



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application 1660 – Diagnostic testing for MET exon 14 skipping alterations in non-small cell lung cancer to determine PBS eligibility for tepotinib treatment

Applicant: Merck Healthcare

Date of MSAC consideration: 83rd MSAC Meeting, 25-26 November 2021

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

1 Purpose of application

An applicant-developed assessment report (ADAR) was received from Merck Healthcare by the Department of Health, which comprised an integrated codependent submission for:

- Medicare Benefits Schedule (MBS) listing of tumour tissue testing for the purpose of detecting MET proto-oncogene, receptor tyrosine kinase (*MET*) exon 14 skipping alterations (*MET*ex14sk) to determine eligibility for treatment with tepotinib in patients with advanced non-small cell lung cancer (aNSCLC).
- Pharmaceutical Benefits Scheme (PBS) General Schedule Authority Required (STREAMLINED) listing for treatment with tepotinib for aNSCLC in patients who have evidence of *MET*ex14sk.

2 MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of a new MBS item for *MET*ex14sk testing in patients with aNSCLC, to determine eligibility for tepotinib. MSAC advised that patients diagnosed with locally advanced or metastatic NSCLC (stage IIIB or IV) with non-squamous (NSQ) or not-otherwise-specified (NOS) histology should be eligible for this test. MSAC preferred not to support testing in patients with squamous (SQ) histology due to insufficient evidence supporting the clinical effectiveness of tepotinib in patients with SQ histology, consistency with testing for other biomarkers (*EGFR*, *ALK* and *ROS1*) and other targeted therapies in NSCLC, and the low prevalence of the *MET*ex14sk biomarker amongst patients with SQ histology. MSAC advised that the absence of these other NSCLC biomarkers need not be a pre-requisite for *MET*ex14sk testing. MSAC advised that the test should not be pathologist-determinable.

MSAC supported the following MBS item descriptor (Table 1).

Table 1 MSAC's supported MBS item for METex14sk testing

Category 6 – PATHOLOGY SERVICES Group P7 – Genetics
A test of tumour tissue from a patient diagnosed with locally advanced or metastatic 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 to determine if the requirements relating to <i>MET</i> exon 14 skipping alteration status for access to tepotinib are fulfilled under the Pharmaceutical Benefits Scheme (PBS).
Fee: \$397.35 Benefit: 85% = \$337.75

Consumer summary

This application was from Merck Healthcare, to create a Medicare Benefits Schedule (MBS) item to test tumour samples from patients who have locally advanced or metastatic non-small cell lung cancer for a particular type of genetic alteration. Patients found to have these alterations would then be eligible to access a drug called tepotinib on the Pharmaceutical Benefits Scheme (PBS).

These genetic alterations are called *MET* exon 14 skipping alterations (or *MET*ex14sk). *MET* is a proto-oncogene. This means that, if it is altered, it can make tumours grow faster. *MET*ex14sk are a specific type of genetic variation that results in a particular region of the gene (called exon 14) not being used, which changes the *MET* protein to make it more active and can result in cancer growth.

Patients with *MET*ex14sk have a worse prognosis than those without these alterations. Tepotinib is a targeted drug that can improve health outcomes in patients who have *MET*ex14sk. For patients with *MET*ex14sk, treatment with tepotinib should provide similar health outcomes to the treatment currently available.

MSAC advised that tumour testing to identify *MET*ex14sk was effective and safe.

MSAC recommended that only patients with non-squamous histology or histology not-otherwise-specified types of non-small cell lung cancer be eligible for this testing, because these patients benefit the most from testing and treatment with tepotinib, and this would be consistent with other targeted treatments for patients with non-small cell lung cancer. There are very few patients with squamous cancer that have *MET*ex14sk, and it is not clear that tepotinib would benefit this group of people. MSAC also recommended that patients should not have to first test negative for other biomarkers for targeted treatments, before having *MET*ex14sk testing.

MSAC's advice to the Commonwealth Minister for Health

MSAC recommended that a new MBS item be created for tumour testing for *MET*ex14sk in patients with locally advanced or metastatic non-small cell lung cancer, and with non-squamous or histology not-otherwise-specified, to access tepotinib on the PBS. This recommendation is based on the testing being effective and safe.

3 Summary of consideration and rationale for MSAC's advice

MSAC noted that this application from Merck Healthcare was for the creation of a new MBS item for testing of tumour samples for the presence of *MET*ex14sk in patients with NSCLC, to determine eligibility for tepotinib on the PBS.

MSAC noted the Pharmaceutical Benefits Advisory Committee (PBAC) had deferred its decision on tepotinib at its November 2021 meeting, with a mind to accept pending MSAC advice on the funding of the codependent *MET*ex14sk testing.

MSAC noted that it was becoming more common for patients with cancer to undergo molecular testing, to detect activating alterations in oncogenic driver genes and thus to treat with specific targeted therapies upfront, instead of chemotherapy. Currently, testing of epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) and c-ROS oncogene (*ROS1*) are MBS-listed for patients with NSCLC, with corresponding targeted therapies funded on the PBS.

In relation to the proposed item descriptor and fee, MSAC advised that testing should be limited to locally advanced/metastatic cancers (Stage IIIB/IV), in line with the applicant's proposal in the pre-ESC response and with the VISION trial. MSAC agreed with ESC that this item should not be pathologist-determinable, as this risks a lack of input from the treating clinician. MSAC agreed that the test fee should be \$397.35, in line with the fees for similar MBS items.

MSAC noted that the prognostic evidence from the VISION trial showed that, although not statistically significant, patients with *MET*ex14sk have worse prognoses than those without the variant. Using a matched-adjusted indirect treatment comparison (VISION trial versus KN189 trial), MSAC noted that PBAC had accepted that first-line treatment with tepotinib provided similar health outcomes to pembrolizumab in combination with chemotherapy in the proposed population of patients with Stage IIIB/IV NSCLC.

MSAC noted that of 152 patients in the VISION trial, only 16 (10.5%) had SQ histology, and the remainder had NSQ histology. MSAC noted that of the Stage IIIB/IV cases in the study, most *EGFR*, *ALK*, *ROS1* and *MET*ex14sk biomarkers were detected in patients with NSQ histology. MSAC noted that the applicant had requested funding of testing for patients irrespective of histology, in line with PBAC's proposed silence on histology for the PBS listing of tepotinib, and with the inclusion of patients with SQ histology in the VISION trial. However, MSAC considered that the trial did not provide sufficient evidence for the clinical effectiveness of tepotinib in patients with SQ histology. MSAC noted that the SQ population was not included in the PICO-defined population, nor eligible for *EGFR/ALK/ROS1* testing (Table 2). However, MSAC noted that the ADAR stated that the *MET*ex14sk frequency in patients with SQ histology is 1.6% compared with 4.4% in patients with NSQ/NOS histology. MSAC noted the lower prevalence in patients with SQ histology, and considered that excluding SQ histology would alter the cost-effectiveness of the testing. MSAC considered it appropriate for *MET*ex14sk testing to be consistent with other NSCLC biomarker testing, which is universally limited to NSQ and NOS histology. The codependent PBS restrictions are similarly limited except for osimertinib. MSAC noted that when osimertinib was originally listed as a second-line treatment, it had been implicit that the patient had met the PBS criteria for first-line treatment, which was limited to NSQ or NOS histology. MSAC considered that the inconsistency with the subsequent first-line osimertinib listing likely arose in the absence of a codependent submission because the MBS item for *EGFR* testing no longer lists individual drugs. Overall, MSAC advised PBAC that it preferred to remain consistent across testing for all tyrosine kinase inhibitors (TKIs), *ALK*, *ROS1* and *MET* inhibitor NSCLC treatments, with respect to disease stage and histology. MSAC noted that PBAC was silent with respect to histology for tepotinib access, and advised that it preferred *MET*ex14sk testing be only for patients with NSQ/NOS histology. However,

should PBAC still decide to include SQ histology, MSAC advised that the MBS item for *MET*ex14sk testing should be consistent on this aspect.

