MSAC Application 1811

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

Applicant: AstraZeneca

PICO Confirmation

Summary of PICO/PPICO criteria to define question(s) to be addressed in an Assessment Report to the Medical Services Advisory Committee (MSAC)

Table 1 PICO for Testing for MET overexpression and amplification in patients with locally advanced or metastatic non-small cell lung cancer to determine eligibility for treatment with PBS subsidised savolitinib in combination with osimertinib

Component	Description
Population	**Test:** 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 and do not demonstrate histological evidence of small cell transformation. **Drug:** 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 and who are found to have MET amplification/overexpression following testing with IHC and/or FISH.
Prior tests	Patients are tested for epidermal growth factor receptor (EGFR)-mutations as part of their NSCLC diagnosis before 1L treatment commences.
Intervention	**Test:** Immunohistochemistry (IHC) for MET overexpression +/- MET fluorescence in situ hybridisation (FISH) for *MET* amplification in IHC-negative or IHC non-assessable cases. **Drug:** Savolitinib in combination with 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.
Comparator/s	**Test:** No testing **Drug:** Standard platinum-based doublet chemotherapy
Clinical utility standard	MET overexpression IHC testing with Roche CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody kit and *MET* amplification testing with Abbott Vysis MET Spectrum Red FISH probe kit.
Outcomes	**Test-related Outcomes:** Safety outcomes: Adverse events associated with biopsy and re-biopsy for patients with inadequate tissue for tumour testing. Diagnostic performance: Sensitivity and specificity, Test failure rate, Assessment of extent of and implications of discordances between Australian IHC and FISH testing and the respective clinical utility standards, Test-retest reliability, inter-rater reliability, diagnostic accuracy of proposed testing sequence (IHC followed by FISH), comparability between IHC assays. Clinical validity: Positive and negative predictive values, positive and negative likelihood ratios.

Component	Description
	Clinical utility of the test: Determine whether testing for MET overexpression/amplification predicts variation in the treatment effect of savolitinib and osimertinib in terms of health outcomes for patients. Relative predictive accuracy of IHC versus FISH assays at proposed cut-off thresholds. Other test-related considerations: Re-biopsy rates, Test turn-around time **Drug-related outcomes:** Safety outcomes: Safety and tolerability of treatment with savolitinib and osimertinib compared to platinum doublet chemotherapy (adverse events, physical examinations, laboratory findings and vital signs). Clinical effectiveness outcomes: Objective response rate (ORR), Overall survival (OS), Progression-free survival (PFS), Partial response (PR), Complete response (CR), Central nervous system (CNS) efficacy, Health-related quality of life (HRQoL) compared to platinum doublet chemotherapy. **Healthcare system outcomes:** Cost of testing per patient with associated biopsies and re-biopsies, Cost of treatment and cost of treating adverse events, Cost effectiveness Financial implications: number of patients tested; number of patients treated.
Assessment questions	What is the safety, effectiveness and cost-effectiveness of MET overexpression/amplification testing and treatment with savolitinib in combination with osimertinib versus no testing and platinum-doublet chemotherapy in patients with locally advanced or metastatic NSCLC who have progressed post osimertinib? Is there a treatment effect modification for the therapy based on MET variant status in population?

Purpose of application

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing of mesenchymal-epithelial transition (MET) immunohistochemistry (IHC) and/or *MET* fluorescence in situ hybridisation (FISH) for patients who have progressed on or after prior osimertinib treatment to evaluate for MET amplification or overexpression. If a MET-driven resistance mechanism is confirmed, patients may then be considered eligible for treatment with the combination of savolitinib and osimertinib.
- Pharmaceutical Benefits Scheme (PBS) Authority Required listing of savolitinib in combination with osimertinib to treat adult patients with locally advanced or metastatic non-small cell lung cancer (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.

PICO criteria

Population

Background and rationale for testing for MET overexpression / MET amplification

Lung cancer is the fifth most commonly diagnosed cancer in Australia and the most common cause of cancer-related death, accounting for 17.0% of cancer-related deaths (Australian Institute of Health and Welfare 2025). NSCLC is the most common type, representing approximately 85% of all diagnoses (Cancer Council Australia 2022). In Australia, epidermal growth factor receptor mutations (EGFRm) account for 12% to 36% of NSCLC and confer sensitivity to epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) including osimertinib, a third-generation EGFR-TKI (Kim et al. 2020; Peters et al. 2014; Yang et al. 2024). Prognosis is poor following progression on a prior EGFR-TKI. A study showed that out of 521 patients who progressed on an EGFR-TKI and went on to receive platinum-based chemotherapy, median overall survival (OS) varied between 6 to 11 months, dependent on their response to their first-line (1L) EGFR-TKI (Song and Zhang 2016; Imai et al. 2019).

For patients with locally advanced (Stage IIIB/C) or metastatic (Stage IV) NSCLC who are not amenable to curative surgery or radiotherapy, and whose tumours harbour EGFR mutations, the current 1L standard-of-care (SoC) is osimertinib monotherapy. Osimertinib has TGA registration and PBS listing currently only for use in the treatment of patients with NSCLC. Disease progression with osimertinib monotherapy still occurs frequently, typically due to the emergence of resistance pathways, with an approximate median time to progression of 19 months in 1L EGFRm NSCLC (Soria et al., 2018). The proposed population 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. Osimertinib may be given in either the 1L locally advanced/metastatic setting or in second line (2L) patients who have progressed after a 1L EGFR-TKI, and whose tumours are found to harbour the *EGFR* T790M mutation at the point of progression.

Treatment of NSCLC can lead to selective pressure being exerted on tumour cells, leading to the emergence of resistant clones with new genetic alterations. As a result, the genetic makeup of the disease may evolve with treatment, making it more difficult to treat effectively. Alterations to the mesenchymal-epithelial transition (*MET*) gene have been identified as the most frequent resistance mechanism to

osimertinib treatment in NSCLC (Leonetti et al. 2019), occurring in approximately 34% of patients (Ahn, Cho, et al. 2022). In some cases, these pressures also induce histological transformation (HT) with conversion of NSCLC to small cell lung cancer (SCLC), further limiting available treatment options and worsening prognosis. The application reported that approximately 25% of patients with EGFR mutation–positive NSCLC who experience disease progression undergo re-biopsy to assess for potential HT to SCLC. This estimate could not be independently verified by the assessment group. Currently available evidence suggests that HT to SCLC may occur in as few as 2.8% of patients following EGFR-TKI resistance, which means that a 25% re-biopsy rate would result in a true-positive result and subsequent treatment change for approximately 10% of those who are re-biopsied, assuming all true positive patients with HT to SCLC were selected for biopsy (Fujimoto et al. 2022). Unless clinicians can select patients for HT to SCLC testing with 100% accuracy, there may be some patients who harbour HT to SCLC who are not currently identified. The selection of patients with an *EGFR* mutation who require HT to SCLC testing is based on risk. This is a challenging, and a complex topic, as the likelihood of HT to SCLC occurring is influenced by a range of clinical and genetic factors. Patients with particularly aggressive disease that develops early resistance to targeted and immune therapies are at higher risk of HT to SCLC (Liu et al. 2025). Patients with NSCLC tumours that harbour mutations in *RB1* and *TP53* genes are at unique risk; additionally, patients with *ALK*, *ROS1, PIK3CA* and *KRAS G12C* mutations may also be at increased risk of HT to SCLC after treatment with targeted therapy, however it is unclear how many patients with HT to SCLC may be currently missed (Offin et al. 2019, Dorantes-Heredia, 2016 #599).

Currently no targeted treatments are available for MET-driven resistance in post-osimertinib patients in Australia. Patients who progress post-osimertinib are not routinely tested for MET amplification/ overexpression; instead, the treatment of choice is platinum-based doublet chemotherapy (Ngo et al. 2023). The submission's algorithm proposed that patients who are tested positive for SCLC do not form part of the target population, however the patients who are negative for SCLC transformation will likely require immunohistochemistry (IHC) / fluorescence in situ hybridisation (FISH) testing if savolitinib in combination with osimertinib is to become the standard of care for patients with MET overexpression/overamplification.

The applicant provided the following estimated utilisation for PASC consideration.

Table 2 Incident (historic) osimertinib monotherapy 1L patients based on 10% PBS data

	Year				
Incidence data	**2021**	**2022**	**2023**	**2024**	**2025**
10% PBS script data incident osimertinib mono 1L patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED

Source: Adapted from Table 1, p 10, Estimated Utilisation document provided with the application.

Table 3 Projected number of patients eligible for osimertinib monotherapy

	Year					
	2026	**2027**	**2028**	**2029**	**2030**	**2031**
Projected incident osimertinib mono 1L patients with application of 3% growth rate	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Project incident osimertinib mono 2L patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Total osimertinib patients in the metastatic setting	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED

Source: Adapted from Table 2, p 10, Estimated Utilisation document provided with the application.

Table 4 Adjusted osimertinib patient numbers to estimate MBS services

	Year					
Savolitinib plus osimertinib listing scenario	**2026**	**2027**	**2028**	**2029**	**2030**	**2031**
Project incident osimertinib mono 1L patients*	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Project incident osimertinib mono 2L patients	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Total osimertinib patients in the metastatic setting	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED

Source: Adapted from Table 3, p 10, Estimated Utilisation document provided with the application.
*2026 and 2027 Project incident osimertinib mono 1L patients based on Table 2 and subsequent years extrapolated

Table 5 Estimated number of MBS services

	Proportion	**Year**					
		2026	**2027**	**2028**	**2029**	**2030**	**2031**
Total osimertinib patients in the metastatic setting (Table 4)		REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Patients undergoing tissue biopsy	90%	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Patients undergoing MET testing, IHC	100%	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Patients undergoing MET testing, FISH followed by IHC	71%	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED
Total proposed MBS services for MET overexpression/amplification		REDACTED	REDACTED	REDACTED	REDACTED	REDACTED	REDACTED

Source: Adapted from Table 4, p 10, Estimated Utilisation document provided with the application.

Test population

The proposed population for MET testing to determine eligibility for savolitinib plus osimertinib combination therapy in the application includes all patients with locally advanced or metastatic NSCLC with documented disease progression on or after prior osimertinib therapy. This is consistent with the population selection for the phase II trial SAVANNAH and ongoing phase III trial SAFFRON, where patients could be enrolled if they had locally advanced or metastatic NSCLC with documented EGFRm (*Ex19* del/ or point mutation in *L858R*) and/or *T790M* substitution), and were eligible for treatment if their tumours demonstrated MET overexpression and/or amplification as determined by a central laboratory.

PASC determined the population definition should include the phrase '...and do not demonstrate histological evidence of small cell transformation'. This has been subsequently added to the test description

(Table 1 above). PASC considered that this would ensure patients who may go on to receive treatment with osimertinib in combination with savolitinib have NSCLC, as the proposed treatment is neither TGA approved nor proposed to be PBS listed for treatment of SCLC.

PASC noted the applicant's comment stating approximately 25% of the target population is currently biopsied and tested for transformation to SCLC. The applicant considered this estimate was reasonable given clinical advice they had received. The applicant stated key external experts concurred that tissue testing at progression is clinically valuable beyond identifying MET overexpression or amplification, for example to detect SCLC transformation. The applicant further noted that currently rebiopsy has largely been driven by EGFR T790M testing (MBS 73351), and uptake of rebiopsy may increase if additional testing is publicly funded. PASC considered that it was unclear if the applicant's 25% estimate is accurate and applicable to the proposed target population for the below reasons:

- *Patients tested for EGFR T790M are not part of the proposed target population (this application is for patients who have progressed on first-line therapy, and are being tested for a genetic variant which is treated with osimertinib monotherapy). After these patients demonstrate progression on osimertinib monotherapy, they will become part of the target population and require a new rebiopsy to test for the MET resistance mutation.*
- *During the PASC meeting, the applicant's clinical expert did not confirm the 25% figure, instead stating that the testing rate is institutionally dependent. They noted testing for transformation to SCLC is not widely recognised and testing is based on clinical trial work. They also added that having the proposed testing publicly funded may prompt more testing for SCLC, and potentially change treatment options for patients.*

PASC noted that estimates of HT of NSCLC to SCLC within the target population range from 2.8% to 15%. PASC considered it is uncertain how many patients will be found to have SCLC if biopsy rates increase. PASC noted that if a separate population (those with SCLC) is to be proposed in the ADAR, it will require sufficient clinical evidence to support its inclusion.

The applicant estimated up to 90% of the target population would be eligible for re-biopsy in the progressed setting with the remaining 10% likely experiencing 'rapid clinical deterioration, refractory disease, severe competing illness or biopsy refusal'. Based on the proposed treatment algorithm and applicant's estimates, the population size is approximately 800 patients per annum, meaning 720 would have MET IHC testing, of which approximately 29% will demonstrate MET IHC90+ positivity, and an additional 5% will demonstrate FISH10+ positivity. Therefore, PASC noted based on these estimates approximately 245 patients per annum would be tested MET positive and be eligible for treatment with osimertinib in combination with savolitinib. However, PASC considered that the potential uptake rate of the MET rebiopsy pathway is uncertain.

PASC noted that the applicant stated that archival tissue may be used when a new rebiopsy is not available after disease progression in the first line. PASC considered the use of archival tissue (when new rebiopsy is not available) may be inappropriate, as the majority of MET overexpression/amplification mutations develop after treatment with a TKI (i.e. the mutations are not present on archival tissue which precedes TKI treatment). PASC requested information from the applicant on how many participants were enrolled in the SAVANNAH study based on archival tissue results, and whether their outcomes were analysed separately.

PASC noted feedback from The Thoracic Oncology Group of Australasia (TOGA) to consider testing in patients with other actionable genomic alterations (e.g. rare cases of patients with ALK fusions who have MET amplifications as part of resistance). However, PASC considered that these patients should not be included in the population for this application because they are not included in the key trial.

PASC noted NSCLC may rarely demonstrate MET amplification at primary diagnosis (0.17%), and MET amplification may also be found in non-EGFR mutant cancers as a resistance mechanism (e.g. ALK rearranged tumours). However, PASC considered that these patients should not be included in the population for this application because they are not included in the key trial.

Drug population

Eligibility for savolitinib in combination with osimertinib requires a diagnosis of locally advanced or metastatic NSCLC with documented disease progression on or after prior osimertinib therapy, where MET overexpression and/or amplification (IHC threshold for eligibility: staining intensity 3+ in ≥90% of tumour cells or FISH threshold: ≥10 *MET* gene copies per cell) is identified as the resistance mechanism. This population is consistent with the population from protocol 7 of the SAVANNAH trial and the treatment population from the currently ongoing SAFFRON trial. Note that the evaluation of the use of savolitinib in combination with osimertinib therapy for the proposed PICO population is the remit of the Pharmaceutical Benefits Advisory Committee (PBAC).

