**Which list/schedule will the other health technologies be listed on?**

Pharmaceutical Benefits Scheme

**Is the application for a new service or health technology, or an amendment to an existing listed service or health technology?**

New

**What is the type of service or health technology?**

Investigative

**Please select the type of investigative health technology:**

Tissue pathology test and molecular diagnostic test

## PICO set

Genetic testing for MET overexpression and amplification (IHC/FISH) in patients with locally advanced or metastatic NSCLC who have progressed post osimertinib to determine eligibility for savolitinib in combination with osimertinib through the PBS

**State the purpose(s) of the health technology for this PICO set and provide a rationale:**

Predictive

**Purpose description:**

To provide predictive information to support selection of a specific therapy or intervention.

## Population

**Describe the population in which the proposed health technology is intended to be used:**

The population proposed comprises patients with locally advanced (Stage IIIB/C ) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), who have progressed on or after treatment with osimertinib.

**Select the most applicable Medical condition terminology (SNOMED CT):**

Carcinoma of lung

## Intervention

**Name of the proposed health technology:**

savolitinib plus osimertinib for testing positive for MET resistance post osimertinib treatment

**Comparator**

**Nominate the appropriate comparator(s) for the proposed medical service (i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system). This includes identifying health care resources that are needed to be delivered at the same time as the comparator service:**

No MET testing and all patients are treated with platinum-based doublet chemotherapy

## Outcomes

**Outcome description – please include information about whether a change in patient management, or prognosis, occurs as a result of the test information:**

In patients diagnosed with non-small cell lung cancer (NSCLC) who are positive for the EGFR mutation following a tissue biopsy, osimertinib is the currently preferred first-line therapy. While osimertinib is highly effective in achieving a high response rate and prolonged disease control, resistance to the treatment inevitably develops. Among the most common mechanisms of acquired resistance is MET overexpression or amplification, occurring in approximately 34% of cases (Ahn et al., 2022).

Currently, MET overexpression and amplification are not considered actionable genetic mutations due to a lack of targeted therapies available on the PBS. As a result, these patients typically transition to platinum-based chemotherapy as their next line of therapy.

Identification of resistance mechanisms to guide subsequent treatment is recommended in treatment guidelines (Bazhenova et al., 2024; Hendriks et al., 2023). However, there are currently no approved, chemotherapy-free, biomarker-selected treatment options specifically indicated to treat MET overexpression and/or amplification-driven resistance for patients with EGFR-mutated NSCLC following progression on first-line osimertinib. As such, following progression on osimertinib, if an appropriate clinical trial is not available, patients typically transition to platinum-based chemotherapy as their next line of therapy. Among patients with tumour MET-driven resistance mechanisms, there remains an unmet need for a treatment approach that inhibits the activity of both EGFR mutation and MET overexpression and/or amplification that can be administered orally and is also chemotherapy-free, to avoid the toxicity associated with chemotherapy and overcome lack of efficacy caused by resistance to previous treatments.

AstraZeneca is planning to seek PBS listing for the combination of savolitinib and osimertinib to treat adult patients with locally advanced or metastatic NSCLC who have progressed on or after osimertinib treatment, with MET overexpression and/or amplification as the mechanism of resistance. Savolitinib is a highly specific inhibitor of the MET tyrosine kinase receptor. Results from the Phase II SAVANNAH trial demonstrate that osimertinib resistance in EGFR-mutated NSCLC with MET overexpression and/or amplification can be overcome by the concomitant use of

savolitinib and osimertinib, leading to clinically meaningful and statistically significant improvements in progression-free survival. It is anticipated the Phase III SAFFRON trial will confirm this earlier study, results of which will underpin this application and the PBAC co-dependent application.