Table 2 Publicly funded targeted therapies and biomarker testing related to NSCLC

Biomarker	<i>ALK</i> rearrangement	<i>ROS1</i> rearrangement	<i>EGFR</i> activating mutation	<i>MET</i> ex14sk
Reference drug	alectinib	entrectinib	osimertinib	tepotinib
TGA indication	Locally advanced or metastatic NSCLC	Advanced NSCLC	Locally advanced or metastatic NSCLC	Locally advanced or metastatic NSCLC
MBS listing for test	Locally advanced or metastatic NSCLC Histology NSQ or NOS	Locally advanced or metastatic NSCLC Histology NSQ or NOS	NSCLC Histology NSQ or NOS	Requested: locally advanced or metastatic NSCLC Requested: histology SQ or NSQ or NOS
PBS listing for drug	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC Histology NSQ or NOS	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC Histology NSQ or NOS	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC Silent on histology (erlotinib and gefitinib remain limited to NSQ or NOS histology)	Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC PBAC proposed: silent on histology

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; locally advanced = stage IIIB; metastatic = stage IV; *MET*ex14sk = *MET* exon 14 skipping alterations; *MET* = *MET* proto-oncogene, receptor tyrosine kinase gene; NOS = histology not otherwise-specified; NSCLC = non-small cell lung cancer; NSQ = non-squamous histology; *ROS1* = c-ROS oncogene 1; SQ = squamous histology; TGA = Therapeutic Goods Administration.

Source: MSAC.

MSAC also noted that laboratories are increasingly utilising panel and parallel genetic testing, and that MSAC application 1634, for a gene panel test for patients with NSQ/NOS NSCLC, has entered the MSAC process. As such, MSAC considered that any MBS funding of a gene panel in lung cancer would be a parallel test consistently defined across cancer histology types for the minimal set of genes tested. For now, unless specified differently in an item descriptor, the timing and order of testing should be determined by the requesting clinician and pathology laboratory as deemed appropriate. Accordingly, MSAC also advised that the absence of other biomarkers (*EGFR*, *ALK* and *ROS1*) need not be a pre-requisite for *MET*ex14sk testing. MSAC considered that requiring a documented absence of other biomarkers would effectively mandate sequential testing, and advised that this was not warranted. MSAC also noted the ASPIRATION observational study evaluating the effectiveness of gene panel testing in patients with NSCLC, which may provide further information about parallel versus sequential testing for biomarkers.

MSAC noted PASC's advice that the evidentiary standard should be that used in the VISION study, and that there is no gold standard testing for *MET*ex14sk. The trial tested for *MET*ex14sk using either of two methods: testing FFPE tissue with the Oncomine Focus Assay (OFA), an off-the-shelf, hybrid DNA/RNA next-generation sequencing (NGS) 52-gene panel assay, or testing blood for circulating tumour DNA using NGS. MSAC noted analytical validity concerns for DNA- and RNA-based *MET*ex14sk testing, but considered that this requirement would form part of quality assurance, and so advised that laboratories performing this test should be NATA-accredited with a quality assurance program in place, as is a standard requirement for genetic testing. On balance, MSAC supported a method-

agnostic item descriptor to allow the requested testing to be on either a DNA or RNA or hybrid basis.

MSAC noted that patients whose testing used tissue had better overall survival (OS) than those whose testing used blood samples, and supported the requested limitation in the item descriptor for testing of tumour tissue only. MSAC also supported the applicant's pre-PBAC response acceptance of a 7% re-test rate being incorporated into the cost-minimisation approach to account for justifying the use of tissue over blood samples.

4 Background

Genetic testing for *MET*ex14sk for access to tepotinib has not previously been considered by MSAC. PASC considered the PICO Confirmation for Application 1660 at its April 2021 meeting.

A related application is Application 1634 – Comprehensive genomic profiling of non-small cell lung cancer tumour tissue specimens using next generation sequencing assays. This application was considered by PASC in April 2021, and proposes a gene panel test for NSCLC biomarkers.

5 Prerequisites to implementation of any funding advice

The ADAR stated that in-vitro diagnostic (IVD) tests are listed on the ARTG as class III medical devices. As the intervention is 'test agnostic', the applicant suggested that commercially available platforms will be able to detect *MET*ex14sk. Laboratories would also be able to develop in-house tests to test for *MET*ex14sk, and receive accreditation through the National Association of Testing Authorities (NATA). The commentary stated it is unclear if these tests are currently conducted in conjunction with an appropriate quality assurance program (QAP), and that a QAP would be required as not all *MET*ex14sk are detected by all panels, and a QAP will ensure that the panels used for testing have been designed to detect all variants leading the deletion of exon 14 in mature *MET* mRNA transcripts.

The National Pathology Accreditation Advisory Council (NPAAC) advised that the major consideration is the conduct of the molecular testing. If RNA-based testing is used, the sample must be sufficient and of good quality to allow a conclusion to be reached. If that is not the case the report must specify the need for a repeat sample to be collected. A DNA-based test is more robust but will not detect all relevant variants. The testing algorithm will need to be specified. NPAAC also advised that EQA programs, while not yet available from RCPA QAP, are offered by international providers, e.g. EMQN or NEQAS.

6 Proposal for public funding

The MBS item proposed in the ADAR is shown in Table 3.

Table 3 MBS listing proposed in the ADAR

Category 6 or 7 – Pathology or genetics service
<p>Proposed item descriptor: A test of tumour tissue from a patient diagnosed with non-small cell lung cancer with the following characteristics:</p> <p>Either:</p> <ul style="list-style-type: none">- shown to have squamous histology or;- shown to have non-squamous histology or histology not otherwise specified, and with documented absence of activating mutations of the epidermal growth factor receptor (<i>EGFR</i>) gene. <p>The test is requested by or on behalf of, a specialist or consultant physician or determinable by a pathologist, to determine:</p> <p>If the requirements relating to <i>MET</i> exon 14 skipping alteration status for access to tepotinib are fulfilled under the Pharmaceutical Benefits Scheme (PBS).</p>
Fee: \$397.35 Benefit: 85% = \$337.75

Source: Commentary, Table MSAC.1.

The ADAR stated that a test method-specific test descriptor (i.e. RNA- versus DNA-based testing) was not needed, as testing should be considered method-agnostic with reliance on NATA accreditation to consider which test would be appropriate. The commentary stated that this does not take into consideration which of the testing methods used in Australia are more concordant with the evidentiary standard (for which clinical utility has been demonstrated through its use in selecting patients for access to tepotinib).

The ADAR proposed requestors be limited to a specialist, consultant physician or determinable by a pathologist. The commentary considered this to be appropriate.

The commentary observed a discrepancy in histology between the MBS item population proposed in the ADAR from that in the PICO confirmation: the PICO confirmation limited the test population to patients with NSQ or NOS histology only, whereas the proposed MBS item descriptor in the ADAR also included patients with SQ histology. The applicant's pre-ESC response reiterated its proposal that patients with SQ histology be included too, in line with the VISION trial.

The commentary stated the population in the submission's MBS item descriptor includes patients of all stages of disease, whereas the population as described in the PICO limits the testing population to patients with confirmed locally advanced or metastatic NSCLC only. PASC noted that for *ROS-1* (MSAC Application 1454), ESC had advised that additional analyses on the cost of testing at initial diagnosis would be informative. PASC therefore recommended assessing both *MET*ex14sk testing at any time after diagnosis of NSCLC (i.e. not limited to those with locally advanced or metastatic disease), and also only testing for *MET*ex14sk in patients with locally advanced or metastatic disease. PASC recommended the applicant justify its proposed timing of testing and present the alternative testing scenario as well (1660 PICO, pg 4). The applicant responded that it "is requesting funding for *MET*ex14[sk] testing of patients independent of histology i.e., including SQ, NSQ, and NOS patients, to ensure alignment with the requested tepotinib listing following advice at the PASC and Pre-PBAC meetings." (1660 PICO, pg 20)

The ADAR stated that the MBS fee is the same as the fee for testing for *EGFR* gene status. The commentary considered this to be appropriate.