Prior tests

All patients will be referred for NSCLC gene testing at the time of initial diagnosis to detect disease variants and to subsequently determine access to targeted therapies. These tests assess for DNA variants in genes including *BRAF*, *EGFR*, *ERBB2*, *KRAS*, *MET exon skipping mutations* (note this is a different mutation to the MET overexpression/amplification which the applicant is proposing), and *PIK3CA*, as well as RNA fusions involving *ALK*, *MET* (exon 14 skipping), *NTRK1*, *NTRK2*, *NTRK3*, *RET*, and *ROS1*. Additionally, testing for the *p.T790M EGFR* mutation may be performed on patients who initially responded to gefitinib and erlotinib; patients who harbour this mutation are eligible for 2L osimertinib; patients who progress from this 2L osimertinib form part of the target population for MET amplification/overexpression testing. The relevant tests on the MBS for determining EGFR mutation (EGFRm) status and other genetic alterations that are relevant to treatment and/or prognosis in the NSCLC setting are listed in Table 6. The MBS currently lists generic histopathology items, in the range items 72823 through to 72838, that support testing for transformation from NSCLC to SCLC at the rebiopsy stage. The item used is dependent upon the specimen type, complexity and number of specimens.

Table 6 MBS items available for EGFRm and NSCLC work-up tests

MBS Item number	Item description	Fee
72846	Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 1 to 3 antibodies except those listed in 72848 (Item is subject to rule 13)	Fee: $61.05 Benefit: 75% = $45.80 85% = $51.90
72847	Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 4-6 antibodies (Item is subject to rule 13)	Fee: $91.55 Benefit: 75% = $68.70 85% = $77.85

MBS Item number	Item description	Fee
72849	Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 7-10 antibodies (Item is subject to rule 13)	Fee: $106.80 Benefit: 75% = $80.10 85% = $90.80
72850	Immunohistochemical examination of biopsy material by immunofluorescence, immunoperoxidase or other labelled antibody techniques with multiple antigenic specificities per specimen - 11 or more antibodies (Item is subject to rule 13)	Fee: $122.05 Benefit: 75% = $91.55 85% = $103.75
72814	Immunohistochemical examination by immunoperoxidase or other labelled antibody techniques using the programmed cell death ligand 1 (PD-L1) antibody of tumour material from a patient diagnosed with: (a) non-small cell lung cancer; or (b) recurrent or metastatic squamous cell carcinoma of the oral cavity, pharynx or larynx; or (c) locally recurrent unresectable or metastatic triple-negative breast cancer.	Fee: $76.30 Benefit: 75% = $57.25 85% = $64.90
73337	A test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, if the test is: to determine if requirements relating to epidermal growth factor receptor (EGFR) gene status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled; and not associated with a service to which item 73437 or 73438 applies	Fee: $397.35 Benefit: 75% = $298.05 85% = $337.75
73437	A nucleic acid-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician, if the test is: to detect variants in at least *EGFR*, *BRAF*, *KRAS* and *MET* exon 14 to determine access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS); and to detect the fusion status of at least *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2* and *NTRK3*; and to determine access to specific therapies relevant to these variants listed on the PBS; or determine if the requirements relating to *EGFR*, *ALK* and *ROS1* status for access immunotherapies listed on the PBS are fulfilled; and not associated with a service to which item 73438, 73439, 73337, 73341, 73344, 73436 or 73351 applies	MBS Fee: $1,247.00 Benefit: 75% = $935.25 85% = $1,148.30 (Greatest Permissible Gap (GPG) will apply)
73438	A DNA-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician, if the test is: to detect variants in at least *EGFR*, *BRAF*, *KRAS* and *MET* exon 14; and to determine access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS); or to determine if the requirements relating to EGFR status for access to immunotherapies listed on the PBS are fulfilled; and not associated with a service to which item 73437, 73337, 73436 or 73351 applies	MBS Fee: $682.35 Benefit: 75% = $511.80 85% = $583.65 (Greatest Permissible Gap (GPG) will apply)

MBS Item number	Item description	Fee
73439	A nucleic acid-based multi-gene panel test of tumour tissue from a patient with a new diagnosis of non-small cell lung cancer and with documented absence of activating variants of the *EGFR* gene, *KRAS*, *BRAF* and *MET* exon14, requested by, or on behalf of, a specialist or consultant physician, if the test is: to determine the fusion status of at least *ALK*, *ROS1*, *RET*, *NTRK1*, *NTRK2*, and *NTRK3* to determine access to specific therapies relevant to these variants listed on the Pharmaceutical Benefits Scheme (PBS) are fulfilled; or to determine if the requirements relating to *ALK* and *ROS1* status for access to immunotherapies listed on the PBS are fulfilled; and not associated with a service to which item 73437, 73341, 73344 or 73351 applies	MBS Fee: $682.35 Benefit: 75% = $511.80 85% = 583.65 (Greatest Permissible Gap (GPG) will apply)
73341	Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with a new diagnosis of locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor (EGFR) gene, requested by a specialist or consultant physician, if the test is: to determine if requirements relating to *ALK* gene rearrangement status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled; and not associated with a service to which item 73437 or 73439 applies	MBS Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00
73344	Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient with a new diagnosis of locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of ROS proto-oncogene 1 (*ROS1*) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+; and with documented absence of both activating mutations of the epidermal growth factor receptor (*EGFR*) gene and anaplastic lymphoma kinase (*ALK*) immunoreactivity by IHC, requested by a specialist or consultant physician, if the test is: to determine if requirements relating to ROS1 gene arrangement status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled: and not associated with a service to which item 73437 or 73439 applies	MBS Fee: $400.00 Benefit: 75% = $300.00 85% = $340.00
73436	A test of tumour tissue from a patient with a new diagnosis of locally advanced or metastatic non-small cell lung cancer requested by, or on behalf of, a specialist or consultant physician, if the test is: to determine if the requirements relating to MET proto-oncogene, receptor tyrosine kinase (MET) exon 14 skipping alterations (METex14sk) status for access to an immunotherapy listed under the Pharmaceutical Benefits Scheme (PBS) are fulfilled: and not associated with a service to which item 73437 or 73438 applies	MBS Fee: $397.35 Benefit: 75% = $298.05 85% = $337.75
73351	A test of tumour tissue that is 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 epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI). The test is to be requested by a specialist or consultant physician, to determine if the requirements relating to *EGFR T790M* gene status for access to osimertinib under the Pharmaceutical Benefits Scheme are fulfilled.	MBS Fee: $397.35 Benefit: 75% = $298.05 85% = $337.75

Source: Small Gene Panel Testing for Non-Small Cell Lung Carcinoma (NSCLC), Department of Health and Aged Care 2023[1]

Intervention

The application sought MBS listing for MET IHC and/or *MET* FISH testing for patients with NSCLC who have progressed on or after treatment with osimertinib, to detect MET overexpression/amplification and

[1] https://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/0FAE1338D92EA3A3CA258A6F0001701A/$File/FS%20-%20Small%20gene%20panel%20test%20for%20non-small%20cell%20lung%20carcinoma.docx

determine eligibility for savolitinib in combination with osimertinib (pending PBS consideration and listing of the proposed treatment). The application proposed that in clinical settings, MET alterations can be assessed using IHC to detect protein overexpression, or by FISH to detect amplification of the *MET* gene. FISH detects amplification by the ratio of *MET* to chromosome 7 centromere (CEP7) copies to distinguish between polysomy and true amplification. In the key trial SAFFRON, patients were selected for savolitinib treatment in combination with osimertinib, based on IHC overexpression (≥90% of tumour cells staining at 3+ intensity) using the Roche CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody or FISH amplification (≥10 MET gene copies per cell) using the Abbott Vysis MET Spectrum Red FISH probe kit. These tests require a trained pathologist to interpret IHC staining intensity and assess the proportion of cells with 3+ intensity on slides; to interpret FISH results, a trained pathologist must count and compare the number of target *MET* gene signals (usually labelled red) with the number of *CEP7* control signals (usually labelled green). There is limited subjectivity regarding interpretation of results, assuming the tests are prepared appropriately and interpreted by a trained pathologist.

PASC noted that the key trials used variable cutoff thresholds in its selection of patients (in both IHC and FISH tests). The applicant stated high cut-off thresholds were justified, as it ensured maximal efficacy of treatment. PASC noted that the IHC/FISH cut-off thresholds were increased during the SAVANNAH trial. PASC queried the high cut-off thresholds for MET overexpression/amplification (3+ in ≥ 90% cells in IHC testing and ≥10 in FISH) as limited evidence was presented to support the cut off thresholds, and PASC had concerns that they may exclude potential responders from treatment. The applicant noted that in the SAVANNAH study, secondary analysis will include comparison of outcomes in the FISH and IHC positive subgroups; this comparison may be more robust in the key SAFFRON trial, which has a chemotherapy control arm. PASC considered that further evidence justifying the chosen cut-off thresholds will be informative for decision-making.

In the post-PASC period, PASC considered that more clarity was required regarding the threshold for identifying MET amplification for the FISH test. PASC noted the applicant's proposed threshold of ≥10 MET gene copies per cell. However, PASC considered that the applicant had not defined the threshold for the number of cells in which the MET variant needed to be found and requested this information from the applicant.

FISH is regarded as the gold standard for identifying MET amplification (Peng, Jie, et al. 2021; Kumaki, Oda, and Ikeda 2023), however there is no 'gold standard' test for detecting the population of patients whose tumours are likely to benefit from savolitinib in combination with osimertinib, apart from the proposed sequential IHC90+ and FISH10+ tests. In lieu of a gold standard or reference standard for this population, the MSAC guidelines (TG 2.4) state that test accuracy will need to be demonstrated by direct from test to health outcomes evidence showing a health benefit from use of the test, or by comparison against a suitable clinical utility standard.

The Human Genetics Society of Australasia provided some references examining the test accuracy of IHC and FISH looking for MET alterations, briefly evaluated as follow:

- (Guo et al. 2019): This paper found IHC was a poor detector of MET amplification, concluding "IHC appears to be an inefficient screen for [MET amplification]". A key feature of this study is they evaluated the role of IHC in detecting MET amplifications; this is a task best suited to FISH, and the applicant has not proposed IHC is used to detect MET amplification. Instead, the proposed role of

MET is in the detection of MET protein overexpression, defined as ≥90% of tumour cells staining at 3+ intensity.

- (Xiang et al. 2024): This paper evaluated the roles of IHC detecting MET overexpression, FISH detecting *MET* amplification (*MET*amp), and using NGS to examine the biological characteristics of different *MET*amp subtypes. This study utilised lower cut-off thresholds than proposed by the application, defining *MET*amp as a *MET/CEP7* ratio ≥2 and/or gene copy number (GCN) ≥5. This cohort did not demonstrate a treatment effect in the phase II SAVANNAH study; only patients who demonstrated a GCN ≥10 demonstrated a treatment effect. As such, the test performance in this study is not applicable to the proposed test population.
- (Han et al. 2024): This is a review article which summarises evidence from clinical trials, and discusses the variations in definitions of MET*amp* and/or alteration utilised by different trials and treatments. It does not discuss test accuracy, but highlights the importance of pairing the correct test cut-off values with the appropriate corresponding treatment option.
- (Arriola et al. 2014): This is a meeting abstract from the 2014 American Society of Clinical Oncology (ASCO) conference. This paper evaluated a range of 127 NSCLC tissue samples, of which only 11% were *EGFR* mutated. They used H-Scores on the IHC test, and defined *MET*amp as a *MET/CEP7* ratio >2 or GCN >5, which are thresholds not applicable to the proposed target population. The results were discussed in relation to the clinical characteristics of the cancers, as targeted therapies had not been developed in 2014.

PASC noted that there were a number of outstanding issues with the proposed IHC testing which will need to be addressed as part of the ADAR. These included:

- *Possible false positive IHC test results (due to variability with tissue fixation/processing/assays)*
- *How a true positive result is defined, noting that there is no reference standard for IHC*
- *Comparability between different IHC assays*
- *Tissue heterogeneity in IHC testing*

PASC noted that focal high-copy amplification of the MET gene is an oncogenic driver event for cancer whereas polysomy (increased numbers of the whole chromosome) is typically not. In FISH testing the ratio of the mean MET gene copy per cell relative to chromosome 7 centromere (CEP7) can be used to distinguish between polysomy and true amplification. However, PASC noted that under the proposed threshold of ≥10 MET gene copies per tumour cell, polysomy was unlikely (although the risk of misclassifying polysomy as amplification was still possible with a threshold of 5 gene copies per tumour cell), therefore PASC considered it was not recommended to undertake dual CEP7 probe in FISH testing (i.e. using the MET/CEP7 ratio as a scoring criteria). PASC noted that not all histopathology labs are accredited to do FISH, and chromogenic ISH may become more widely available on automated platforms. PASC noted that there was no discussion of tissue heterogeneity for MET amplification in the application although this is recognised as a significant issue in the literature.