## **Proposed MBS items**

### **Proposed item:**

AAAAA

### **MBS item number (where used as a template for the proposed item):**

N/A

### **Category number:**

PATHOLOGY SERVICES

### **Category description:**

TISSUE PATHOLOGY

### **Proposed item descriptor:**

Immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using the mesenchymal-epithelial transition (MET) antibody of tumour material from a patient diagnosed with recurrent epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer to determine if requirements for access to savolitinib in combination with osimertinib as listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

### **Proposed MBS fee:**

\$74.50

### **Indicate the overall cost per patient of providing the proposed health technology:**

\$74.50

### **Please specify any anticipated out of pocket expenses:**

\$0.00

### **Provide any further details and explain:**

N/A

**Proposed item:**

BBBBB

**MBS item number (where used as a template for the proposed item):**

N/A

**Category number:**

PATHOLOGY SERVICES

**Category description:**

GENETICS

**Proposed item descriptor:**

Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient diagnosed with recurrent epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer, and with documented evidence of mesenchyma-epithelial transition (MET) expression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or less, requested by a specialist or consultant physician, to determine if requirements relating to MET gene amplification status for access to savolitinib in combination with osimertinib as listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled

**Proposed MBS fee:**

\$400.00

**Indicate the overall cost per patient of providing the proposed health technology:**

\$400.00

**Please specify any anticipated out of pocket expenses:**

\$0.00

**Provide any further details and explain:**

N/A

**How is the technology / service funded at present? (For example: research funding; State-based funding; self-funded by patients; no funding or payments):**

No funding or payments

## **Claims**

**In terms of health outcomes (comparative benefits and harms), is the proposed technology claimed to be superior, non-inferior or inferior to the comparator(s)?**

Superior

**Please state what the overall claim is, and provide a rationale:**

The overall clinical claim is that proposed codependent technologies (testing for MET overexpression/amplification and treatment with osimertinib plus savolitinib) are superior in terms of clinical effectiveness, patient safety and quality of life versus the main comparator (no testing and treatment with platinum-based doublet chemotherapy).

Data from the SAVANNAH (Phase II) study demonstrate that the combination of savolitinib plus osimertinib yields a high, clinically meaningful, and durable response in patients with EGFR-mutated advanced NSCLC and MET IHC3+ and/or FISH10+ status who have experienced disease progression on first-line osimertinib. According to investigator assessment, the objective response rate (ORR) was 56.3% (55.0% by BICR), with a median duration of response (DoR) of 7.1 months (9.9 months by BICR) and a median progression-free survival (PFS) of 7.4 months (7.5 months by BICR).

Further comparative evidence will be provided by SAFFRON, a confirmatory Phase III study evaluating the efficacy and safety of savolitinib (300 mg b.i.d.) in combination with osimertinib (80 mg o.d.) versus platinum-based chemotherapy in patients with EGFR-mutated, MET-overexpressed, and/or amplified advanced NSCLC following progression on first- or second-line osimertinib.

These findings highlight the clinical importance of MET testing and reporting in routine practice to optimise treatment access and improve patient outcomes.



## Estimated utilisation

### **Estimate the prevalence and/or incidence of the proposed population:**

The proposed population eligible for MET IHC and FISH testing are patients with EGFR-mutated NSCLC who have progressed on or after initial osimertinib treatment. As IHC is the least expensive test, it is proposed that MET IHC is performed first, and then FISH testing is performed if the IHC result is negative.

The patient population has been quantified below by analysis of PBS/RPBS 10% script data and the number of patients commencing osimertinib since its PBS listing on 1 January 2021 to July 2024. From 2025 onwards, it has been assumed that the underlying incidence of patients initiating on osimertinib will grow at the same rate as lung cancer incidence. The growth rate used is consistent with the growth rate assumptions in the current osimertinib deed.

All patients receiving first-line osimertinib therapy will eventually experience disease progression, with the average duration of treatment estimated to be REDACTED months. While the timing of progression may vary among individuals, for the purposes of this model, it is assumed that all patients receive osimertinib for REDACTED months prior to initiating treatment with savolitinib plus osimertinib. Consequently, patients expected to start savolitinib plus osimertinib in 2026 will be those who began first-line osimertinib in 2024. It is further assumed that all patients who test positive for MET alterations upon re-biopsy will receive targeted therapy with the combination of osimertinib and savolitinib.

A small proportion of patients may continue osimertinib as a second-line therapy. Based on PBS utilization patterns, it is assumed that the number of patients initiating second-line osimertinib remains constant at approximately REDACTED. Of all patients starting osimertinib, it is estimated that 90% will undergo re-biopsy to evaluate eligibility for subsequent targeted treatments.