PASC queried whether there should be a frequency restriction to once per lifetime (consistent with MBS item number 73295) or once per primary tumour diagnosis (consistent with MBS

item number 73301 or 73302) in the proposed item. PASC noted that the specific criteria to be set out in the item descriptor should prevent leakage into untargeted populations.

The applicant's pre-ESC response proposed a revised MBS item descriptor, which differs from that proposed in the ADAR in that it seeks to restrict the proposed testing to patients with locally advanced or metastatic NSCLC, and also that it adds a requirement for negative *ALK* and *ROS1* biomarker tests (whether via immunohistochemistry and fluorescence *in situ* hybridisation).

7 Summary of public consultation feedback/consumer issues

PASC noted that the Royal College of Pathologists of Australasia (RCPA) expressed support for parallel testing (e.g. MSAC 1634) rather than sequential testing. PASC noted that letters of support from Rare Cancers Australia and Genomics for Life were received with the application.

Consultation feedback was also received from a specialist who currently performs diagnostic pathology testing for patients with NSCLC including *MET*ex14sk upon request. The specialist supported the proposed testing, including supporting both parallel and sequential testing in accordance with the PICO's testing algorithm. In addition, the specialist supported including the SQ population for *MET*ex14sk testing, as proposed in the ADAR.

No consumer feedback/consumer comments were received for this application.

8 Proposed intervention's place in clinical management

Lung cancer is the fifth most common cancer in Australia, with an estimated 13,604 cases in 2020.¹ The ADAR sought listing for use in all histological subtypes of NSCLC, which accounts for approximately 85% of all lung cancer cases.² *EGFR* is the most common NSCLC biomarker. *MET*ex14sk and *ALK* variants are less prevalent, and *ROS-1* is the least prevalent of these four biomarkers.

The *MET* proto-oncogene, receptor tyrosine kinase (*MET*) gene is located on chromosome 7, bands 7q21-31 and is approximately 125 kilobases long, with 21 exons. It encodes a protein receptor tyrosine kinase, which is part of the hepatocyte growth factor (HGF) receptor family, and is a critical regulator of cell growth and development. In patients with NSCLC, abnormal activation of the tyrosine-protein kinase *MET* (c-*MET*) pathway can occur through a variety of mechanisms. One of these mechanisms has been described as a *MET*ex14sk at RNA splice acceptor or donor sites, leading to alternative splicing, which results in exon 14 skipping in the subsequent mRNA, though genetic alterations outside splice sites can also cause exon 14 skipping. This leads to a shortened c-*MET* receptor lacking a juxtamembrane domain, but still has affinity for HGF. *MET*ex14sk can occur via diverse genetic aberrations involving the splice sites and other locations, resultant in in-frame skipping of the juxtamembrane domain encoding exon 14. This increases the stability of c-*MET* and consequently the induction of cell proliferation and tumour growth. *MET* abnormalities have been associated with rapid tumour growth, aggressively invasive disease, and a poor prognosis³.

¹ <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/cancer-summary-data-visualisation>

² <https://www.cancer.org.au/cancer-information/types-of-cancer/lung-cancer>

³ Salgia, R., et al. (2020). The promise of selective *MET* inhibitors in non-small cell lung cancer with *MET* exon 14 skipping. *Cancer Treat Rev*, **87**: 102022.

To test for *MET*ex14sk, RNA and/or DNA extracted from tumour tissue is analysed using commercially available platforms or laboratory-accredited in-house tests (e.g. polymerase chain reaction (PCR) or next generation sequencing (NGS)).

The ADAR proposed testing for *MET*ex14sk after *EGFR* testing and receiving a negative result (and testing for *ALK* and *ROS-1* expression via immunohistochemistry triage if no *MET*ex14sk is detected). Testing for *MET*ex14sk is proposed as an addition to the currently available tests and investigations.

The ADAR's current (Figure 1) and proposed (Figure 2) clinical management algorithms are shown below.

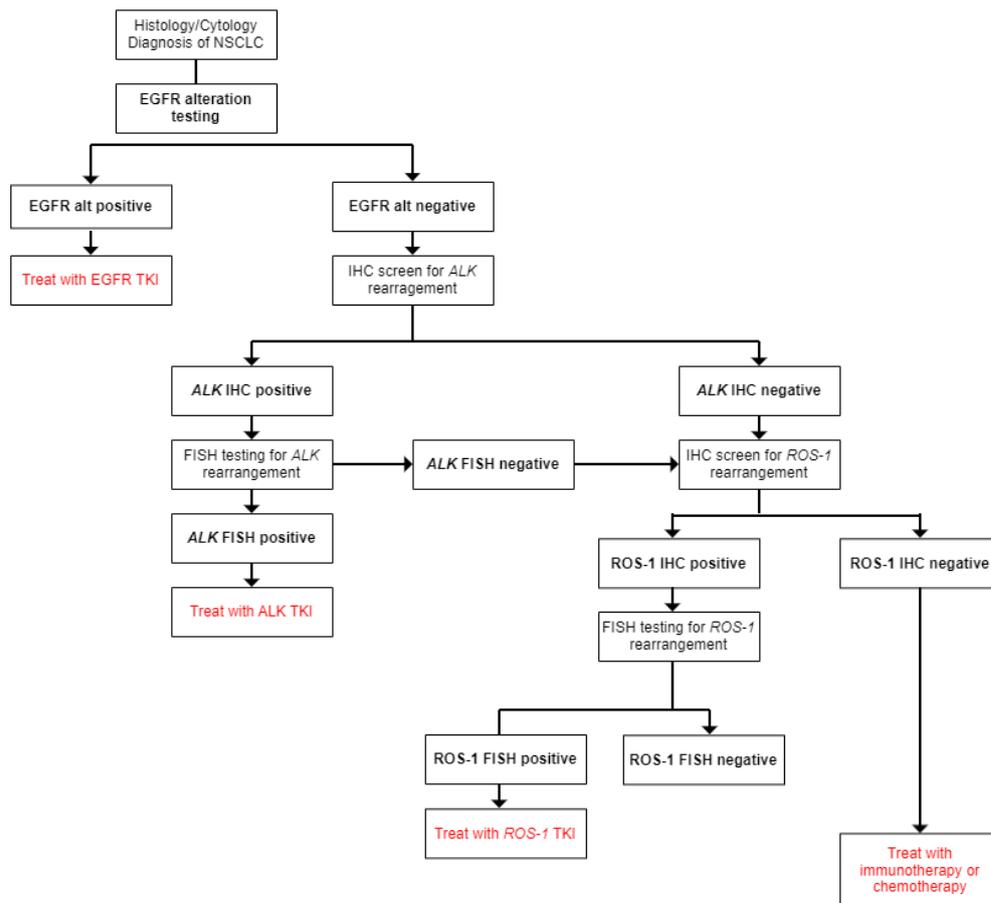


Figure 1 Current clinical management algorithm for testing and treatment for advanced NSCLC NSQ/NOS

Abbreviations: *ALK*=anaplastic lymphoma kinase; alt=alteration; *EGFR*=epidermal growth factor receptor; FISH=fluorescence *in situ* hybridisation; IHC=immunohistochemistry; NSCLC=non-small cell lung cancer; *ROS-1*=*ROS-1* receptor tyrosine kinase; TKI=tyrosine kinase inhibitor. Pembrolizumab is listed on the PBS for treatment naïve patients with metastatic NSCLC, who have no evidence of *EGFR* pathogenic variant, *ALK* gene rearrangement or a *ROS-1* gene rearrangement

Source: ADAR, Figure 1-5.