Table 7 Summary and comparison of potential tests for MET overexpression/amplification

Test / laboratory technique	Immunohistochemistry	Fluorescence in situ hybridization	Next-generation sequencing
Tissue used	Core needle Tissue sample	Fine/core needle Tissue sample	Fine/core needle biopsy Tissue sample†
Test target	MET protein overexpression	*MET* gene amplification	*MET* gene copy number as a proxy for amplification
Testing process	Prepare and stain a slide with antibodies which specifically bind to the MET protein. The intensity and quantity of staining is then read by a trained pathologist.	Prepare a slide, and *MET* DNA is labelled with a fluorescent probe (usually red) and compared to the control signals from *CEP7* (usually green). The ratio of *MET* genes per *CEP7* copies is then read by a trained pathologist.	A glass flow cell with oligonucleotides bound to its surface has denatured DNA strands attached. A repeat process of copying and denaturing is performed until a cluster of DNA strands are attached to the oligonucleotides and are ready to be bound by fluorescent DNA tags which are read by a camera. Results are compared to a pooled baseline, and a high coverage or fold change in the *MET* gene region indicates amplification (too many copies). A specific threshold, usually gene copy number ≥5, is the threshold to define *MET* amplification. Additional analysis can be performed to distinguish between focal (only *MET* gene is amplified) and non-focal amplification (*MET* amplification amplified with additional duplication of neighbouring regions on the chromosome, such as *CDK6* and *BRAF*).
Proposed test threshold	Staining intensity 3+ in ≥90% of tumour cells	≥10 *MET* gene copies per cell	*MET* gene copy number ≥10 appears to be the optimal approximation of a FISH threshold of ≥10 *MET* gene copies per cell, however uncertainties around the sensitivity of this threshold remain.
Strengths	Typically a relatively cheap test. Can be a strong test option when used in conjunction with follow-up testing, such as FISH.	Gold standard for detection of *MET* amplification High accuracy: low false-negative and false-positive rate High interlaboratory reproducibility	High throughput; ability to sequence millions of DNA strands in parallel High resolution and sensitivity Versatile applications, rapid results
Limitations	Lower accuracy than FISH: high false-negative and false-positive rate. Lower interlaboratory reproducibility (these limitations may be partially mitigated by requirements of high staining intensity and follow-up FISH test in negative cases).	A targeted test which can only detect abnormalities in the specific region where probes are applied to the genome. The test has low resolution, limited probe capacity, and cannot detect all types of genetic changes such as point mutations or uniparental disomy.	Cannot discern the *MET* to *CEP7* ratio and therefore focal amplification from polysomy. While accuracy is very high, challenges remain; low sequencing depth (number of times a particular nucleotide is read during the sequencing process) can lead to false negatives, and the sheer number of potential variants can lead to false positives. Ongoing uncertainty of the clinical significance for many identified genetic variations. NGS generates an 'average' picture of a given population of cells; this can become more unreliable in the presence of multiple mutations and increased cellular heterogeneity. Expensive, however prices are decreasing over time.

† While NGS can be used with circulating tumour DNA (ctDNA) derived from a plasma sample, this has been found to be unreliable when testing for *MET* amplification.

Testing Methodology

Alterations to the MET protein expression can be assessed using IHC to detect overexpression, by FISH to detect amplification of the *MET* gene, or by next generation sequencing (NGS) to detect exon 14 skipping mutations and amplifications (Feldt and Bestvina 2023). MET exon 14 skipping refers to mutation that causes exon 14 of the MET gene to be skipped during RNA processing leading to a protein that is described as more stable that leads to greater stability and increased MET signalling. Both national and international consensus best practice recommendations made in the last 12 months advocate for molecular and biomarker testing for patients with NSCLC following progression during treatment with a targeted therapy (Zhou et al. 2024; Cooper et al. 2025). The specimen types required for these tests typically include tissue, circulating tumour DNA (ctDNA) and NGS panel testing. These tests may only be relevant and/or appropriate in settings where prognosis or treatment may depend upon the results; as additional targeted treatments are developed and listed on the PBS, broader testing will likely become part of the mainstream workup for these patients in the Australian setting.

The Australian consensus statement noted that non-formalin-fixed paraffin-embedded tissue (FFPE) cytology specimens (e.g., samples from fine needle aspiration [FNA]) are appropriate for molecular testing but not recommended for IHC (Cooper et al. 2025). In addition, the National Comprehensive Cancer Network (NCCN) noted 'judicious use of IHC is strongly recommended to preserve tissue for molecular testing, most notably in small specimens' (National Comprehensive Cancer Network 2025). The application did not provide information regarding the feasibility of conducting both testing methods with the typical tissue yields obtained from biopsy and declined to provide details on tissue biopsy technique in the SAVANNAH and SAFFRON trials. Based on this advice, if IHC is to be performed on all samples as part of testing for MET overexpression and/or amplification, then it may be prudent to avoid FNA tissue collections.

The applicant suggested that all patients with NSCLC EGFRm who have progressed on osimertinib should initially be tested with IHC for MET overexpression as supported by evidence from the SAVANNAH trial (Figure 1). Patients who yielded a negative result to IHC would then be tested by FISH to identify a small subset who are positive for *MET* amplification. Due to the difference in test performances, it was proposed that IHC is the initial method used followed by FISH. According to the application, the IHC test will detect approximately 85% of true positive cases, however the IHC test will have a false-negative rate of 15%. To identify the remaining 15% of true positive cases, the subsequent FISH test was proposed for all negative cases. The submission did not consider the false positive rate of the IHC test.

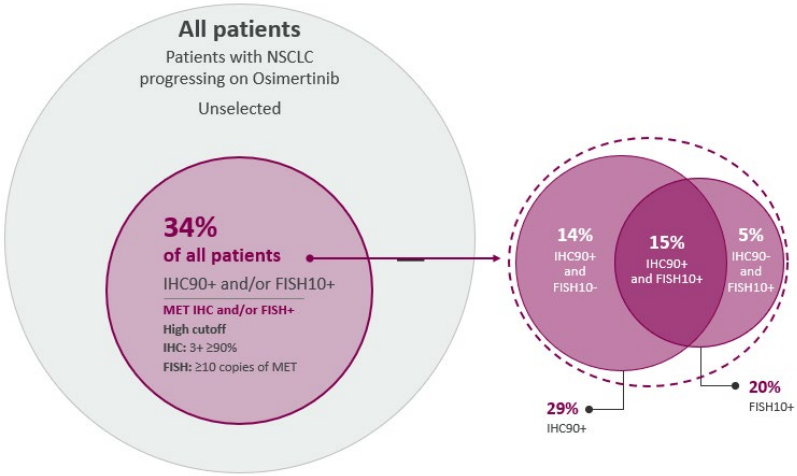
PASC noted no evidence was presented in the application to justify the proposed sequence of IHC testing followed by FISH testing for IHC negative samples. The applicant stated that in the key SAFFRON and SAVANNAH trials, both IHC and FISH testing were performed on all patient samples. The applicant stated the testing sequence that was proposed was to keep the process cost-effective and reduce the number of FISH tests, if IHC alone can identify patients likely to respond to the addition of savolitinib to osimertinib. PASC noted the justification for the testing sequence, however considered that further evidence to support the testing sequence will need to be presented within the ADAR.

PASC considered that in Table 1, where the intervention is described as 'Immunohistochemistry (IHC) for MET overexpression and/or MET fluorescence in situ hybridisation (FISH) for *MET* amplification', the phrase *'and/or' should be replaced with '+/-', as 'and/or' suggests FISH/IHC testing sequences may be*

bidirectional, however the application proposed that all eligible patients have the IHC test first, and only IHC negative patients (as per the algorithm defined as patients who fail to meet the staining intensity 3+ in ≥90% of their tumour cells) will proceed to FISH testing. PASC proposed the following rewording of the intervention: "IHC for MET overexpression with MET FISH for MET amplification in IHC-negative or IHC non-assessable cases". PASC considered there are cases where an IHC test may not be assessable, such as where only FNA/cytology samples are available. PASC considered that these cases may skip IHC testing and proceed directly to FISH testing.

The application did not provide any discussion or data on the potential for IHC90+ to identify false positive cases; as the application has proposed that samples which are IHC90+ positive undergo no further MET FISH testing, false positive cases could inappropriately be treated with savolitinib in combination with osimertinib.

Figure 1 Venn diagram of IHC and FISH MET cut-offs



FISH = fluorescence in situ hybridisation; FISH10+ = ≥10 MET gene copies; IHC = immunohistochemistry; IHC90+ = IHC 3+ in ≥90% of tumour cells; MET = Mesenchymal-Epithelial Transition factor; NSCLC = non-small cell lung cancer.
Note: The Phase II SAVANNAH trial determined the prevalence of MET overexpression or amplification would be 34% when applying the SAFFRON IHC and FISH cut-offs. Of note, prevalence appeared similar between lines of therapy and regions (Ahn et al. 2022).

Under the applicant's proposal, there are four post-MET test population groups, described in the table below and adapted from Figure 1.

Population	IHC90+	FISH10+	% of testing population	% of MET positive cases	Eligible for savolitinib plus osimertinib?
A‡	Positive	Negative	14	41	Yes
B	Negative	Positive	5	15	Yes
C‡	Positive	Positive	15	44	Yes
D	Negative	Negative	66	0	No

‡As there will be no further testing performed after a positive IHC90+ result under the applicant's proposal, these two populations will be combined into a single group representing approximately 29% of the test population and 85% of the MET positive population. The remaining 71% of the test population will have the additional FISH test performed.

The applicant noted some of the patients from FLAURA, a phase 3 trial which compared first-line osimertinib with other EGFR-TKIs in patients with EGFR mutation–positive advanced NSCLC, were also screened (with MET testing) for enrolment in SAFFRON. PASC recognised this may present a unique

opportunity to compare outcomes across populations A, B, C and D in a single trial cohort, representing key comparative cohort data for population D (as these patients were otherwise screened out of the key SAFFRON and SAVANNAH trials).

PASC considered that it was unclear whether strong MET protein overexpression or gene amplification is the best predictor of response (since there is not a direct overlap between patients who are IHC positive and FISH positive). PASC noted that there is an absence of a valid reference standard to evaluate samples which are IHC90+ positive but FISH10+ negative (14% of total; 41% of "positives"). PASC considered that in the absence of a valid reference standard, the ADAR will need to supply supplementary evidence to demonstrate clinical effectiveness of savolitinib plus osimertinib treatment versus platinum-based doublet chemotherapy in patients whose tissue samples were IHC90+ positive but FISH10+ negative. This is consistent with the MSAC guidelines (Technical guidance 2.4) which state that in the absence of a reference standard, test accuracy will need to be demonstrated by direct from test to health outcomes evidence showing a health benefit from use of the test.

A recent publication by the Royal College of Pathologists of Australasia, in collaboration with the Thoracic Oncology Group of Australasia, recommended that molecular testing results should be available as soon as possible, with best practice defined as ideally within 5 business days but no more than 10 business days from receipt of the specimen in the molecular laboratory. This means that the sequential IHC and FISH testing may take up to 10 business days (Cooper et al. 2025). Added to this time, it is reasonable to expect at least a 1-to-2-week delay for scheduling/booking/performing the biopsy. This means overall the proposed biopsy, IHC and FISH testing may take up to 3-4 weeks. This delay may be increased for rural/remote patients who face additional barriers to accessing healthcare. With the proposed intervention in place, approximately 66% of patients in the target population who do not have a MET alteration will undergo a biopsy and have their doublet platinum chemotherapy delayed by up to 4 weeks (i.e. one full cycle). A recently published systematic review found that given the aggressiveness and lethality of this type of lung cancer, waiting times and delays in management must be reduced to achieve optimal management and prognosis (Guirado et al. 2022). However, it is also noted that a range of targeted therapies for this population are in development; if additional tests/treatments become available in Australia, then the proportion of target population which will benefit from the biopsy/testing process will likely increase.

The application stated that Australian practice relating to re-biopsy at disease progression is variable across centres that treat EGFR-mutated NSCLC. The availability of osimertinib has led to a shift away from re-biopsy in the progressed setting due to removing *EGFR* T790M resistance mutations as a target. The application also described key opinion leader (KOL) advice that suggested that around 25% of patients currently undergo biopsy in the progressed setting to look for histologic transformation (HT) to small cell lung cancer (SCLC); this test is primarily a hematoxylin and eosin (H&E) stain, however a small percentage may demonstrate an equivocal result and require an alternative method such as IHC testing to identify HT to SCLC.

The application assumed that as many as 90% of patients will be eligible for re-biopsy in the progressed setting with the remaining 10% likely experiencing 'rapid clinical deterioration, refractory disease, severe competing illness or biopsy refusal'. This could not be verified by the assessment group. Previously, the applicant suggested that only 82% of progressed patients would be eligible for biopsy after first line Osimertinib (Pharmaceutical Benefits Advisory Committee 2019). If treatment with savolitinib in

combination with osimertinib demonstrates superior clinical effectiveness, then it is likely that clinicians will recommend the biopsy and testing process for all clinically amenable patients.

Assessment of concordance of NGS, FISH and IHC

The applicant stated that NGS is not currently considered an appropriate technology to detect MET resistance for two reasons. Firstly, MET exon 14 skipping mutations, which are detected by NGS, occur *de novo* in lung adenocarcinomas and have yet to be reported as a resistance mechanism to osimertinib (Gomatou, Syrigos, and Kotteas 2023), meaning these may be reported as 'false positives' in terms of identifying a *MET* dependent resistance pathway which is likely to respond to savolitinib in combination with osimertinib. Secondly, FISH amplification is assessed by the ratio of *MET* to chromosome 7 centromere (CEP7) copies to distinguish between polysomy and true amplification (Coleman et al. 2021). NGS assays are unable to control for CEP7 to comparably evaluate gene copy number gain to FISH (Piper-Vallillo, Sequist, and Piotrowska 2020). Due to these issues, the application is not seeking NGS testing. The European Society for Medical Oncology (ESMO) guidelines considered available tests in the space and stated "Increased *MET* signalling may result from high gene copy number (GCN), either due to polysomy or true gene amplification. Detection is reliable by *in situ* hybridisation (ISH) techniques, but NGS or comparative genomic hybridisation may also identify cases. Definitions of high GCN vary and, in absence of current standardisation, confound existing data." (Hendriks et al. 2023). In addition, the NCCN recommends the use of IHC to test for MET overexpression and FISH to test for amplification of the *MET* gene (National Comprehensive Cancer Network 2025).

The assessment group's view aligns with the Royal College of Pathologists Australia (RCPA) and the applicant's conclusion that NGS is inappropriate for this target population. Whilst NGS has demonstrated reasonable performance compared to fluorescence in situ hybridisation (FISH) in identifying MET amplifications in tissue samples, it does not appear to be a robust method of identifying patients who will respond to savolitinib plus osimertinib (Gomatou, Syrigos, and Kotteas 2023). Defining *MET* amplification to guide treatment strategies poses a unique diagnostic challenge, as the thresholds for what 'counts' as resistance is not well characterised, and may vary between trials/treatments. The task is not simply differentiating between a 'present' or 'absent' marker but seeking to meet a quantitative threshold.