### **Provide the percentage uptake of the proposed health technology by the proposed population:**

#### **Year 1 estimated uptake (%):**

95%

#### **Year 2 estimated uptake (%):**

95%

#### **Year 3 estimated uptake (%):**

95%

#### **Year 4 estimated uptake (%):**

95%

**Estimate the number of patients who will utilise the proposed technology for the first full year:**

REDACTED

**Optionally, provide details:**

In 2026 the projected incidence of patients progressing after treatment with osimertinib is REDACTED. 90% of patients will be able to undergo a tissue biopsy at progression indicating a maximum number of eligible patients with tissue for IHC testing is REDACTED.

**Will the technology be needed more than once per patient?**

No, once only

## **Consultation**

**List all entities that are relevant to the proposed service / health technology. The list can include professional bodies / organisations who provide, request, may be impacted by the service/health technology; sponsor(s) and / or manufacturer(s) who produce similar products; patient and consumer advocacy organisations or individuals relevant to the proposed service/health technology.**

**Entities who provide the health technology/service:**

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

PATHOLOGY AUSTRALIA LIMITED

THE HUMAN GENETICS SOCIETY OF AUSTRALASIA LIMITED

**Entities who request the health technology/service:**

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA LIMITED

Medical Oncology Group of Australia ASM 2012

Private Cancer Physicians of Australia (PCPA)

THORACIC ONCOLOGY GROUP OF AUSTRALASIA LTD

**Entities who may be impacted by the health technology/service:**

Medical Oncology Group of Australia ASM 2012

THORACIC ONCOLOGY GROUP OF AUSTRALASIA LTD

CLINICAL ONCOLOGY SOCIETY OF AUSTRALIA LIMITED

THE THORACIC SOCIETY OF AUSTRALIA AND NEW ZEALAND LIMITED

THE ROYAL COLLEGE OF PATHOLOGISTS OF AUSTRALASIA

PATHOLOGY AUSTRALIA LIMITED

THE HUMAN GENETICS SOCIETY OF AUSTRALASIA LIMITED

Australian Genomics Health Alliance

PATHOLOGY TECHNOLOGY AUSTRALIA LTD

**Patient and consumer advocacy organisations relevant to the proposed service/health technology:**

LUNG FOUNDATION AUSTRALIA

## **Regulatory information**

**Would the proposed health technology involve the use of a medical device, in-vitro diagnostic test, radioactive tracer or any other type of therapeutic good?**

Yes

**Has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?**

No

**Is the therapeutic good classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?**

Class III

**Is the therapeutic good to be used in the service exempt from the regulatory requirements of the Therapeutic Goods Act 1989?**

No

**Is the therapeutic good classified by the TGA as for Research Use Only (RUO)?**

No

## **Codependent details**

**Will a submission be made to the Pharmaceutical Benefits Advisory Committee (PBAC)?**

Yes

**Please provide a rationale for the codependency and indicate how the proposed PBS restriction would reference the intervention(s) proposed for MSAC consideration:**

In patients diagnosed with non-small cell lung cancer (NSCLC) who are positive for the EGFR mutation following a tissue biopsy, osimertinib is the currently preferred first-line therapy. While osimertinib is highly effective in achieving a high response rate and prolonged disease control, resistance to the treatment inevitably develops. Among the most common mechanisms of acquired resistance is MET overexpression or amplification, occurring in approximately 34% of cases.

Currently, MET overexpression and amplification are not considered actionable genetic mutations due to a lack of targeted therapies available on the PBS. As a result, these patients typically transition to platinum-based chemotherapy as their next line of therapy.

AstraZeneca is planning to seek PBS listing for the combination of savolitinib and osimertinib to treat adult patients with locally advanced or metastatic NSCLC who have progressed on or after osimertinib treatment, with MET overexpression and/or amplification as the mechanism of resistance. Savolitinib is a highly specific inhibitor of the MET tyrosine kinase. Results from the Phase III SAFFRON trial demonstrate that osimertinib resistance in EGFR-mutated cell lines with MET overexpression and/or amplification can be overcome by the concomitant use of savolitinib and osimertinib, leading to clinically meaningful and statistically significant improvements in progression-free survival.

The PBS listing criteria for the savolitinib and osimertinib combination would require patients to show evidence of MET overexpression and/or amplification, verified through IHC and/or FISH testing. Therefore, MBS items xxx and xxx is proposed to include MET overexpression and/or amplification.