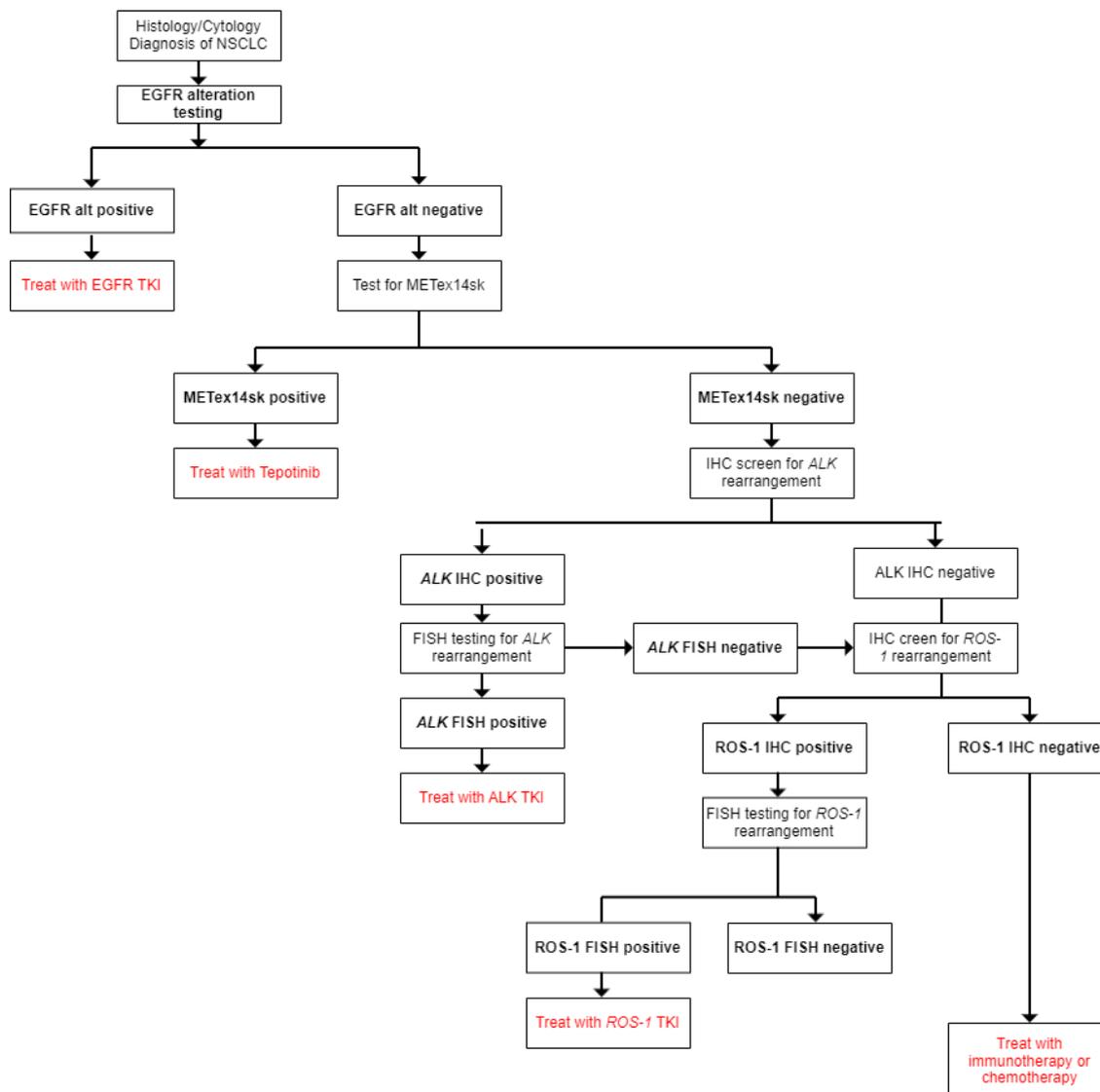


Figure 2 ADAR-proposed clinical management for testing and treatment of aNSCLC after inclusion of *METexon14sk* test for NSQ/NOS

Abbreviations: *ALK*=anaplastic lymphoma kinase; alt=alteration; *EGFR*=epidermal growth factor receptor; *FISH*=fluorescence *in situ* hybridisation; IHC=immunohistochemistry; *METex14sk*=mesenchymal-epithelial transition exon 14 skipping alteration; NSCLC=non-small cell lung cancer; *ROS-1*=ROS-1 receptor tyrosine kinase; TKI=tyrosine kinase inhibitor

Pembrolizumab is listed on the PBS for treatment naïve patients with metastatic NSCLC, who have no evidence of *EGFR* pathogenic variant, *ALK* gene rearrangement or a *ROS-1* gene rearrangement.

Source: ADAR, Figure 1-6.

The ADAR proposed that *METex14sk* testing should be done at the time of diagnosis; it did not propose restricting use of the test to those with locally advanced or metastatic disease. The commentary stated that this corresponds with the MBS item for *EGFR* testing (73337), which is also not restricted to patients with locally advanced or metastatic disease. However, it does not correspond with the population in the ADAR’s PICO, or the ADAR’s proposed financial impacts, which limited the testing population to adults (18 years or older) with confirmed locally advanced or metastatic NSCLC.

In its pre-ESC response, the applicant stated that MBS funding for the test is being sought for patients with locally advanced or metastatic disease only. The applicant also added a proposed requirement for negative *EGFR*, *ALK*, and *ROS1* biomarker test results, which would reposition this test after those three biomarkers in the clinical management algorithm.

The commentary noted that in the future, testing for *MET* exon 14 skipping may be performed as part of the comprehensive genomic profiling of NSCLC patients, as proposed in MSAC application 1634. Under the proposed item descriptor for application 1634, NSQ and NOS NSCLC patients would be eligible for comprehensive genomic profiling by NGS at the time of initial diagnosis, without restrictions based on stage of disease – replacing the proposed sequential testing algorithm with simultaneous testing. Although application 1634 is only for variants clinically actionable to be reported on for codependent medicines (currently only for the detection of *EGFR*, *ALK* and *ROS1* biomarkers), PASC noted that the applicant foreshadowed additional biomarkers could also be reported on in the near future. If *MET* is included in the comprehensive genomic profiling, its cost would be included in the NGS fee.

9 Comparator

As the proposed test is used in addition to currently available tests, the comparator is no genetic *MET* exon 14 skipping testing.

10 Comparative safety

Adverse events from testing

No safety issues were discussed in the ADAR, and no patient-relevant safety outcomes regarding the testing were specified in the PICO Confirmation. The commentary stated that no reported harms from the proposed test were identified, apart from the indirect harms produced when test results were inaccurate and led to inappropriately targeted treatment.

The commentary stated that a re-biopsy should only be necessary if insufficient tumour material is available for the *MET* exon 14 skipping test. Any procedure where the skin is penetrated carries a risk of bleeding or infection or other complications. Re-biopsy rates have previously been considered by MSAC to be around 8–12%. However, as this is lung cancer, re-biopsy is associated with a higher rate of adverse events: one study reported that 30% of patients undergoing a lung biopsy suffered at least one Patient-Safety Indicator (PSI) event during their hospitalisation⁴. The most common PSIs reported were iatrogenic pneumothorax (10.9%), postoperative respiratory failure (9.8%), secondary diabetes or acute kidney failure (5.0%), and postoperative deep vein thrombosis or pulmonary embolus (4.0%).

Adverse events from changes in management

The ADAR stated that tepotinib safety data from the VISION trial demonstrated a likely favourable adverse event profile compared to pembrolizumab + chemotherapy from the KN189 trial. The most common treatment emergent adverse event (TEAE) of Grade ≥ 3 severity associated with tepotinib was peripheral oedema, reported in 20 patients (7.8%). Other frequently reported TEAEs of Grade ≥ 3 severity were hypoalbuminaemia (14 patients; 5.5%), pleural effusion (13 patients; 5.1%), disease progression (12 patients; 4.7%), and pneumonia (11 patients; 4.3%). Compared to tepotinib, pembrolizumab + chemotherapy was associated with significantly higher rates of asthenia, diarrhoea, fatigue, neutropenia, anaemia and thrombocytopenia.