The phase II SAVANNAH trial evaluating savolitinib plus osimertinib following disease progression on osimertinib determined that the optimum cut-off was MET IHC+/≥90% (3+ staining intensity in ≥90% of tumour cells) and/or FISH10+ (≥10 MET gene copies per cell) (Ahn, De Marinis, et al. 2022). Earlier versions of the trial's protocols allowed enrolment of patients with lower cut-offs (IHC3+/FISH≥50%) and local NGS testing (with retrospective confirmation by central IHC and/or FISH), however this option was removed in the latest protocol version, with the following table showing only patients with IHC3+/≥90% and/or FISH10+ demonstrated a statistically significant benefit of treatment (de Marinis et al. 2025):

Table 8 Patient responses parsed by a range of MET, FISH and NGS values

	All patients; MET IHC3+/≥50% and/or FISH5+ status (*N* = 193[b])	Patients with MET IHC3+/≥90% and/or FISH10+ status (*n* = 108)	Patients without MET IHC3+/≥90% and/or FISH10+ status (*n* = 77)
ORR, % (95% CI)	32 (26, 39)	49 (39, 59)	9 (4, 18)
Complete response, *n* (%)	0	0	0
Partial response, *n* (%)	62 (32)	53 (49)	7 (9)
Median DoR, months (95% CI)	8.3 (6.9, 9.7)	9.3 (7.6, 10.6)	6.9 (4.1, 16.9)
PFS			
Events, *n* (%)	153 (79)	80 (74)	68 (88)
Median, months (95% CI)	5.3 (4.2, 5.8)	7.1 (5.3, 8.0)	2.8 (2.6, 4.3)

Source: Supplementary Table S1. Efficacy outcomes by IHC and/or FISH MET status in EGFR-mutated advanced NSCLC following disease progression on osimertinib (Data Cut-off August 27, 2021)

[a]Patients with EGFR-mutated locally advanced or metastatic NSCLC and MET overexpression and/or amplification with disease progression following treatment with osimertinib (first or ≥second-line), who received savolitinib 300 mg QD plus osimertinib 80 mg QD.

[b]Includes 8 patients with invalid or missing results for MET IHC3+/≥90% and/or FISH10+ status, these patients were excluded from subgroup analyses based on MET alteration levels.

CI, confidence interval; DCO, data cut-off; DoR, duration of response; EGFR, epidermal growth factor receptor; FISH, fluorescence in-situ hybridization; FISH5+, MET gene copy number ≥5 and/or MET:CEP7 ratio ≥2 by FISH; FISH10+, MET gene copy number ≥10; NSCLC, non-small cell lung cancer; IHC, immunohistochemistry; MET IHC3+/≥50%, 3+ staining in ≥50 of tumours cells; MET IHC3+/≥90%, 3+ staining in ≥90% of tumour cells; NGS = next generation sequencing; ORR, objective response rate; PFS, progression-free survival; QD, once daily.

A range of studies have evaluated concordance of NGS and FISH in evaluating *MET* amplification in the advanced NSCLC setting, however some studies examined treatment-naïve tissue samples which is not consistent with our target population. The assessment group performed a rapid review seeking data to the point of saturation. The best NGS test performances were only obtained with tissue samples, ruling out the possibility of using circulating tumour DNA (ctDNA) by NGS. While agreement has been reasonably high in some recent studies, there are conflicting data with little between-study consistency (these studies defined *MET* amplification positive as a *MET* gene copy number (GCN) ≥5 unless otherwise specified, which is below the ≥10 threshold identified in SAVANNAH). Note that in the following studies below, which assess concordance between NGS and FISH, the applicability of the evidence may be limited due to differences in the study populations to the PICO population, including in the areas of: treatments received, FISH threshold used to determine eligibility for treatment and anatomical site of cancer (it is unclear whether the samples were lung tissue, unless specifically stated below).

- (Schubart et al. 2021): sought to determine if NGS could replace FISH in a real-world setting using treatment-naïve patients. It found that out of the 205 evaluable cases, only n = 9 cases (43.7%) of n = 16 high-level MET amplified cases (*MET/CEN7* ratio >2) assessed by FISH were classified as amplified by NGS. Cases where the gene copy number was high (>10) had the greatest concordance (80%), noting that one of the five cases was not classified as *MET* gene amplified by NGS. Given the very small sample size, it is unclear how many 'false positives' may be associated with NGS compared to FISH. The paper concluded that NGS assessment of the MET GCN detects high-level MET amplified cases harbouring a MET GCN >10 but fails to detect the various facets of MET gene amplification in the context of a therapy-induced resistance mechanism; particularly, ambiguity around 'true' high-level *MET* amplified cases, defined as a high *MET/CEN7* ratio ≥5.0 without concomitant polysomy, and in differentiating 'intermediate' from 'low' MET (not relevant for the proposed target population).

- (Peng, Jie, et al. 2021): 40 patients with advanced NSCLC eligible for MET-TKI treatment found the concordance rate among FISH and NGS was 62.5% (25/40); *MET* amplification identified by FISH, defined as *MET/CEP7* ratio >2 or GCN >5, showed the optimal predictive value to MET inhibitor therapy, which included crizotinib, savolitinib and bozitinib. In addition, amplification identified by NGS was found to be an ineffective predictive biomarker, and failed to distinguish significant clinical outcomes in terms of partial response and progression-free survival, concluding "*MET* amplification testing by NGS remains uncertain and it could not be directly used in clinical practice." The same author published another paper (Peng, Li, et al. 2021) which found that IHC, FISH and NGS had only 54% concordance when defining *MET*amp as *MET/CEP7* ratio >2 or GCN >6, concluding "Compared to MET amplification identified by FISH, copy number gain (CNG) dysregulation by NGS or MET protein over-expression by IHC could not serves as the predictive biomarker for MET inhibitors."
- (Lai et al. 2019): 200 treatment-naïve patients were evaluated for concordance, first evaluated by FISH. Of the 18 out of 39 patients identified as *MET*-high (two amplification and 16 polysomy) who had sufficient tissue, only eight of 18 were deemed to have *MET* CNG by NGS. Of the two amplified tumours identified by FISH (3.4 and 2 by ratio), the latter was found to not be *MET* amplified on NGS. In addition, only one of three tumours with *MET* CNG >8 by FISH, were *MET* amplified on NGS. Overall, findings suggest that concordance is low and likely reflects the differences in assay resolution (sequencing reads *v* fluorescent signals) and input material (single section *v* pooled DNA from multiple sections).
- (Lin et al. 2023): 67 patients with EGFR-TKI resistant disease were enrolled to detect focal *MET* amplification on biopsied tissue. FISH detected *MET*amp in 22 patients; 8 cases were polysomy, and 14 with focal amplification (note that the application excluded cases of polysomy from the target population, and noted NGS cannot differentiate between *MET*amp due to polysomy versus focal ('true') amplification). FISH and tissue NGS achieved an overall agreement in focal MET amplification of 94.6% (53/56). Sensitivity and specificity of tissue NGS for detecting focal MET amplification were 78.6% (11/14), and 100.0% (42/42) respectively.
- (Zheng et al. 2024): 116 patients were enrolled after progression on 1st-, 2nd- or 3rd-generation EGFR-TKIs; 83 had progressed after a 3rd generation EGFR-TKI, the same class as osimertinib. Patients were tested by FISH and NGS, then the NGS results had their thresholds 'optimised' to achieve maximum accuracy. The study investigated a subgroup of patients which used a FISH CN ≥10, which is consistent with the key trial cut-off value. In this group, NGS tissue samples achieved concordance of 91.46%, with sensitivity 68.42% and specificity 98.41%.

Two other studies have demonstrated NGS and FISH may demonstrate higher concordance, however the assessment group believes these results are not applicable to the proposed target population and test thresholds. These were:

- (Solomon et al. 2022): Validated NGS analysis of MET copy number alterations in >50,000 solid tumours across a range of cancers. If read-depth and focality analyses were incorporated, a 91% concordance, 97% sensitivity, and 89% specificity was achieved, however the study noted that tumour heterogeneity, neoplastic cell proportions, and genomic focality affected MET amplification assessment. No subgroup of test performance for NSCLC or at the proposed test-thresholds could be identified in this paper, limiting the applicability of the results.

- (John et al. 2024): This poster abstract compared NGS and FISH in patients with EGFR NSCLC. The cut-off used was a *MET*:*CEN7* ratio of >2, which is lower than the cut-off for our target population. They found that FISH identified 7 *MET*amp cases, while NGS only identified 5 (71%).

It is the assessment group's view that the above results suggest that NGS is an imperfect replacement for FISH testing in this setting.

Only one study (Zheng et al. 2024) compared the performance of FISH and NGS on patients who progressed following an EGFR-TKI utilising the same cut-off value as proposed by the application (GCN ≥10). This study found NGS tissue samples achieved concordance of 91.46%, with a relatively low sensitivity of 68.42%, and and specificity of 98.41%. This means out of 100 patients positive for *MET*amp GCN ≥10 by FISH testing, only 68 would be correctly identified by NGS and go on to qualify for savolitinib in combination with osimertinib. The other study to compare test performance of GCN ≥10 did so on treatment-naïve patients, and found the concordance of NGS and FISH was 80%. This improvement may be due to the fact that treatment-naïve tissue has less heterogeneity and may therefore be easier to analyse by NGS compared to post-treatment tissue samples, which have substantially increased intratumour mutations and heterogeneity (Oh et al. 2025). With an increase in heterogeneity, NGS signal and sequencing depth may be lower, and as bulk NGS reads an 'average' picture of all cells in the sample, the target cell mutation may be diluted, therefore increasing false negative results (Kim et al. 2019; Goldman et al. 2019).

Finally, the diagnostic challenge is further compounded by the fact that the sequential IHC then FISH test is being proposed to identify a small, specific group of patients who had a 'false negative' on IHC, as described by the submission's Venn diagram (Figure 1). In the proposed context, the only reason to perform the FISH test is to identify the 5% of the target population which the IHC test classified as 'false negatives'. This proportion makes up 25% of the FISH 'true positive' cases; this means that even if NGS and FISH had high agreement (e.g. 80%), it is unclear how many of the 'true positive' cases identified by NGS correspond to the 'false negative' cases identified by IHC. Stated another way, a scenario where almost all the NGS true positive cases fall within the IHC true positive cases cannot be ruled out; in this scenario, there would be little benefit in performing sequential IHC and NGS tests. To resolve this knowledge gap, a comparison of IHC90+, FISH10+ and NGS on NSCLC who had progressed following a 3rd generation EGFR-TKI would be required.

PASC noted the potential suitability of NGS for assessment of high level MET amplification. PASC noted that there were issues with using NGS to assess MET gene copy numbers because of the difficulty in differentiating between high level polysomy and genuine gene amplification under NGS testing (given the lack of relevant centromere control in NGS testing). PASC also noted the reduced reliability of NGS in heterogeneous cell populations with low tumour cell percentages. This is because the relevant measure of MET amplification is the average number of MET gene copies per tumour cell and not the average number across all cells in a sample (as measured by NGS), meaning that NGS can lead to a high false negative rate in cases of low tumour cellularity or heterogeneity. The applicant stated that FISH is likely more reliable (sensitive) than NGS at detecting MET amplification. This is reflected in the relatively low NGS sensitivity of 68.42% as reported by Zheng et al 2024 in the NGS tissue sample subgroup with a threshold of GCN ≥10, which achieved concordance of 91.46%, with sensitivity 68.42% and specificity 98.41%.

PASC noted that while NGS studies generally seem to use a copy number >5 as the cut off for MET amplification this is also problematic as there is a risk of misclassifying polysomy as amplification under this threshold, leading to more false positives than under FISH testing. The applicant further stated that in cases of high levels of MET amplification (>10 copies), NGS can have close correlation to FISH, particularly when utilising new methodologies of computational ploidy, which may provide good accuracy with high cell/chromosome numbers, potentially making the accuracy of NGS acceptable. However, PASC noted that setting the gene copy cutoff number to 10 for NGS would likely lead to more false negative results than under FISH testing (as per reasons discussed above). Performing NGS for MET assessment also represents a more expensive option than IHC/FISH.

Therefore, PASC ultimately did not find NGS to be a relevant substitute for IHC or FISH testing, and concluded that it is not necessary to compare with FISH and IHC in the ADAR.

Registration status

The application stated MET overexpression/amplification testing with IHC/FISH has not been listed or registered or included in the ARTG by the Therapeutic Goods Administration (TGA), and described that currently there are MBS Items for IHC and FISH which have generic descriptors not specific to MET testing; an independent search performed by the assessment group confirmed there are currently no specific MET overexpression/amplification listings. There are generic IHC items on the MBS that could be used for MET testing. The application anticipated that laboratories would develop in-house in vitro diagnostic (IVD) solutions that meet the National Pathology Accreditation Advisory Council (NPAAC) Companion Diagnostic standards, and that manufacturers, including the clinical trial manufacturers, may register their IVDs on the Australian Register of Therapeutic Goods (ARTG). A letter from Peter MacCallum Cancer Centre dated 16 September 2025 confirmed that the notification for MET IHC and FISH testing has been submitted for National Association of Testing Authorities (NATA) accreditation. An independent search found a range of NATA accredited laboratories which could test for *MET* skipping mutations, however none which were NATA accredited for testing for MET overexpression/amplification.

Tissue specimen collection

A specialist (e.g. thoracic surgeon, interventional radiologist) collects the specimen and completes a test request form (e.g. medical oncologist, thoracic surgeon) for IHC and FISH testing for MET alterations. A registered anatomical pathologist is responsible for conducting the detection, diagnosis and reporting of the pathology results which guide treatment.

The application stated that obtaining the tissue sample will be the primary limitation on the provision of the new technology. No details were provided in the application to highlight the anticipated re-biopsy procedures undertaken, the estimated success rates of the different re-biopsy techniques, or the associated risk of complication with the procedures.

Potential approaches to biopsy collection, listed in order of invasiveness are as follow:

- Fine needle aspirate
- Core needle biopsy
- Tissue sample

Method of collection of these biopsies may include:

- Percutaneous Transthoracic Lung Biopsy (interventional radiology)
- Transbronchial biopsy (flexible bronchoscopy)
- Video-Assisted thoracic surgery (VATS) (thoracic surgery)
- Open Lung Biopsy (thoracic surgery) – note this is an unlikely approach for this target population

Biopsy technique/approach primarily depends on the location and least invasive access to tumour tissue, as well as clinician advice and preference. In the re-biopsy setting, percutaneous transthoracic lung biopsy and transbronchial biopsies are preferable. The transthoracic lung biopsy may be performed using either a fine needle aspirate or core needle biopsy; transbronchial typically take multiple small tissue samples, noting these samples are prone to crush artefact which may be ameliorated through use of cryobiopsy (freezing tissue prior to collection). Test accuracy may be affected by biopsy type; for example, fine needle aspirates are not recommended for use with IHC, and crush artefacts may affect the test accuracy of IHC and FISH. VATS has largely replaced open lung biopsy due to its less invasive nature, and is reserved for collecting larger tissue samples and/or lymph nodes to establish initial diagnosis (Modi and Uppe 2025).