The commentary considered that the naïve comparison of tepotinib and pembrolizumab + chemotherapy supports the ADAR's claim of non-inferior safety. None of the safety data

⁴ von Itzstein, M. S., et al. (2019). Increasing Numbers and Reported Adverse Events in Patients with Lung Cancer Undergoing Inpatient Lung Biopsies: A Population-Based Analysis. *Lung*, **197**(5): 593-599.

addressed the issue of false positive and false negative *MET*ex14sk test results, and *MET*ex14sk status was unknown for the safety data from KN189.

11 Comparative effectiveness

Overview of the evidence base

The approach taken in the ADAR was to present linked evidence to support the claim that targeting of *MET* hyperactivation with tepotinib will improve patient outcomes.

Table 4 Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence identified by the commentary	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	One case-control study (level III-3) and two comparative studies (level III-2)	<input checked="" type="checkbox"/> k=3 n=387	Medium to high risk of bias
Prognostic evidence	Comparison of outcomes in patients receiving <u>usual care</u> conditioned on the presence or absence of biomarker positive status	<input checked="" type="checkbox"/> k=6 n=1,741	Medium risk of bias
Change in patient management	No evidence provided.	<input type="checkbox"/> k=0 n=0	-
Treatment effectiveness	Efficacy data from the first-line treatment subgroup in the key VISION trial, which enrolled patients with <i>MET</i> ex14sk, were indirectly compared to the pembrolizumab + chemotherapy arm of KN189, which enrolled patients who were negative for <i>EGFR</i> and <i>ALK</i> ; it is unknown how many, if any, harboured a <i>MET</i> ex14sk.	<input checked="" type="checkbox"/> k=2 n=65+410	Each trial was determined to be at a low risk of bias, however the inherent limitations of VISION, as a single-arm Phase II trial, must be acknowledged. An unanchored, match-adjusted indirect treatment comparison (MAITC) was performed.
Predictive effect (treatment effect variation)	No evidence for the predictive effect in patients with and without a <i>MET</i> ex14sk were provided.		
Treatment effect (enriched)	No single randomised controlled trial of tepotinib vs usual care in patients that are test positive in both arms was provided.	<input type="checkbox"/> k=0 n=0	
Other	An indirect treatment comparison was performed on efficacy outcomes in the VISION trial and a small South Korean study of chemotherapy in patients with a <i>MET</i> ex14sk.	<input checked="" type="checkbox"/> k=2 n=65+15	High; the low numbers of the comparator trial, combined with limited baseline characteristics, made this comparison vulnerable to confounders.

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor; k = number of studies; KN189 = Keynote 189; MAITC = match-adjusted indirect treatment comparison; *MET*ex14sk = MET proto-oncogene, receptor tyrosine kinase gene alteration that causes skipping of exon 14; k=number of studies, n=number of patients.

Source: Commentary, Table MSAC.4

The ADAR presented evidence to address parts of the analytic framework as outlined in Table 5. The evidence provided in the ADAR, in addition to the evidence identified by the commentary, is presented below. As tepotinib is targeted against *MET*ex14sk, it would be

inappropriate to administer it to a *METex14sk* negative population. The ADAR did not provide any data on the efficacy of pembrolizumab in *METex14sk* positive or negative populations, however the likely prevalence of *METex14sk* in KN189 may have been approximately 3%.

Table 5 Data availability to inform comparisons

Proposed test vs alternative test	DNA-NGS vs Hybrid DNA/RNA NGS: 1 case-control study Sanger sequencing vs Hybrid DNA/RNA NGS: 1 case-control and 1 comparative study qRT-PCR vs Hybrid DNA/RNA NGS: 1 case-control and 1 comparative study ArcherDX RNA NGS vs Hybrid DNA/RNA NGS: 1 case-control study DNA-NGS vs RNA-NGS: 1 comparative study	
	Tepotinib	Pembrolizumab + chemotherapy
Biomarker test positive	VISION trial	NA
Biomarker test negative	NA	NA
Unselected	NA	Keynote189 ITT population, where approximately 3% may have had <i>METex14sk</i>

DNA = deoxyribonucleic acid; ITT = intention to treat; *METex14sk* = MET proto-oncogene, receptor tyrosine kinase gene alteration that causes skipping of exon 14; NA = not applicable; NGS = next generation sequencing; PCR = polymerase chain reaction; qRT-PCR = quantitative real-time polymerase chain reaction; RNA = ribonucleic acid.

Source: Commentary, Table MSAC.5

The commentary stated that the populations, tests, and treatment regimens were not always transferrable across the evidence linkages, as they varied considerably. The application stated that *METex14sk* are stable (so testing should select the same patients for treatment, regardless of timing of testing). However, the commentary noted that no evidence was provided on the stability of *METex14sk*.

The commentary also stated that it was unclear whether patient/disease characteristics differed between the test accuracy studies, as the reporting on patient characteristics in the different studies was very limited. It is therefore unclear whether there are likely to be transitivity issues between the test accuracy studies and treatment effectiveness studies.

The ADAR stated that the key VISION trial was a single-arm Phase II open-label study; the internal study design was judged to be of low risk of bias, acknowledging the lack of a randomised study population, or a placebo/comparator arm make the efficacy results vulnerable to unknown confounders. Comparatively, the KN189 trial was a robust Phase III randomised, placebo-controlled double-blinded trial which demonstrated convincing superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy. The match-adjusted indirect treatment comparison (MAITC) was unanchored, making it vulnerable to unknown confounders, and the two trials were on patients with different genetic pathophysiology (*METex14sk* NSCLC in VISION, compared to the general *EGFR/ALK*-negative Stage IV NSCLC population of KN189). These differences gave the MAITC a high risk of bias.

Effectiveness (based on linked evidence)

Prognostic evidence

Five studies were identified by the ADAR that provided prognostic evidence, and one study was added by the commentary. The commentary stated that the available prognostic evidence was limited. *METex14sk* are closely correlated with poor prognostic factors: patients with *METex14sk* are generally older than patients without *METex14sk* and are more likely to have

two or more metastases at the time of diagnosis⁵. This would suggest that, generally, patients with *MET*Ex14sk (eligible for receiving tepotinib) would already have a worse prognosis at baseline compared to patients without *MET*Ex14sk (receiving the comparator treatment). In univariate analyses, having a *MET*Ex14sk therefore appears related to a poor prognosis.

To control for other prognostic factors, the commentary conducted a pooled analysis including all prognostic studies with multivariate analyses (adjusting for other prognostic factors). Studies were not limited on disease stage or histology (i.e. patients of all stages of NSCLC were included). The overall pooled result for the six studies was not statistically significant, but there was a trend suggesting that those with *MET*Ex14sk have a worse prognosis than those without variants (HR = 1.38, 95%CI 0.81, 2.34, $I^2 = 46.6\%$). However, when the two studies that only included patients with advanced disease were pooled, no prognostic effect of *MET*Ex14sk was observed (HR = 1.02, 95%CI 0.67, 1.54). The commentary stated it is therefore unclear whether *MET*Ex14sk are an independent prognostic factor.

Predictive evidence

The ADAR stated there is a strong biological rationale for the use of tepotinib in patients whose tumours harbour a *MET*Ex14sk. There was no direct evidence comparing efficacy outcomes of patients with a *MET*Ex14sk who were treated with tepotinib versus pembrolizumab + chemotherapy. The commentary stated that the ADAR specified chemotherapy as a secondary comparator, for patients unable to receive an immune checkpoint inhibitor. It provided an indirect treatment comparison (ITC) between the VISION trial and a small South Korean trial, which measured the response to pemetrexed-based chemotherapy of 15 patients with *MET*Ex14sk⁶. This ITC found tepotinib was superior in terms of efficacy, however its validity was limited due to low numbers and limited baseline characteristic data in the chemotherapy trial.

Comparative analytical performance

The ADAR stated that there is no gold standard nor routine testing for testing for *MET*Ex14sk in Australia. The testing method with OFA (Oncomine Focus Assay) is considered the evidentiary standard. This is an Ion Torrent off-the-shelf NGS panel, developed by Life Technologies, Inc. (now part of Thermo Fisher). The assay is designed to simultaneously detect various genetic alterations in DNA and RNA from extracted formalin-fixed, paraffin-embedded (FFPE) tumour tissue specimens.