The biopsy procedure is not trivial, with a range of risks depending on approach and technique. A recent publication estimated that following a minimally invasive percutaneous CT-guided core needle biopsy in patients with NSCLC, 32.7% of patients in this population experienced a complication at re-biopsy with 10.6% experiencing a pulmonary haemorrhage and 20.4% experiencing a pneumothorax, however most of these were low-grade (Grade 1-2) (Wang et al. 2024).

Currently no targeted treatments are available for MET-driven resistance in post-osimertinib patients in Australia. Patients who progress post-osimertinib are not currently routinely tested for MET amplification/overexpression; instead, they receive platinum-based doublet chemotherapy or move onto palliative care (Ngo et al. 2023).

The application's proposed clinical algorithm did not include in the population, patients who are tested for HT to SCLC and noted to still have NSCLC who may require further testing for MET amplification or overexpression with IHC and/or FISH testing. In the pre-PASC teleconference, the applicant confirmed that patients who tested negative for HT to SCLC should form part of the target population. The applicant confirmed that MET amplification/overexpression may occur in patients' tumours which have had HT to SCLC. Without confirming the specimen's morphology, it is possible a small number of patients with HT to SCLC, who are outside the target population, could be treated with savolitinib in combination with osimertinib.

Comparator

The proposed comparator reflects the current testing and treatment pathways for patients with locally advanced or metastatic NSCLC who have progressed on or after Osimertinib.

Test

There is currently no testing for MET overexpression. The comparator test therefore is 'no MET overexpression testing'.

Drug

Currently no targeted treatments are available for MET-driven resistance in post-osimertinib patients. Patients who progress post osimertinib are not tested for MET amplification/overexpression, instead, the current standard treatment for these patients is stated by the applicant as platinum-based doublet chemotherapy as the next line of therapy. For patients who have failed 2L osimertinib, the most appropriate comparator may be single-agent chemotherapy instead of doublet. The comparator for the drug will need to be confirmed by the Pharmaceutical Benefits Advisory Committee (PBAC) when they consider savolitinib for this population.

Therefore, the proposed comparator is 'no testing and the standard platinum-based doublet chemotherapy'. It is noted that in the key SAFFRON trial, the comparator population underwent IHC/FISH testing followed by platinum-based doublet chemotherapy.

PASC found the comparators appropriate.

Clinical utility standard (for codependent investigative technologies only)

In the key SAFFRON trial, patients were selected for treatment based on IHC overexpression using the Roche CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody and *MET* amplification using the Abbott Vysis MET Spectrum Red FISH probe kit. Central MET testing was carried out on tumour tissue collected after radiologic disease progression on osimertinib. Therefore, a combination of IHC testing with Roche CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody kit and *MET* amplification testing with Abbott Vysis MET Spectrum Red FISH probe kit forms the clinical utility standard demonstrating the clinical utility of MET testing and treatment with savolitinib in combination with osimertinib. Thresholds for higher MET overexpression and/or amplification cut-offs were defined as MET IHC 3+ intensity staining in ≥90% tumour cells and/or 10 or more *MET* gene copies per cell (FISH10+).

At the time of evaluation, only an abstract for SAFFRON was published, and it is unclear from the wording in the publication and application whether all patients' samples had both IHC and FISH tests performed, or whether a sequential testing approach was used where patients found to be positive via IHC testing would not require a FISH test (or vice versa).

PASC noted that in the SAFFRON trial (which at the time of PASC consideration was still ongoing), the tests used were:

- *MET overexpression IHC testing with Roche CONFIRM anti-Total c-MET (SP44) Rabbit Monoclonal Primary Antibody kit (defined as 3+ staining in 90% of tumour cells for the trial).*
- *MET gene amplification testing with Abbott Vysis MET Spectrum Red FISH probe kit (compared to chromosome 7 centromere; defined as > 10 MET copies per cell), however there was no MET:CEP7 ratio requirement.*

PASC considered that FISH is the gold standard for identifying MET amplification but noted that there is no reference standard for identifying the population of patients likely to respond to the addition of savolitinib treatment.

As noted in the intervention section, in the absence of a valid reference standard to evaluate samples which are IHC90+ positive but FISH10+ negative (14% of total; 41% of "positives"), efficacy data demonstrating a consistent clinical benefit of savolitinib + osimertinib in patients whose tissue samples demonstrated IHC90+ positive but FISH10+ negative are required. The applicant noted these data should be forthcoming

from a SAVANNAH secondary analysis or from the SAFFRON trial. PASC considered that these data will be necessary for further consideration of the proposed testing algorithm.

Outcomes

PASC noted that MET overexpression is not stable over time and considered that the outcome measure 'evidence of stability in MET overexpression status over time' should be removed.

Given the discussion on the application's proposed cut off thresholds, PASC considered that 'Relative predictive accuracy of IHC vs FISH assays at proposed cut-off thresholds' should be included as a relevant test-related outcome. PASC considered this should demonstrate the treatment effect of savolitinib and osimertinib in terms of health outcomes for patients.

PASC noted that there is potential for variation in IHC assays between pathology laboratories. PASC considered that the comparability between different IHC assays should be included in the ADAR.

PASC considered that central nervous system (CNS) efficacy should be added to the drug-related outcomes.

The final set of outcomes is presented below.

Test-related outcomes

Safety outcomes:

- Adverse events associated with biopsy
- Re-biopsy for patients with inadequate tissue for tumour testing.

Diagnostic performance of IHC and FISH:

- Sensitivity and specificity
- Test failure rate
- Assessment of extent of and implications of discordances between Australian IHC and FISH testing and the respective clinical utility standards
- Test-retest reliability
- Inter-rater reliability
- Diagnostic accuracy of proposed testing sequence (IHC followed by FISH).
- Comparability between IHC assays.

Clinical validity: Positive and negative predictive values, positive and negative likelihood ratios.

Clinical utility of the test: Determine whether testing for MET overexpression/amplification predicts variation in the treatment effect of savolitinib and osimertinib in terms of health outcomes for patients. Relative predictive accuracy of IHC vs FISH assays at proposed cut-off thresholds.

Other test-related considerations:

- Re-biopsy rates (test failure and inadequate sample rate as a proxy for re-biopsy rate)
- Test turn-around time

Drug-related outcomes

Safety outcomes: Safety and tolerability of treatment with savolitinib and osimertinib compared to platinum doublet chemotherapy (adverse events, physical examinations, laboratory findings and vital signs).

Clinical effectiveness outcomes:

- Objective response rate (ORR)
- Overall survival (OS)
- Progression-free survival (PFS)
- Partial response (PR)
- Complete response (CR)
- Health-related quality of life (HRQoL) compared to platinum doublet chemotherapy.
- Central nervous system (CNS) efficacy.

Healthcare system outcomes

- Cost of testing per patient with associated biopsies and re-biopsies
- Cost of treatment and cost of treating adverse events
- Cost effectiveness
- Financial implications: number of patients tested; number of patients treated.

Assessment framework (for investigative technologies)

A linked evidence approach is the most appropriate as there is unlikely to be direct evidence of the impact of MET overexpression testing on health outcomes. An assessment framework linking MET overexpression testing to relevant health outcomes is presented in Figure 2.

Questions relevant to this assessment framework are as follows:

1. Does the use of the MET overexpression/amplification test in place of no testing result in the claimed superior health outcomes?

2. What is the accuracy of the proposed testing sequence (IHC followed by FISH)? What are the implications of discordances occurring between the proposed testing procedure and the clinical utility standard?

3. Does the availability of new information (MET overexpression/amplification status) from MET overexpression/amplification testing lead to a change in management of the patient?

4. Do the differences in the management derived from MET overexpression/amplification testing result in the claimed superior health outcomes (OS, HRQoL)?

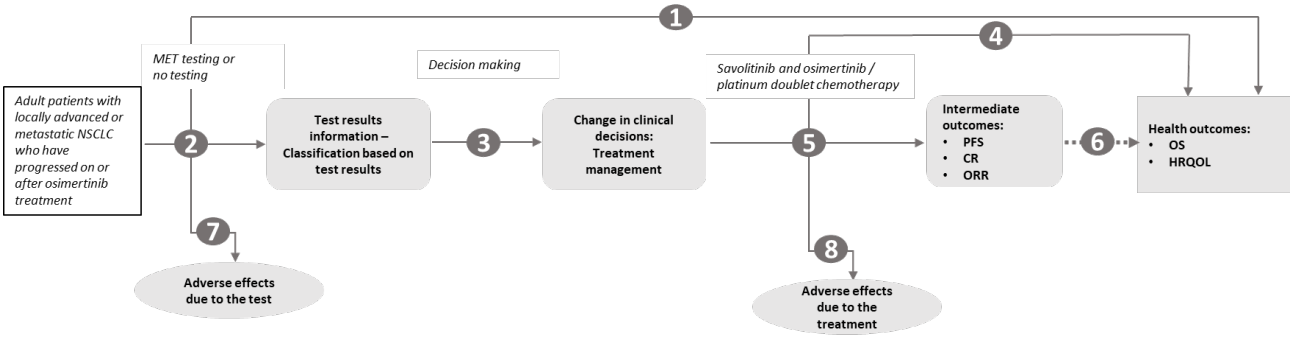
5. Do the differences in the management derived from the proposed test result, relative to the comparator (e.g. differences in treatment/intervention), result in the claimed intermediate (PFS, CR, ORR) outcomes?

6. Is the observed change in intermediate outcomes (PFS, CR, ORR) associated with a concomitant change in the claimed health outcomes (OS, HRQoL), and how strong is the association?

7. What are the adverse events associated with MET overexpression/amplification testing (including the adverse events associated with biopsy) compared to a no testing strategy?

8. What are the adverse events associated with treatment with savolitinib and osimertinib compared to platinum doublet chemotherapy?

Figure 2 Assessment framework showing the links from the test population to health outcomes



CR = complete response; HRQOL = health related quality of life; MET = Mesenchymal-Epithelial Transition factor; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Figure notes: 1: direct from test to health outcomes evidence; 2: test accuracy; 3: change in diagnosis/treatment/management; 4: influence of the change in management on health outcomes; 5: influence of the change in management on intermediate outcomes; 6: association of intermediate outcomes with health outcomes; 7: adverse events due to testing; 8: adverse events due to treatment

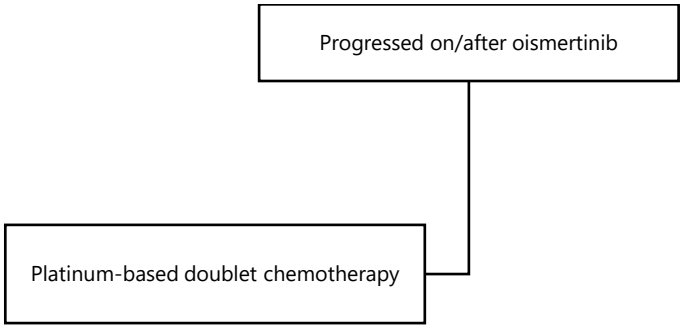
PASC noted that the proposed testing sequence (IHC followed by FISH, for patients who were IHC negative), differs from the testing sequence in the pivotal trial and therefore additional new evidence may be required to assess the accuracy of this testing sequence under a linked evidence assessment framework.

Clinical management algorithms

Currently, patients who experience disease progression on or after treatment with osimertinib receive platinum-based doublet chemotherapy as the subsequent line of therapy, or they are palliated.

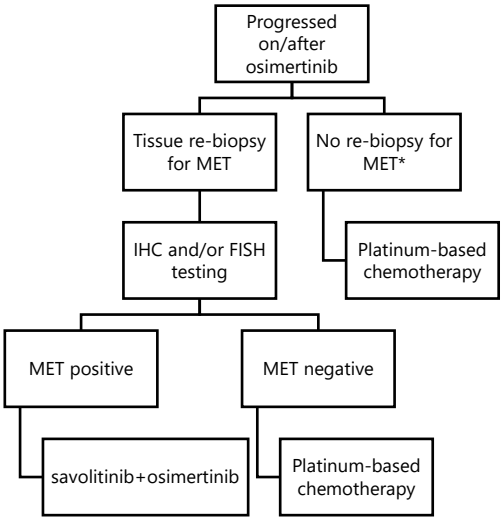
The application for the proposed health technology specifies that patients progressing on osimertinib should undergo re-biopsy to assess for acquired resistance mechanisms involving MET overexpression/ amplification, assessed through IHC and/ or FISH testing. Patients identified as MET-positive would then be eligible for targeted therapy with savolitinib plus osimertinib, whereas those who test MET-negative would proceed to receive platinum-based chemotherapy in line with the current standard of care. Alternatively, the treatment algorithm recognises that some patients may not undergo re-biopsy for MET testing and would instead continue with current clinical management, receiving platinum-based chemotherapy or, in selected cases, being evaluated for HT to SCLC. The application's current and proposed future treatment algorithm are presented in Figure 3 and Figure 4 below.

Figure 3 Clinical management algorithm without the proposed health technology



Source: Page 12 of the application

Figure 4 Clinical management algorithm with proposed health technology



*Some patients receive re-biopsy for determining other resistance mechanisms such as small cell transformation

Source: Page 12 of the application

The submission's algorithm failed to account for patients who are tested for HT to SCLC and found to be negative; these patients may then go on to be tested for MET overexpression/amplification. The submission stated that advice from a clinical expert estimated that in Australian practice, 25% of patients in the progressed setting are currently being re-biopsied to assess for HT to SCLC although this evidence is not verified by the assessment group. The application's clinical algorithm also does not explicitly detail the sequential nature of IHC then FISH testing, instead stating 'IHC and/or FISH' which may be misleading. These issues have been addressed in a revised treatment algorithm developed by the assessment group, presented in Figure 5 and Figure 6 below. These algorithms are presented as a clearer and more explicit version of the applicant's algorithm, and do not claim to depict the 'ideal' sequence of tests. For example, PASC may wish to consider the cost-efficacy of testing all tissue samples for HT to SCLC prior to conducting the MET tests; as this approach doesn't rely on clinicians' judgement, all HT to SCLC would be identified, removing the risk of performing unnecessary MET testing and assigning inappropriate treatments to patients with HT to SCLC (i.e. either savolitinib in combination with osimertinib, or doublet platinum-based chemotherapy).

The revised algorithms have clarified the application's algorithm, which may have been misleading. The applicant has proposed performing the HT to SCLC tests on a clinician-selected subgroup prior to MET testing, as patients with demonstrated HT to SCLC are not eligible for savolitinib in combination with

osimertinib. This is now depicted in both algorithms which show that patients should be considered for HT to SCLC testing and the testing performed if appropriate, before progressing to platinum-based chemotherapy or palliative care, or testing for MET alteration.