The commentary stated that when the evidentiary standard is used for measures of test performance, the terms ‘sensitivity’ and ‘specificity’ should not be used. Positive and negative percent agreements (PPA and NPA) between the evidentiary standard and other assays were presented in the commentary. The ADAR did not provide a list of included studies and discussed the results of one study only.⁷ A literature search conducted by the

⁵ Gow, C. H., et al. (2017). A comprehensive analysis of clinical outcomes in lung cancer patients harboring a *MET* exon 14 skipping mutation compared to other driver mutations in an East Asian population. *Lung Cancer*, **103**: 82-89.

⁶ Hur, J. Y. et al. (2020). Characteristics and Clinical Outcomes of Non-small Cell Lung Cancer Patients in Korea With *MET* Exon 14 Skipping. *In Vivo*, **34**(3): 1399-1406

⁷ Validation Report for Detection of *MET* Exon 14 Skipping in FFPE Lung Adenocarcinoma Samples Using Ion Torrent Oncomine Focus Assay, Document number VR-0162, Property of MolecularMD

commentary identified two additional studies on test performance.^{8,9} The PPA and NPA of assays compared to the evidentiary standard are presented below in Table 6.

Table 6 PPA and NPA of assays compared to RNA-NGS or hybrid DNA/RNA NGS

	Positive percent agreement	Negative percent agreement
DNA-NGS compared to RNA-based NGS or hybrid DNA/RNA NGS		
DNA-based NGS ⁸ (compared to RNA-based NGS)	40% (4/10)	99.3% (274/276)
DNA-based NGS ⁷ (compared to hybrid DNA/RNA NGS)	100% (6/6)	Not performed
DNA sequencing compared to hybrid DNA/RNA NGS		
Sanger sequencing ⁹	61.5% (8/13)	100% (38/38)
Sanger sequencing ⁷	100% (2/2)	Not performed
RNA-based testing compared to hybrid DNA/RNA NGS		
qRT-PCR ⁹	100% (13/13)	97.4% (37/38)
qRT-PCR ⁷	100% (9/9)	Not performed
ArcherDX RNA-based NGS ⁷	33.3% (1/3)*	100% (43/43)

DNA = deoxyribonucleic acid; NGS = next generation sequencing; NPA = negative percent agreement; PPA = positive percent agreement; RNA = ribonucleic acid; qRT-PCR = quantitative reverse transcription polymerase chain reaction

*ArcherDX assays may have had reduced sensitivity due to limited sample amounts for retesting

Source: Commentary, Table MSAC.6

The commentary stated that the included studies had small sample sizes and encountered technical problems with the tests and/or the samples (leading to a high risk of bias). Furthermore, all studies were done on FFPE samples of tumour tissue from NSCLC patients, however none of the three studies provided details about how the samples were selected. The information on baseline characteristics of the patients from whom the samples were obtained was also limited. Thus, overall, the applicability of the study populations was unclear and there was a high risk of selection bias in the findings.

The commentary stated that DNA-based assays would be easier to conduct than RNA-based assays, as DNA is less vulnerable to degradation and less difficult to obtain. However, commercially available amplicon-based NGS panels have reduced accuracy. In silico analysis revealed that due to their design, none of the eight evaluated commercial NGS panels (DNA-based) would detect more than 63% of literature-reported cases of *MET*Ex14sk.^{10,11} RNA-based tests will generally have better accuracy, because they detect all *MET*Ex14sk, including those detected at RNA level as *MET*Ex13-*MET*Ex15 fusions, regardless of the underlying DNA alterations. A DNA assay should cover all regions involved in splicing (the branch site, polypyrimidine tract, splice acceptor and donor site), as well as other regions where alterations have been observed to cause *MET*Ex14sk, to be accurate in *MET*Ex14sk detection. Detection using DNA-based assays will therefore rely on the set of alterations known to cause *MET*Ex14sk and its accurate curation.

PASC advised that the variations in detection rates by RNA- vs DNA-based tests would be a consideration for NATA, to ensure that the most appropriate test is used for the intended purpose.

⁸ Davies, K. D., et al. (2019). DNA-Based versus RNA-Based Detection of *MET* Exon 14 Skipping Events in Lung Cancer. *J Thorac Oncol*, **14**(4): 737-741.

⁹ Kim, E. K., et al. (2019). Molecular Diagnostic Assays and Clinicopathologic Implications of *MET* Exon 14 Skipping Mutation in Non-small-cell Lung Cancer. *Clin Lung Cancer*, **20**(1): e123-e132.

¹⁰ Poirot, B., et al. (2017). *MET* Exon 14 Alterations and New Resistance Mutations to Tyrosine Kinase Inhibitors: Risk of Inadequate Detection with Current Amplicon-Based NGS Panels. *J Thorac Oncol*, **12**(10): 1582-1587.

¹¹ Pruis, M. A., et al. (2020). Highly accurate DNA-based detection and treatment results of *MET* exon 14 skipping mutations in lung cancer. *Lung Cancer*, **140**: 46-54.

Prevalence

The commentary stated that according to the ratified PICO Confirmation, the applicant estimated that *MET*Ex14sk drive approximately 3%-5% of NSCLC. The majority of identified studies reported a prevalence of 3%-4%. The *MET*Ex14sk positive rate varies across different patient pools and histologies. Studies show that the prevalence is higher in patients with non-squamous NSCLC compared to patients with squamous NSCLC^{12,13} and after removing *EGFR/ALK*+ patients. The studies by Huang et al. and Reungwetwattana et al. reported *MET*Ex14sk in approximately 3% of non-squamous and around 2% of squamous NSCLC, although the prevalence might vary slightly across studies.

Assessment of the consequences of incorrect test results

The commentary calculated the number of true positive, false positive, false negative and true negative patients expected from testing of the proposed population using median PPA and NPA values for various tests reported above. The prevalence rate was assumed to be 3.5% for these calculations. The results presented in Table 7 are based on limited evidence (k=3, small studies). Furthermore, the studies included had technical problems with the test and/or samples. Therefore, the commentary considered true PPA and NPA values were indeterminable.

Table 7 Comparative number of false positive and false negative of *MET*Ex14sk test results compared to evidentiary standard (Hybrid DNA/RNA-NGS or RNA-NGS)

Test	Median PPA	Median NPA	Number of with a positive test result (TP:FP)	Number of with a negative test result (FN:TN)	NNT to obtain one positive result	NNT to obtain one TP result
DNA-NGS	70%, k=2	99.3%, k=1	141:39	60:5,498	31	39
Sanger sequencing	80.8%, k=2	100%, k=1	162:0	39:5,537	34	34
qRT-PCR	100%, k=2	97.4%, k=1	201:144	0:5,393	16	28
ArcherDx RNA-NGS	33.3%, k=1	100%, k=1	67:0	134:5,537	83	83

DNA = deoxyribonucleic acid; FN = false negative; FP = false positive; k = number of studies; NNT = number needed to test; NPA = negative percent agreement; PPA = positive percent agreement; TN = true negative; TP = true positive.

Source: Commentary, Table MSAC.7

The commentary stated that the false negative results obtained by DNA-NGS and Sanger sequencing compared to the RNA-based evidentiary standard were due to methodological limitations. To be effective, the DNA-NGS panels would need to be redesigned to cover all regions involved in splicing of the RNA transcript between exon 13 and exon 15¹⁴.

The commentary stated that overall, the results suggest that most patients who receive a false negative or false positive test result would only do so if there were methodological problems, either with the DNA-based test itself, or with the quantity or quality of the RNA sample extracted from the FFPE tissue block. It is important for laboratories to participate in a stringent quality assurance program for *MET*Ex14sk testing to minimise the number of false negative patients who miss out on potentially beneficial treatment with tepotinib and false positive patients who would receive potentially inappropriate treatment.