If there is only a small sample of tissue available, test prioritisation may be required. According to the application, the IHC test would have the highest yield of positive MET overexpression (IHC detects 29% out of 34% positive cases, as described in Figure 1), however if a patient is determined to be at high risk of HT to SCLC then this test should be performed first. There are emerging technologies available which allow for concurrent viewing of H&E (to assess for HT to SCLC) and IHC specimens on the same specimen slide, which may be a future solution to the problem of tissue/slide limitations by combining the MET IHC test and HT to SCLC test on a single slide (Morrison et al. 2025).

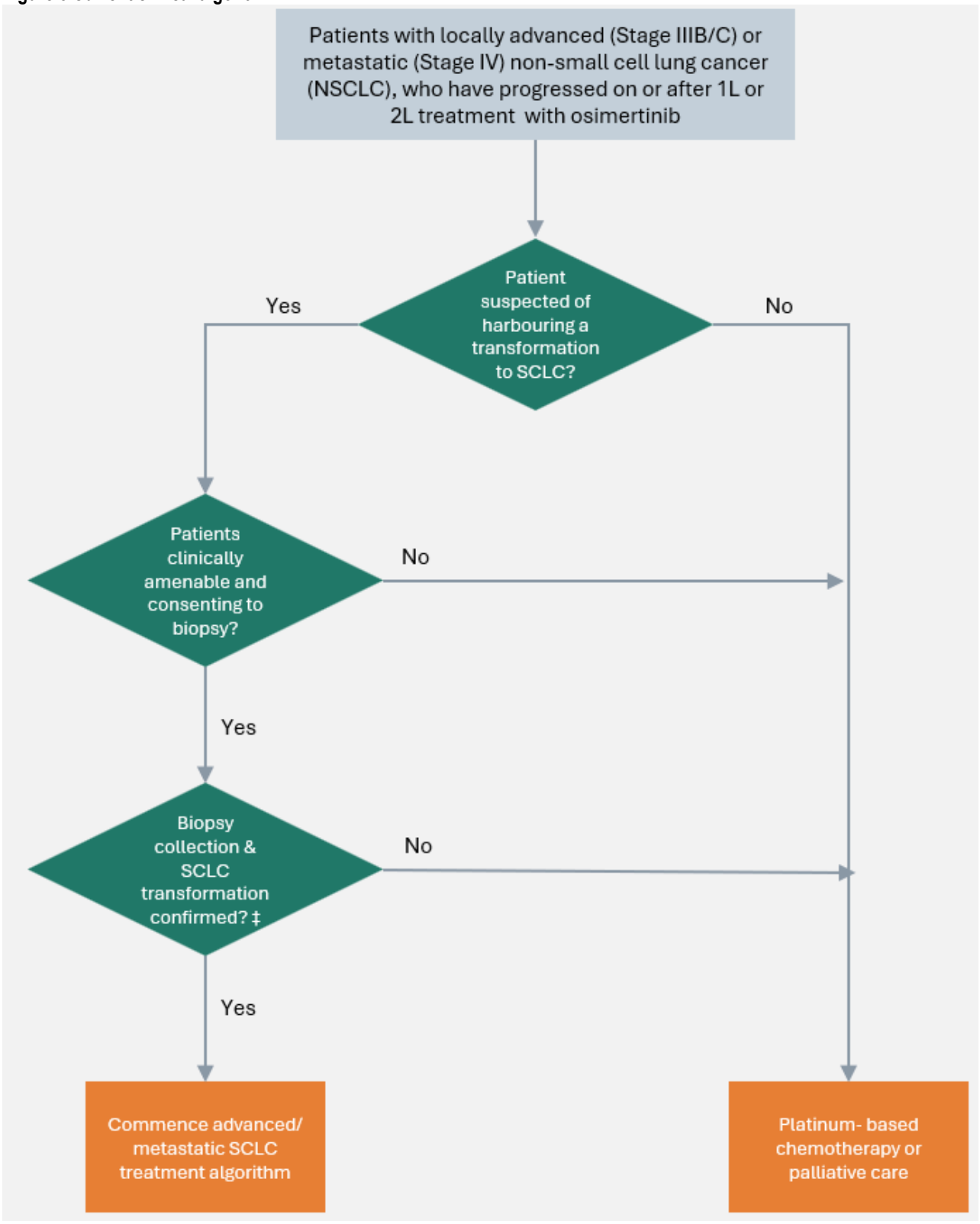
PASC considered that currently combined visualization (as described in the paragraph above) may not be widely available in pathology laboratories. PASC also considered that it would be highly unusual that there would be too small a sample of tissue to be able to perform HT to SCLC testing, and then a panel of IHC/FISH.

PASC noted the applicant's statement that histologic confirmation of NSCLC (i.e. to confirm the patient does not have SCLC) must be mandated prior to MET guided therapy. PASC considered it is important to rule out HT to SCLC before performing MET testing, as the evidence base for savolitinib in combination with osimertinib is for use in patients with NSCLC, and the proposed treatment is not TGA registered for the treatment of SCLC.

PASC considered the same biopsy used to test for transformation to SCLC could be used for MET evaluation and stated the proposed treatment algorithm could be simplified. PASC considered patients would no longer need to be selected for testing for HT to SCLC, as this possibility can be excluded by pathologists on all patients prior to testing for MET alteration. After biopsy, only patients who have histologic confirmation of NSCLC will proceed to MET testing. These changes have been reflected in the revised future treatment algorithm, however, PASC considered that this algorithm remains subject to change pending further evidence (as noted in the intervention section).

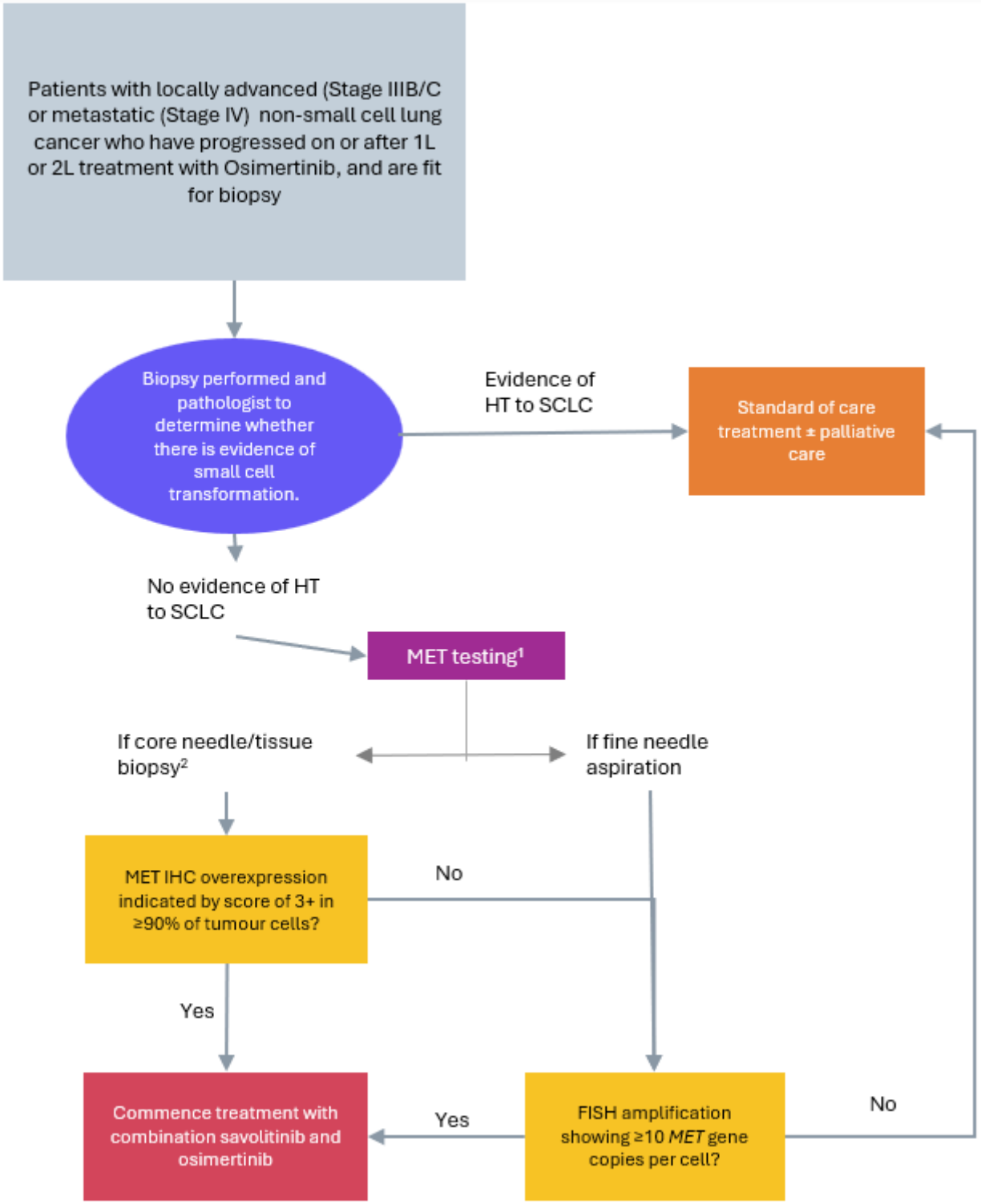
PASC noted the applicant's comment that if only cytology/FNA is available, analysis of cell block material may be performed. PASC also noted liquid biopsy samples are not recommended for assessing MET overexpression/amplification (unlike their potential utility in identifying a specific mutation). PASC considered that use of archival tissue samples may not be appropriate in this setting, as the genetic alterations being tested for are primarily developed in response to TKI treatments, and unlikely to be present in archival tissue which predates osimertinib treatment. PASC considered that if only FNA is possible, then IHC testing should be skipped and samples should proceed directly to FISH testing (as discussed in the intervention section).

Figure 5 Current clinical algorithm



Source: Developed during evaluation
1L = first line; 2L = second line; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer.
‡ This test is primarily a hematoxylin and eosin (H&E) stain, however a small percentage may be equivocal and require a separate IHC test to determine NSCLC or SCLC status.

Figure 6 PASC revised future treatment algorithm



Source: Developed during evaluation, modified to reflect PASC outcomes.
1L = first line; 2L = second line; FISH = fluorescence in situ hybridisation; IHC = immunohistochemistry; MET = mesenchymal-epithelial transition protein or MET gene; NSCLC = non-small cell lung cancer; SCLC = small-cell lung cancer.
Yellow boxes = proposed tests; red box = proposed treatment

[1] Individuals who have undergone biopsy for HT to SCLC testing will not need a repeat biopsy for MET testing, as the same sample that was used for HT to SCLC testing can also be used for MET testing.
[2] Core/needle tissue biopsy preferred.

Proposed economic evaluation

The applicant claimed the proposed codependent technology (MET overexpression/amplification testing and treatment with savolitinib plus osimertinib) is 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). It is unlikely that performing an invasive tumour biopsy is superior to not performing any biopsy in terms of safety, and it is unclear whether the safety profile of savolitinib plus osimertinib as superior safety compared to platinum-based doublet chemotherapy, pending safety outcomes from the key SAFFRON trial.

Based on the applicant's proposed clinical claim of superior effectiveness and safety, a cost-effectiveness analysis (CEA)/cost-utility analysis (CUA) would be the appropriate type of economic evaluation. Table 9 provides a guide for determining which type of economic evaluation is appropriate.

In the event that the proposed codependent technology is superior in terms of clinical effectiveness but inferior in terms of safety, the applicant may wish to perform a CEA/CUA noting the effect of inferior safety.

Table 9 Classification of comparative effectiveness and safety of the proposed intervention, compared with its main comparator, and guide to the suitable type of economic evaluation

Comparative safety	Comparative effectiveness			
	Inferior	Uncertain[a]	Noninferior[b]	Superior
Inferior	Health forgone: need other supportive factors	Health forgone possible: need other supportive factors	Health forgone: need other supportive factors	? Likely CUA
Uncertain[a]	Health forgone possible: need other supportive factors	?	?	? Likely CEA/CUA
Noninferior[b]	Health forgone: need other supportive factors	?	CMA	CEA/CUA
Superior	? Likely CUA	? Likely CEA/CUA	CEA/CUA	CEA/CUA

CEA=cost-effectiveness analysis; CMA=cost-minimisation analysis; CUA=cost-utility analysis
? = reflect uncertainties and any identified health trade-offs in the economic evaluation, as a minimum in a cost-consequences analysis
[a] 'Uncertainty' covers concepts such as inadequate minimisation of important sources of bias, lack of statistical significance in an underpowered trial, detecting clinically unimportant therapeutic differences, inconsistent results across trials, and trade-offs within the comparative effectiveness and/or the comparative safety considerations
[b] An adequate assessment of 'noninferiority' is the preferred basis for demonstrating equivalence

A preliminary search yielded three relevant studies investigating the clinical effectiveness of the proposed codependent technology: SAVANNAH (Phase 2), SACHI (Phase 3) and SAFFRON (Phase 3). The applicant's clinical claim was primarily based on the SAVANNAH study. However, the study investigated the efficacy and safety of savolitinib plus osimertinib versus savolitinib plus placebo which is not the proposed comparator (platinum-based doublet chemotherapy). The SACHI study demonstrated savolitinib plus osimertinib significantly improved median PFS (8.2 months vs 4.5 months, p<0.0001) versus chemotherapy in the proposed population, however the median OS was not significantly different (22.9 months vs 17.7 months, p=0.4191); this may be due to 52.4% of patients in the chemotherapy group were crossed over to receive savolitinib plus osimertinib or other MET inhibitors. The applicant stated comparative evidence will be provided by SAFFRON, a confirmatory Phase 3 study evaluating the efficacy and safety of savolitinib in combination with osimertinib versus platinum-based chemotherapy in patients with EGFR-mutated, MET-overexpressed, and/or amplified advanced NSCLC following progression on first- or second-line

osimertinib. Given the nature of all three studies, results from SAFFRON would be most appropriate to inform the clinical claim. At the time of preparation of PICO document, results from the SAFFRON study were not available. Therefore, the comparative effectiveness and safety of the proposed codependent technology remain uncertain at this time.

PASC noted that based on the applicant's proposed clinical claim of superior effectiveness and safety, a cost-effectiveness analysis (CEA)/cost-utility analysis (CUA) would be the appropriate economic evaluation but that the outcomes of the SAFFRON trial are awaited as evidence to justify this proposed clinical claim.

Proposal for public funding

Currently there are no existing MBS items specifically for MET testing. There are generic IHC items that could already accommodate IHC testing for MET. The applicant proposed two new MBS items for IHC and FISH testing respectively.

As per the proposed population, patients with locally advanced or metastatic NSCLC who have progressed on or after osimertinib treatment, with MET overexpression and/or amplification are eligible for treatment with savolitinib in combination with osimertinib. The wording in the applicant's originally proposed item descriptors did not include "progression on or after osimertinib".

PASC considered that a number of changes should be made to the applicant's proposed descriptor. These included:

- *The test for tumour tissue must specify 'A test of tumour tissue derived from a new sample', as PASC considered the use of archival tissue is inappropriate in this setting, where most MET genetic variants manifest after treatment with osimertinib.*
- *FISH on FNA samples needs to be included as a potential testing option for patients where optimal tissue collection for IHC cannot be performed.*
- *Minor grammatical changes.*

PASC noted the concerns expressed in the consultation feedback by the RCPA around the varying definitions of the IHC threshold (negative, non-3+, 2+ or less) and considered that the IHC threshold should be described in a standardised manner, and based on the available evidence to be presented in the ADAR on threshold cut offs.

PASC noted the item descriptor for FISH should include the possibility of direct FISH testing without the need for IHC (if IHC testing is not technically feasible e.g. on cytology cell block preparations). PASC noted that the proposed item descriptors specified that the test was "… to determine eligibility for savolitinib in combination with osimertinib under the Pharmaceutical Benefits Scheme (PBS)". PASC considered that this wording should be amended to allow the item descriptor to be drug agnostic.

PASC considered that there was a low risk of leakage, and therefore a frequency restriction was not required.

The proposed item descriptors with amendments by the Department, assessment group and PASC are presented in Table 10 and Table 11.

The proposed fee for IHC and FISH testing are $76.30 and $400.00 respectively. These fees are consistent with the current IHC listing for PD-L1 and other FISH testing in SCLC.

Table 10 Proposed item descriptor for IHC

Category 6 – PATHOLOGY SERVICES - P5 - Tissue Pathology
MBS item *XXXX ~~Immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using the mesenchymal-epithelial transition (MET) antibody of tumour material~~ A test of tumour tissue **derived from a new sample** 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~~ who **has** ~~have~~ progressed on or after osimertinib treatment requested by, or on behalf of, a specialist or consultant physician, if the test is: (a) using immunohistochemical examination of biopsy material by immunoperoxidase or other labelled antibody techniques using ~~**the** mesenchymal epithelial~~ **a** mesenchymal-epithelial transition (MET) antibody **on** tumour material; and (b) for MET gene expression status; and (c) to determine eligibility for a relevant treatment ~~access to savolitinib in combination with osimertinib as listed~~ under the Pharmaceutical Benefits Scheme (PBS) ~~are fulfilled~~.
Fee: $76.30 Benefit: 75% = $57.25 85% = $64.90

Source: Table 1, p 9 of the application. Departmental changes to the descriptor are in red. Assessment group changes to the descriptor are in blue. ***PASC changes to the descriptor are in bold****.*

Table 11 Proposed item descriptor for FISH

Category 6 – PATHOLOGY SERVICES – P7 - Genetics
MBS item *XXXX Fluorescence in situ hybridisation (FISH) test of tumour tissue **derived from a new sample** from a patient diagnosed with recurrent epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer who **has** progressed on or after osimertinib treatment ~~and with documented evidence of mesenchymal-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~~, if the test is: **(a)** ~~to determine if requirements relating to~~ for a patient with documented evidence of ~~mesenchymal epithelial~~ mesenchymal-epithelial transition (MET) expression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or less; **or if MET assessment is technically not possible; and** (b) for MET gene amplification status; and (c) to determine eligibility for a relevant treatment ~~access to savolitinib in combination with osimertinib as listed~~ under the Pharmaceutical Benefits Scheme (PBS) ~~are fulfilled~~.
Fee: $400.00 Benefit: 75% = $300 85% = $340

Source: Table 2, p 10 of the application. *Departmental changes to the descriptor are in red. Assessment group changes to the descriptor are in blue.* ***PASC changes to the descriptor are in bold****.*

A letter from the Peter MacCallum Cancer Centre dated 16 September 2025 suggested that notification for MET IHC and FISH testing has been submitted to NATA to be included in their scope, and the quoted costs to provide MET testing were listed as:

IHC: $REDACTED
FISH: $REDACTED

The quote for MET IHC testing is substantially higher than the applicant proposed MBS item ($REDACTED vs $74.50 respectively), and MET FISH testing is slightly lower than the proposed MBS item ($REDACTED vs $400.00 respectively). The applicant also claimed they are not anticipating any out-of-pocket expenditures

due to MET IHC and FISH testing. Therefore, it is not clear who will be responsible for covering any potential shortfall in fees.

PASC considered that histological examination to exclude transformation to SCLC should be performed prior to MET testing and transformed cases should not proceed to MET testing. This examination may require use of additional immunohistochemical stains. PASC considered whether initiating MET testing on samples that are confirmed to be NSCLC should be pathologist determinable, advising that justification and clinical evidence will be required in the ADAR. PASC noted that the FISH test could be pathologist-determinable, rather than require the clinical team to specify the additional FISH test, if the IHC test is negative. The applicant stated that with pathologist education, it may be reasonable to allow pathologists to order the FISH test rather than having the clinical team submit the request. However, PASC considered further evidence would be required on this issue to inform decision-making.

PASC acknowledged that the applicant's proposed fees align with current MBS fees for IHC and FISH and noted variation exists in fees charged for MET testing across laboratories.

PASC noted the applicant's proposed fee of $74.50 for IHC testing, noting concerns that the fee may be considered low for a complex IHC item, the viability of testing in laboratories due to low utilisation and high service costs, and the potential impact for patients regarding out-of-pocket costs. PASC noted consultation feedback from Public Pathology Australia which stated that a fee of $112 for the IHC test would be more appropriate. PASC considered the fee for the MBS item for IHC testing should be $112.

For the MBS item for FISH testing, PASC considered $400 as an appropriate fee. PASC considered that further justification is required for any proposed changes to the fee.

PASC noted that there may be future applications also requiring analysis of MET amplification (e.g. gastric cancer) and queried if generic IHC items based on complexity may future-proof the item.

Summary of public consultation input

PASC noted and welcomed consultation input from 10 organisations and no individuals. The 10 organisations that submitted input were (list in dot points):

- Royal College of Pathologists of Australasia (RCPA)
- Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP)
- Public Pathology Australia (PPA)
- Thoracic Oncology Group of Australasia (TOGA)
- Rare Cancers Australia (RCA)
- Lung Foundation Australia (LFA)
- Australian Pathology (AP)
- Pathology Technology Australia (PTA)
- Human Genetics Society of Australasia (HGSA)
- Omico

Consultation input was supportive of public funding for testing for MET overexpression and amplification in patients with locally advanced or metastatic NSCLC to determine eligibility for treatment with PBS subsidised savolitinib in combination with osimertinib.

Consumer Experience

Consumer and patient advocacy organisations highlighted the significant social, emotional, and financial burdens faced by patients with advanced NSCLC and their families. Out-of-pocket costs for treatment, travel, and medical care can be substantial, and the disease often impacts patients' ability to work and participate in daily life.

There was strong support for public funding of MET testing to enable access to targeted therapies, which are seen as offering hope, improved prognosis, and better quality of life. Equity of access was a key concern, with stakeholders emphasising the need to remove financial barriers and ensure all eligible patients, regardless of location or socioeconomic status, can benefit from advanced diagnostics and treatments.

Benefits and Disadvantages

The main benefits of public funding for MET testing included enabling access to targeted therapies that may improve clinical outcomes, extend survival, and enhance quality of life, including by allowing patients to avoid or delay chemotherapy and its associated side effects. Public funding was seen as essential for ensuring equitable access to testing and therapies, regardless of a patient's financial situation or geographic location.

The main disadvantage from the consultation input was the proposed tissue biopsy, with RCA noting that by this point patients will have already had a biopsy to determine *EGFR* variant status prior to first line treatment. RCA recommended ensuring that patients are informed and aware of the clinical reasoning for tissue biopsies by their clinicians at first-line treatment, not at the point where resistance starts to develop.

Population, Comparator (current management), and Delivery

Consultation input largely agreed with the proposed population—patients with locally advanced or metastatic NSCLC who have progressed on or after osimertinib. However, TOGA recommended that eligibility be broadened to include patients who have received osimertinib in combination with chemotherapy (not just as monotherapy), as well as patients with other oncogenic driver mutations (such as variants in the *ALK*, *ROS1*, and *KRAS* genes) due to the emerging evidence that MET amplification and overexpression represent important resistance mechanisms in these subgroups as well. TOGA stated that inclusion of these patient groups would help address a significant unmet need in Australia, as similar to those with EGFR-mutated NSCLC who progress after first-line therapy, these patients currently have limited or no effective treatment options beyond chemotherapy.

Stakeholders generally agreed that the appropriate comparator is no MET testing, with patients managed by platinum-based doublet chemotherapy, reflecting current standard of care in the absence of targeted testing and therapy.

Some stakeholders raised concerns about the reliability and appropriateness of different testing methodologies. While the proposed pathway is IHC followed by FISH testing if IHC is negative, several organisations noted that IHC may be unreliable for detecting MET overexpression, and that FISH, although considered a gold standard for gene amplification, may be superseded by NGS in some settings. Specifically, the HGSA advocated for the use of NGS panels, which can assess *MET* amplification alongside other resistance mechanisms, and suggested that new standalone IHC or FISH items may duplicate services already available through established NGS-based workflows. HGSA stated that the current RCPA best practice guidelines for lung cancer biomarker testing recommend the use of multi-gene NGS panels for comprehensive assessment of resistance mutations in NSCLC. Additionally, PTA raised that NGS is most

appropriate in newly diagnosed advanced NSCLC whereas FISH and IHC are preferred in confirmatory and recurrent settings.

PTA also stated that NGS copy number alterations (CNA) is a potential alternative methodology, however, reiterate the significant amount of time and resources that would be needed to be invested in determining local validation, clear cut-offs, and lab specific validation processes including appropriate external quality assurance (EQA). Without this infrastructure, they believe that FISH will remain the orthogonal standard.

Equity of access to tissue biopsy and testing, especially for patients in rural and remote areas, was also noted as a key consideration for implementation.

MBS Item Descriptor and Fee

The consultation input ranged from agreeing to expressing concerns with the proposed service descriptor, with the HGSA disagreeing with the creation of MBS items specifying IHC and FISH methods. Most feedback supported the intent of the proposed MBS items for MET IHC and FISH testing, recognising their alignment with the clinical need for targeted therapy eligibility. There were also calls for clear and consistent definitions in the item descriptors to avoid confusion regarding eligibility criteria and testing thresholds for MET positivity.

Regarding the proposed fee, PPA raised concerns that the proposed IHC fee ($74.50) may be too low to cover the costs of providing the service, given the complexity and quality assurance requirements.

Additional Comments

The importance of ongoing review of testing methodologies as new evidence and technologies emerged was highlighted, particularly less invasive (than tissue biopsy) techniques of determining MET protein overexpression.

PASC noted that the majority of inputs were supportive of the testing. PASC noted multiple issues had been raised throughout the input including concerns regarding the need for a repeat tissue biopsy, patient population and reliability of the proposed testing methodologies. PASC noted that PTA stated that NGS CNA may be a potential alternative to FISH testing, however stated that IHC and Fish testing was the preferred option for assessing protein overexpression. As discussed in the Intervention section, PASC did not consider NGS to be a potential alternative. PASC also noted a number of organisations had commented on the potential fees of the proposed items. PASC considered this input during discussion around the potential fee for the items, and this is reflected in the Proposal for public funding section.

Next steps

The results from the SAFFRON trial are pending, which will inform the timeline for the ADAR submission.

Applicant Comments on Ratified PICO

The results from SAFFRON are expected in Q3 2026.

References

Ahn, M. j, F. De Marinis, L. Bonanno, B. C. Cho, T. M. Kim, S. Cheng, S. Novello, C. Proto, S. W. Kim, J. S. Lee, G. Metro, J. C. Yang, W. Xu, R. Hartmaier, A. Telaranta-Keerie, L. Poole, and L. Sequist. 2022. 'EP08.02-140 MET Biomarker-based Preliminary Efficacy Analysis in SAVANNAH: savolitinib+osimertinib in EGFRm NSCLC Post-Osimertinib', *Journal of Thoracic Oncology*, 17: S469–S70.

Ahn, M. J., B. C. Cho, X. Ou, A. Walding, A. W. Dymond, S. Ren, M. Cantarini, and P. A. Jänne. 2022. 'Osimertinib Plus Durvalumab in Patients With EGFR-Mutated, Advanced NSCLC: A Phase 1b, Open-Label, Multicenter Trial', *J Thorac Oncol*, 17: 718–23.

Arriola, Edurne, David Casadevall, Javier Gimeno, Sergi Clave, Alvaro Taus, Marta Lorenzo, Silvia Menendez, Joan Albanell, Blanca Espinet, and Marta Salido. 2014. 'Met heterogeneity evaluation by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) in nonsquamous non-small cell lung cancer (nsNSCLC)', *Journal of Clinical Oncology*, 32: 11005–05.

Australian Institute of Health and Welfare. 2025. 'Cancer data in Australia'. https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/about.

Cancer Council Australia. 2022. 'Understanding Lung Cancer'. https://www.cancer.org.au/cancer-information/types-of-cancer/lung-cancer.

Coleman, N., L. Hong, J. Zhang, J. Heymach, D. Hong, and X. Le. 2021. 'Beyond epidermal growth factor receptor: MET amplification as a general resistance driver to targeted therapy in oncogene-driven non-small-cell lung cancer', *ESMO Open*, 6: 100319.