¹² Huang, C., et al. (2020). Management of Non-small Cell Lung Cancer Patients with *MET* Exon 14 Skipping Mutations. *Curr Treat Options Oncol*, **21**(4): 33.

¹³ Reungwetwattana, T., et al. (2017). The race to target *MET* exon 14 skipping alterations in non-small cell lung cancer: The Why, the How, the Who, the Unknown, and the Inevitable. *Lung Cancer*, **103**: 27-37.

¹⁴ Pruis, M. A., et al. (2020). Highly accurate DNA-based detection and treatment results of *MET* exon 14 skipping mutations in lung cancer. *Lung Cancer*, **140**: 46-54.

Change in management in practice

The ADAR provided no evidence on whether test results guided changes in treatment decisions in a clinical setting. The applicant proposed that patients with advanced or metastatic NSCLC who are found to have *MET*ex14sk will all receive targeted treatment with tepotinib instead of pembrolizumab and/or platinum-based therapy as per the proposed clinical management algorithm. Patients who do not have a *MET*ex14sk would not have a change in management and will receive pembrolizumab and/or platinum-based chemotherapy, as per the current clinical management algorithm.

The commentary considered this assumption to be appropriate. The commentary did not identify any other evidence of change in management based on a (non-systematic) literature review.

Claim of codependence

NSCLC is genomically diverse and offers the potential to define molecular subsets of patients treated with personalised therapies. Most adenocarcinoma can be classified based on molecular testing for predictive biomarkers in oncogenic drivers such as *EGFR*, *ROS1*, *ALK*, *BRAF*, and *MET*.

Some oncogenic *MET* gene alterations identified in NSCLC affect the splice sites of exon 14 of the *MET* gene (*MET*ex14). *MET*ex14sk appear to be mutually exclusive with other established driver mutations in NSCLC such as *EGFR*, *KRAS*, *ALK* or *ROS1*. *MET*ex14sk are regarded as a primary oncogenic driver in NSCLC, and are sufficient to promote carcinogenesis and tumour progression.

The ADAR stated that tepotinib is an orally administered, highly selective, ATP-competitive, Type 1b tyrosine kinase inhibitor (TKI) that is highly specific for the c-MET receptor with fewer off target effects as compared with a type 1a TKI. It further stated that identification of patients suitable for tepotinib requires a test currently not covered by the MBS. As such tepotinib was requested to be appraised as a codependent submission by MSAC/PBAC to apply for both the test as well as the drug.

12 Economic evaluation

The ADAR presented a cost-minimisation approach (CMA) of tepotinib compared with pembrolizumab in combination with platinum-based chemotherapy for treatment of *MET*ex14sk positive aNSCLC.

The ADAR stated that the CMA took into account the cost associated with identifying one patient eligible for tepotinib therapy. The ADAR determined the number of patients needed to be tested per *MET*ex14sk positive case, by estimating the *MET*ex14sk prevalence in squamous NSCLC and in *EGFR* wild-type non-squamous NSCLC. The weighted average number of NSCLC patients needed to be tested to identify one patient with *MET*ex14sk was estimated to be 32.9 patients. The commentary stated that the reference papers used to estimate the weighted average of *MET*ex14sk prevalence in all NSCLCs and in squamous NSCLCs were not provided in the ADAR. The calculation of *MET*ex14sk prevalence by NSCLC histology, therefore, could not be verified. More importantly, the MBS item descriptor proposed by the ADAR was for all NSCLC patients, regardless of disease stage. In contrast, first-line tepotinib would be given to those with locally advanced and metastatic disease according to the requested PBS listing. Therefore, the CMA should also consider the cost for testing of patients with Stage I-IIIa NSCLC who do not progress into Stage IIIB/IV

(ineligible for tepotinib therapy). The ADAR also did not consider whether there were implications for retesting of unevaluable test results. Overall, the number of patients needed to be tested for METex14sk per tepotinib-treated patient has been underestimated in the ADAR; and this favoured tepotinib.

The ADAR did not propose alternate listing scenarios.

The commentary reported the results of sensitivity analyses for factors related to the test. Excluding patients with squamous histology would allow up to a 3.3% increase in tepotinib price; increasing the number needed to test per patient treated with tepotinib from the base case of 32.9 to 50 would require a 5.5% decrease in tepotinib price to maintain the cost minimisation approach.

The pre-ESC response added other sensitivity analyses related to the test, which were not subject to independent verification. Increasing the retesting rate from a base case assumption of 0% to 8% was estimated to require a 0.9% decrease in tepotinib price, and testing patients who are positive for the *ALK* and *ROS1* biomarkers would require a 0.2% decrease in tepotinib price.

13 Financial/budgetary impacts

The ADAR took an epidemiological approach to estimate the number of patients eligible for METex14sk testing. The cost of METex14sk testing to the MBS was estimated by assuming that this test would only be performed in patients who are diagnosed with Stage IIIB or IV NSCLC. The commentary stated that this was not consistent with the ADAR's proposed MBS item descriptor for METex14sk testing, which did not limit the disease stage of NSCLC. Patients with Stages I-III A disease would also be eligible for METex14sk testing according to the ADAR's requested MBS listing. Even if the eligibility criteria for METex14sk testing is to be limited to locally advanced or metastatic NSCLC, the ADAR still underestimated the size of the patient population eligible for testing, as those diagnosed with Stages I-III A but subsequently progressing into a later stage were not included in the ADAR's estimates.

The commentary stated that the ADAR further underestimated the number of patients eligible for METex14sk testing, as it excluded 26.1% ($=1-(90\% * 82.1\%)$) of patients with squamous NSCLC, by assuming that these patients would be ineligible for *EGFR* testing or having a positive result from the *EGFR* test and, thus, become ineligible for METex14sk testing. This was not appropriate. Only patients with non-squamous NSCLC will undergo an *EGFR* test; and only those testing negative will be eligible for METex14sk testing. Patients with squamous NSCLC do not require an *EGFR* test to determine their eligibility for METex14sk testing, as per the requested MBS descriptor.

Table 8 Estimated use and financial implications of METex14sk testing to the MBS

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of METex14sk testing						
Number of patients tested	Redacted ¹					
Number of patients likely to receive a positive test result (5% positivity rate)	Redacted ²					
Estimated financial implications of the METex14sk testing to the MBS						
Cost to the MBS less copayments (80% of the proposed MBS Schedule fee)	\$Redacted ³					
Estimated changes in financial implications for chemotherapy administration to the MBS						
Cost to PBS/RPBS less copayments (80% of the MBS Schedule fee for item 13950)	-\$Redacted ³					
<i>Revised^a</i>	-\$Redacted ³					
Net financial implications						
Net cost to MBS	\$Redacted ³					
<i>Revised^a</i>	\$Redacted ³					

^a The commentary revised the MBS cost of chemotherapy infusion by: 1) revising the number of patients eligible for tepotinib therapy; 2) correcting the calculation of pemetrexed administrations; and 3) including changes in administration of third-line nivolumab and docetaxel. Source: Commentary, Table MSAC.8

The redacted values correspond to the following ranges:

¹ 5,000 to < 10,000

² <500

³ \$0 to < \$10 million

The commentary stated the MBS cost was underestimated in the ADAR’s financial analysis. If METex14sk testing were to be conducted in patients with EGFR negative non-squamous NSCLCs and all squamous NSCLC, regardless of disease stage, the net costs to the MBS would increase by 81%.

14 Key issues from ESCs to MSAC

ESCs key issue	ESCs advice to MSAC
METex14sk testing in clinical algorithm: sequential vs parallel testing	Parallel testing would be more time-effective, by using the same tissue sample; conversely sequential testing by limiting to patients with locally advanced or metastatic NSCLC would be in line with current ALK and ROS1 testing (proposed by the pre-ESC response to be after ALK and ROS1 testing, rather than before as proposed in the ADAR), and not all lung cancer patients will go on to being considered for tepotinib treatment.
Item descriptor	The revised Pre-ESC item descriptor is appropriate. MSAC may accept allowing testing in patients with squamous histology if PBAC supports tepotinib in patients with squamous histology, although MSAC should also consider the inconsistency with existing MBS-funded testing of NSCLC biomarkers. Consider removing pathologists as a requestor group from the item descriptor. No restriction on the frequency of testing is required.
Analytical platforms in Australian labs	For different reasons, there is a risk of false negatives with RNA or DNA NGS testing. NATA/NPAAC have governance/processes in place to ensure accurate analytical performance, however it is unclear on what basis NATA/NPAAC or TGA would establish the validation of companion diagnostic tests.
Clinical validity and clinical utility – lack of evidence	The evidence is unclear whether a patient would have 1) a different prognosis or 2) respond differently to tepotinib based on their METex14sk status.

Comprehensive genomic profiling MSAC application (1634) is underway	Any MBS listing would need to be reviewed if 1634 proceeds to MSAC and is supported. Conversely, MSAC's decision on 1634 may also be influenced by whether this test and drug codependency is supported for public funding by MSAC/PBAC. The complexity and flow-on consequences of molecular testing in NSCLC makes it difficult to make accurate cost projections. From both clinical (time to treatment, lack of tissue, international guidelines, increasing targets) and economic (cost break-even point) perspectives, the use of gene panels for NSCLC such as proposed in application 1634 should be considered.
MBS costs	The estimated costs to the MBS would be increased if the ADAR's proposed MBS item descriptor is used: <ul style="list-style-type: none"> • The financial analysis was restricted to locally advanced / metastatic patients. Including all NSCLC patients would increase the cost to the MBS to \$0 to < \$10 million. • Including 15% retesting rates would increase cost to the MBS to \$0 to < \$10 million.
Impact of testing on CMA and PBS	The uncertainty around the eligible population was addressed in the sensitivity analysis for the CMA by increasing the "Number needed to test" from 32.9 to 50. This change has little impact on the cost-minimised drug price (5.5% reduction). The CMA only includes the testing cost for the restricted population (patients at stage IIIB/IV), which may need consideration.

ESCs discussion

The ESCs noted that this codependent application was for MBS funding for testing for *MET*14sk, to help determine eligibility for treatment with tepotinib in patients with advanced NSCLC.

On disease stage, the ESCs noted the applicant had initially proposed testing patients with locally advanced or metastatic NSCLC only, however PASC had recommended in the PICO assessing *MET*14sk testing any time after diagnosis of NSCLC, with assessment of both options. The ESCs noted the test item descriptor proposed in the ADAR did not include any restriction on disease stage, but that the pre-ESC response proposed a revised item descriptor that restricted testing to patients with locally advanced or metastatic disease. The ESCs considered that upfront testing was worth considering. The ESCs considered that eligibility for testing based on disease stage had the potential to affect the number of tests to be performed, the cost minimised price, and the budget impact to the MBS.

The ESCs noted that the PICO specified NSQ or NOS histology, but that the ADAR and pre-ESC response reiterated the applicant's request to also include patients with SQ NSCLC, in line with the key VISION trial. The ESCs considered that including patients with SQ histology may be reasonable if the uncertainty around the clinical efficacy claim for those patients was accepted. However, the ESCs also noted that MSAC application 1634 for a comprehensive genomic profiling panel test for NSCLC biomarkers would, if supported, subsume existing separate biomarkers tests and result in simultaneous testing for all biomarkers. Application 1634 is for patients with NSQ/NOS histology; complexities would therefore be created if patients with SQ histology were to be included in the population eligible for *MET*14sk testing, as they are ineligible for other existing testing of biomarkers in NSCLC.

The ESCs noted that the applicant proposed this testing be requestable by not only by or on behalf of a specialist or consultant physician, but also that it be pathologist-determinable, so that further testing can commence immediately if the sample is *EGFR* negative. The ESCs did not support the testing being pathologist-determinable because this risks a lack of input from the treating clinician, and could potentially result in patients being tested for eligibility

for a medicine for which they may not be considered. In addition, as MBS-funded *EGFR* testing is not limited to locally advanced or metastatic NSCLC but *ALK* and *ROS1* FISH testing are, this proposal was inconsistent with the proposed item descriptor.

The ESCs discussed a frequency restriction for this MBS item, noting that PASC had referred to *BRCA* testing having a once per lifetime frequency restriction, but that at present there is no frequency restriction on other comparable lung molecular MBS items. The ESCs considered no frequency restriction on testing was reasonable.

The ESCs noted that the PICO and ADAR proposed testing for *METex14sk* only in patients who are negative for *EGFR* pathogenic variants, though the applicant had altered its proposal in the pre-ESC response to propose testing only in patients negative for *EGFR*, *ALK* and *ROS1* biomarkers, consistent with sequential testing.

The ESCs discussed the clinical validity and clinical utility of the proposed testing. The ESCs noted that the ADAR concluded patients with *METex14sk* have a poorer prognosis, however the commentary had found only a non-significant trend so regarded it as unclear whether *METex14sk* are an independent prognostic factor. The ESCs noted that there was no evidence available of a change in management based on *METex14sk* testing, and considered that at present there is no evidence from any clinical trial to prove whether patients respond differently to tepotinib based on whether a *METex14sk* is present or not. The ESCs noted the ADAR referred to the single-arm VISION trial in which all patients with *METex14sk* were treated with tepotinib. The ESCs noted that only a small number of patients were treated with first-line tepotinib in the VISION trial (n=65), and considered the unanchored naïve comparisons across VISION and KN189 increased uncertainty in the analysis. The ESCs considered this makes it difficult to distinguish between the prognostic value (clinical validity) and predictive value (clinical utility) of *METex14sk*.

The ESCs noted that *METex14sk* testing can be conducted using DNA and/or RNA, but that both have limitations. RNA-based testing is more accurate than DNA-based but relies on the successful retrieval of high-quality RNA for testing, which is not possible in many cases as RNA is more vulnerable to degradation. The ESCs noted that PASC had advised the evidentiary standard against which *METex14sk* testing is assessed should be that of the VISION trial, however that trial allowed two types of test sample: liquid biopsy and tissue biopsy; and two test methods: RNA-based and DNA-based. The ESCs noted the ADAR considered one validation study using the OFA. The ESCs noted the commentary added two studies to the assessment of analytical performance, but that there remained a risk of bias due to small sample size, so the true positive and negative percent agreement was indeterminable. The ESCs noted the ADAR and pre-ESC response stated that testing will rely on NATA/NPAAC accreditation, though considered it is unclear on what basis NATA/NPAAC (or TGA) would establish the validation of companion diagnostic tests.

The ESCs noted that the ADAR did not consider retesting rates. The commentary considered 15% may be appropriate, and the RCPA commented that retesting rates may be similar to *EGFR* re-testing rates. The commentary conducted a sensitivity analysis to account for re-testing by increasing the number of patients needed to test per positive case from 32.9 to 50. The ESCs noted this reduced the cost-minimised price of tepotinib by 5.5%, and advised it would increase the cost to the MBS from \$0 to < \$10 million per year in the base case, to \$0 to < \$10 million per year. The ESCs noted the pre-ESC response provided sensitivity analyses with 6% and 8% re-testing rates.

The ESCs noted that consumer issues included the provision of early or prophylactic conservative support measures (e.g. leg elevation and support stockings)¹⁵, and whether testing should be performed on all patients with lung cancer, including those with squamous histology, because this is a targetable alteration¹⁶.

15 Other significant factors

Nil.

16 Applicant comments on MSAC's Public Summary Document

Merck Healthcare will continue to work with the Department to bring tepotinib to patients.

17 Further information on MSAC

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

¹⁵ Morise, M. et al. (2021). O13-4 Tepotinib safety in *MET* exon 14 (*MET*ex14) skipping NSCLC: Updated results from the VISION trial. *Annals of Oncology*, **32**: Supplement 4, Page S291.

¹⁶ Heist, R. S. et al. (2016). *MET* exon 14 skipping in non-small cell lung cancer. *The Oncologist*, **21**(4): 481-486.