Cooper, Wendy A., Benhur Amanuel, Caroline Cooper, Stephen B. Fox, Jon W. A. Graftdyk, Peter Jessup, Sonja Klebe, Wei-Sen Lam, Trishe Y. M. Leong, Zarnie Lwin, Rachel Roberts-Thomson, Benjamin J. Solomon, Rebecca Y. Tay, Rebecca Trowman, Janney L. Wale, and Nick Pavlakis. 2025. 'Molecular testing of lung cancer in Australia: consensus best practice recommendations from the Royal College of Pathologists of Australasia in collaboration with the Thoracic Oncology Group of Australasia', *Pathology*, 57: 425–36.

de Marinis, F., T. M. Kim, L. Bonanno, S. Cheng, S. W. Kim, M. Tiseo, Q. Chu, C. Proto, A. Sacher, Y. H. Luo, S. Novello, D. Hao, C. Baik, L. Bazhenova, J. S. Lee, B. C. Cho, J. Cadranel, T. B. Diep, G. Metro, P. Narayanan, Y. Yoneshima, J. de Castro Carpeño, C. Baldotto, C. Nyhus, J. C. Yang, L. V. Sequist, B. Levy, R. Hartmaier, I. Igwegbe, L. Poole, W. Xu, and M. J. Ahn. 2025. 'Savolitinib plus osimertinib in epidermal growth factor receptor (EGFR)-mutated advanced non-small cell lung cancer with MET overexpression and/or amplification following disease progression on osimertinib: primary results from the phase II SAVANNAH study', *Ann Oncol*, 36: 920–33.

Feldt, S. L., and C. M. Bestvina. 2023. 'The Role of MET in Resistance to EGFR Inhibition in NSCLC: A Review of Mechanisms and Treatment Implications', *Cancers (Basel)*, 15.

Fujimoto, Daichi, Hiroaki Akamatsu, Takeshi Morimoto, Kazushige Wakuda, Yuki Sato, Yoshitaka Kawa, Toshihide Yokoyama, Motohiro Tamiya, Ryota Hiraoka, Naoki Shingu, Hideki Ikeda, Akihiro Tamiya, Masaki Kanazu, Eisaku Miyauchi, Satoru Miura, Masaaki Yanai, Makiko Yomota, Ryotaro Morinaga, Takashi Yokoi, Akito Hata, Hidekazu Suzuki, Hirotaka Matsumoto, Shinya Sakata, Naoki Furuya, Yuhei Harutani, Ichiro Nakachi, Ayumu Otsuki, Shinya Uematsu, Satoshi Hara, Keiki Yokoo, Takeya Sugimoto, and Nobuyuki Yamamoto. 2022. 'Histologic transformation of epidermal growth factor receptor–mutated lung cancer', *European Journal of Cancer*, 166: 41–50.

Goldman, S. L., M. MacKay, E. Afshinnekoo, A. M. Melnick, S. Wu, and C. E. Mason. 2019. 'The Impact of Heterogeneity on Single-Cell Sequencing', *Front Genet*, 10: 8.

Gomatou, G., N. Syrigos, and E. Kotteas. 2023. 'Osimertinib Resistance: Molecular Mechanisms and Emerging Treatment Options', *Cancers (Basel)*, 15.

Guirado, M., E. Fernández Martín, A. Fernández Villar, A. Navarro Martín, and A. Sánchez-Hernández. 2022. 'Clinical impact of delays in the management of lung cancer patients in the last decade: systematic review', *Clin Transl Oncol*, 24: 1549–68.

Guo, R., L. D. Berry, D. L. Aisner, J. Sheren, T. Boyle, P. A. Bunn, Jr., B. E. Johnson, D. J. Kwiatkowski, A. Drilon, L. M. Sholl, and M. G. Kris. 2019. 'MET IHC Is a Poor Screen for MET Amplification or MET Exon 14 Mutations in Lung Adenocarcinomas: Data from a Tri-Institutional Cohort of the Lung Cancer Mutation Consortium', *J Thorac Oncol*, 14: 1666–71.

Han, Y., Y. Yu, D. Miao, M. Zhou, J. Zhao, Z. Shao, R. Jin, X. Le, W. Li, and Y. Xia. 2024. 'Targeting MET in NSCLC: An Ever-Expanding Territory', *JTO Clin Res Rep*, 5: 100630.

Hendriks, L. E., K. M. Kerr, J. Menis, T. S. Mok, U. Nestle, A. Passaro, S. Peters, D. Planchard, E. F. Smit, B. J. Solomon, G. Veronesi, and M. Reck. 2023. 'Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up[☆]', *Annals of Oncology*, 34: 339–57.

Imai, Hisao, Kyoichi Kaira, Keita Mori, Mie Kotake, Masumi Mitani, Naoko Kawashima, Takeshi Hisada, and Koichi Minato. 2019. 'Post-progression survival is highly linked to overall survival in patients with non-small-cell lung cancer harboring sensitive EGFR mutations treated with first-line epidermal growth factor receptor-tyrosine kinase inhibitors', *Thoracic Cancer*, 10: 2200–08.

John, Alexius, Thanika Ketpueak, Suzanne MacMahon, Marianne Wall, Lina Yuan, Nadza Tokaca, Jaishree Bhosle, Anna Minchom, Michael Davidson, Mary O'Brien, David McMahon, Maria Rodriguez Nevado, and Sanjay Popat. 2024. '7 Concordance of MET amplification detection between FISH and NGS in NSCLC', *Lung Cancer*, 190: 107568.

Kim, R. H., A. Lapuk, J. Harraway, E. Lee, M. Walsh, E. Topkas, V. Jones, J. Burn, T. Baillie, C. Lim, K. Nejad, A. Muljono, E. Gagne, M. K. McConechy, Y. Zein, F. Maclean, A. J. Gill, and A. C. Vargas. 2020. 'Prevalence of the EGFR T790M and other resistance mutations in the Australian population and histopathological correlation in a small subset of cases', *Pathology*, 52: 410–20.

Kim, Y. H., Y. Song, J. K. Kim, T. M. Kim, H. W. Sim, H. L. Kim, H. Jang, Y. W. Kim, and K. M. Hong. 2019. 'False-negative errors in next-generation sequencing contribute substantially to inconsistency of mutation databases', *PLoS One*, 14: e0222535.

Kumaki, Y., G. Oda, and S. Ikeda. 2023. 'Targeting MET Amplification: Opportunities and Obstacles in Therapeutic Approaches', *Cancers (Basel)*, 15.

Lai, G. G. Y., T. H. Lim, J. Lim, P. J. R. Liew, X. L. Kwang, R. Nahar, Z. W. Aung, A. Takano, Y. Y. Lee, D. P. X. Lau, G. S. Tan, S. H. Tan, W. L. Tan, M. K. Ang, C. K. Toh, B. S. Tan, A. Devanand, C. W. Too, A. Gogna, B. H. Ong, T. P. T. Koh, R. Kanesvaran, Q. S. Ng, A. Jain, T. Rajasekaran, J. Yuan, T. K. H. Lim, A. S. T. Lim, A. M. Hillmer, W. T. Lim, N. G. Iyer, W. L. Tam, W. Zhai, E. H. Tan, and D. S. W. Tan. 2019. 'Clonal MET Amplification as a Determinant of Tyrosine Kinase Inhibitor Resistance in Epidermal Growth Factor Receptor-Mutant Non-Small-Cell Lung Cancer', *J Clin Oncol*, 37: 876–84.

Leonetti, A., S. Sharma, R. Minari, P. Perego, E. Giovannetti, and M. Tiseo. 2019. 'Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer', *Br J Cancer*, 121: 725–37.

Lin, X., Q. Zheng, W. Qi, J. Li, Y. Wang, W. Wang, and Z. Liang. 2023. 'P1.22-11 Comparison of NGS and FISH Platforms to Test MET Amplification in Chinese Lung Cancer Patients: A Prospective Study', *Journal of Thoracic Oncology*, 18: S249.

Liu, Shiyi, Tao Xu, Xiaojing Cao, Hecheng Li, and Runsen Jin. 2025. 'Histological transformation in lung cancer: Mechanisms, clinical characteristics, and therapeutic approaches', *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1880: 189413.

Modi, P., and A. Uppe. 2025. 'Lung Biopsy Techniques and Clinical Significance.' in, *StatPearls* (StatPearls Publishing

Morrison, Larry E., Tania M. Larrinaga, Brian D. Kelly, Mark R. Lefever, Rachel C. Beck, and Daniel R. Bauer. 2025. 'Concurrent Viewing of H&E and Multiplex Immunohistochemistry in Clinical Specimens', *Diagnostics*, 15: 164.

National Comprehensive Cancer Network. 2025. 'Guidelines for Non-Small Cell Lung Cancer'. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.

Ngo, P., D. Karikios, D. Goldsbury, S. Wade, Z. Lwin, B. G. M. Hughes, K. M. Fong, K. Canfell, and M. Weber. 2023. 'Development and Validation of txSim: A Model of Advanced Lung Cancer Treatment in Australia', *Pharmacoeconomics*, 41: 1525–37.

Offin, M., J. M. Chan, M. Tenet, H. A. Rizvi, R. Shen, G. J. Riely, N. Rekhtman, Y. Daneshbod, A. Quintanal-Villalonga, A. Penson, M. D. Hellmann, M. E. Arcila, M. Ladanyi, D. Pe'er, M. G. Kris, C. M. Rudin, and H. A. Yu. 2019. 'Concurrent RB1 and TP53 Alterations Define a Subset of EGFR-Mutant Lung Cancers at risk for Histologic Transformation and Inferior Clinical Outcomes', *J Thorac Oncol*, 14: 1784–93.

Oh, M. S., J. Abascal, A. K. Rennels, R. Salehi-Rad, S. M. Dubinett, and B. Liu. 2025. 'Tumor Heterogeneity and the Immune Response in Non-Small Cell Lung Cancer: Emerging Insights and Implications for Immunotherapy', *Cancers (Basel)*, 17.

Peng, L., A. Li, S. Liu, H. Sun, M. Zheng, J. Zhou, J. Zhang, X. Zhang, Q. Zhou, W. Zhong, X. Yang, H. Tu, J. Su, H. Yan, L. Gou, H. Gao, and Y. Wu. 2021. 'P85.02 NGS could not Replace FISH Regarding to MET Amplification as an Optimal Biomarker', *Journal of Thoracic Oncology*, 16: S669.

Peng, L. X., G. L. Jie, A. N. Li, S. Y. Liu, H. Sun, M. M. Zheng, J. Y. Zhou, J. T. Zhang, X. C. Zhang, Q. Zhou, W. Z. Zhong, J. J. Yang, H. Y. Tu, J. Su, H. H. Yan, and Y. L. Wu. 2021. 'MET amplification identified by next-generation sequencing and its clinical relevance for MET inhibitors', *Exp Hematol Oncol*, 10: 52.

Peters, M. J., J. J. Bowden, P. Carpenter, J. Lewis, and B. Solomon. 2014. 'Outcomes of an Australian testing programme for epidermal growth factor receptor mutations in non-small cell lung cancer', *Internal Medicine Journal*, 44: 575–80.

Pharmaceutical Benefits Advisory Committee. 2019. 'Osimertinib Public Summary Document, July 2019 PBAC Meeting'. https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2019-07/files/osimertinib-psd-july-2019.pdf

Piper-Vallillo, A. J., L. V. Sequist, and Z. Piotrowska. 2020. 'Emerging Treatment Paradigms for EGFR-Mutant Lung Cancers Progressing on Osimertinib: A Review', *J Clin Oncol*: Jco1903123.

Schubart, Christoph, Robert Stöhr, Lars Tögel, Florian Fuchs, Horia Sirbu, Gerhard Seitz, Ruth Seggewiss-Bernhardt, Rumo Leistner, William Sterlacci, Michael Vieth, Christoph Seidl, Michael Mugler, Markus Kapp, Wolfgang Hohenforst-Schmidt, Arndt Hartmann, Florian Haller, and Ramona Erber. 2021. 'MET Amplification in Non-Small Cell Lung Cancer (NSCLC)—A Consecutive Evaluation Using Next-Generation Sequencing (NGS) in a Real-World Setting', *Cancers*, 13: 5023.

Solomon, J. P., S. R. Yang, N. J. Choudhury, R. N. Ptashkin, N. Eslamdoost, C. J. Falcon, A. Martin, A. Plodkowski, C. Wilhelm, R. Shen, M. Ladanyi, M. Berger, Y. Zhang, A. Drilon, and M. E. Arcila. 2022. 'Bioinformatically Expanded Next-Generation Sequencing Analysis Optimizes Identification of Therapeutically Relevant MET Copy Number Alterations in >50,000 Tumors', *Clin Cancer Res*, 28: 4649–59.

Song, Z., and Y. Zhang. 2016. 'Treatment and prognosis after progression in long-term responders to EGFR-tyrosine kinase inhibitor in advanced non-small cell lung cancer', *Arch Med Sci*, 12: 107–11.

Wang, Y., Y. Zhang, N. Ren, F. Li, L. Lu, X. Zhao, Z. Zhou, M. Gao, and M. Wang. 2024. 'Repeat biopsy versus initial biopsy in terms of complication risk factors and clinical outcomes for patients with non-small

cell lung cancer: a comparative study of 113 CT-guided needle biopsy of lung lesions', *Front Oncol*, 14: 1367603.

Xiang, C., X. Lv, K. Chen, L. Guo, R. Zhao, H. Teng, M. Ye, T. Kuang, T. Hou, C. Liu, H. Du, Z. Zhang, and Y. Han. 2024. 'Unraveling the Significance of MET Focal Amplification in Lung Cancer: Integrative NGS, FISH, and IHC Investigation', *Mod Pathol*, 37: 100451.

Yang, Zane, Navin Niranjan, Tracey Guan, Robert Mason, Bryan Anthony Chan, and Jasotha Sanmugarajah. 2024. 'EGFR mutation testing trends for patients with metastatic, non-squamous non-small cell lung cancer (non-SQ NSCLC) in Queensland, Australia from 2014-2021', *Journal of Clinical Oncology*, 42: e13505–e05.

Zheng, Q., X. Lin, W. Qi, J. Yin, J. Li, Y. Wang, W. Wang, W. Li, and Z. Liang. 2024. 'NGS and FISH for MET amplification detection in EGFR TKI resistant non-small cell lung cancer (NSCLC) patients: A prospective, multicenter study in China', *Lung Cancer*, 194: 107897.

Zhou, Qing, Hongyun Zhao, Shun Lu, Ying Cheng, Ying Liu, Mingfang Zhao, Zhuang Yu, Chengping Hu, Li Zhang, Fan Yang, Jun Zhao, Renhua Guo, Rui Ma, Yingying Du, Xiaorong Dong, Jiuwei Cui, Daniel S. W. Tan, Myung-Ju Ahn, Masahiro Tsuboi, Si-Yang Maggie Liu, Tony S. Mok, and Yi-Long Wu. 2024. 'Consensus on the lung cancer management after third-generation EGFR-TKI resistance', *The Lancet Regional Health – Western Pacific*, 53.