Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1454- Diagnostic testing for ROS proto-oncogene1 (ROS1) rearrangements in patients with non-small cell lung cancer (NSCLC) to determine eligibility for crizotinib treatment

Applicant: **Pfizer Australia Pty Ltd**

Date of MSAC consideration: **MSAC 73rd Meeting, 26-27 July 2018**
MSAC 71st Meeting, 23 November 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

The codependent application requested:

- a new Medicare Benefits Schedule (MBS) item number for *ROS* proto-oncogene 1 (*ROS1*) fluorescent *in situ* hybridisation (FISH) testing as a codependent medical service that is performed to inform eligibility for crizotinib treatment in patients with locally advanced (Stage IIIB) or metastatic (Stage IV), non-squamous or histology not otherwise specified (NOS), non-small cell lung cancer (NSCLC) without either activating mutations of the epidermal growth factor receptor (*EGFR*) gene or an anaplastic lymphoma kinase (*ALK*) gene rearrangement; and
- a new Section 85 Authority Required Pharmaceutical Benefits Scheme (PBS) listing for crizotinib for the treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) *ROS1*-positive NSCLC, who have disease progression on or following treatment with platinum-based chemotherapy.

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

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC supported MBS funding for fluorescent *in situ* hybridisation (FISH) testing for *ROS* proto-oncogene 1 (*ROS1*) rearrangements in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) to determine access to crizotinib under the Pharmaceutical Benefits Scheme.

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

MSAC recalled that it had previously foreshadowed its support for an MBS item for fluorescent *in situ* hybridisation (FISH) testing for ROS proto-oncogene 1 (*ROS1*) rearrangements in patients with non-small cell lung cancer (NSCLC) to determine eligibility

for crizotinib treatment, pending a positive recommendation from the PBAC to extend the listing for crizotinib to patients with *ROS1*-positive advanced NSCLC. Crizotinib is currently listed on the PBS for the treatment of patients with anaplastic lymphoma kinase (*ALK*)-positive advanced NSCLC.

MSAC recalled that the patient population for this application was patients with locally advanced (stage IIIB) or metastatic (stage IV), non-squamous cell or histology not otherwise specified (NOS), non-small cell lung cancer, without either activating mutations of epidermal growth factor receptor (*EGFR*) or an *ALK* gene rearrangement.

MSAC confirmed that evidence supports the clinical effectiveness and safety of *ROS1* FISH testing to determine eligibility for access to crizotinib.

MSAC confirmed that the agreed clinical management algorithm includes immunohistochemical (IHC) testing to triage upregulated *ROS1* gene. If the ROS1 IHC is positive, FISH testing is then conducted to confirm *ROS1* gene rearrangement.

MSAC advised that *ROS1* testing should be requested by the treating clinician at the same time as *EGFR* and *ALK* testing; the *ROS1* test would be needed in the event that the pathology laboratory found that the *ALK* test was negative, in the same way that the *ALK* test would be needed in the event that the pathology laboratory found that the *EGFR* test was negative. MSAC requested that these intentions be reflected in the *EGFR*, *ALK* and *ROS1* MBS item descriptors, and in the decisions about whether the *ALK* and *ROS1* MBS items are pathologist determinable.

MSAC noted the minor increase in the costs to the MBS since its consideration of the application in November 2017, due to a small increase in the number of patients per year (from **redacted** patients to **redacted** patients).

MSAC accepted the more detailed item descriptor provided by the applicant, with the minor change to spell out *ROS1* at its first use.

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

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost effectiveness, MSAC deferred its advice until such time as PBAC subsequently decides to recommend the PBS listing of crizotinib for patients with locally advanced or metastatic non-squamous or "not otherwise specified" (NOS) non-small cell lung cancer (NSCLC). MSAC foreshadowed its support for a new MBS item for *ROS1* fluorescent *in situ* hybridization (FISH) testing to inform eligibility for crizotinib treatment in this population.

MSAC advised that the MBS item descriptor should be pathologist determinable, with a fee of $400, and limited to *ROS1* FISH testing of samples that have undergone appropriate epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) and immunohistochemistry ROS1 testing.

MSAC further advised that the current MBS items 73341 for *ALK* FISH testing and 73342 for *HER2* FISH testing in gastric cancer should also be made pathologist determinable.

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

MSAC noted that, under the proposed algorithm, *ROS1* testing and crizotinib treatment would be limited to patients with advanced NSCLC who have normal *EGFR* test results (and therefore are not eligible for treatment with gefitinib or erlotinib) and normal *ALK* test results (and therefore are not eligible for treatment with crizotinib on that basis). MSAC considered that the proposed item descriptor should therefore be amended to make it clear that, to be eligible for *ROS1* testing, patients must have documented **absence** of **both** activating mutations of the *EGFR* gene **and** *ALK* gene rearrangements.

MSAC noted that, under the proposed algorithm, immunohistochemical (IHC) testing is conducted first to triage for the up-regulated gene, and patients with a positive ROS1 IHC test result would then undergo FISH testing to confirm *ROS1* gene rearrangement. MSAC considered that this is appropriate and noted that the proposed methodology for *ROS1* testing is consistent with triaging for *EGFR* and *ALK* gene rearrangements, which have previously been assessed by MSAC and listed on the MBS. MSAC also advised that at this time an MBS item for *ROS1* testing should be specific to FISH testing.

MSAC advised that it would be appropriate that *ROS1* FISH testing be pathologist determinable, on confirmation of a positive ROS1 IHC test result. The rationale for this decision was that in making the initial request the oncologist would already have initiated the process of determining the most appropriate treatment for the patient. This approach also applies to *ALK* FISH testing, and *HER2* ISH testing in patients with adenocarcinoma of the stomach or gastro-oesophageal junction, both of which MSAC advised should also be pathologist determinable.

MSAC noted ESC's conclusion that, in the absence of evidence to the contrary, it is reasonable to assume that the mutation status is constant over time. MSAC concluded that this assumption is appropriate, taking into consideration the risk that re-biopsy carries for patients.

MSAC noted that if crizotinib treatment was PBS-listed as first-line for patients with *ROS1*-positive locally advanced or metastatic non-squamous or NOS NSCLC, a single test panel conducted at diagnosis of NSCLC or at progression to advanced NSCLC could help determine between multiple subsequent targeted chemotherapy options for these patients. MSAC noted that the final PICO Confirmation document shows the test as informing first-line treatment, though crizotinib was assessed by PBAC as second-line treatment, for patients with progression on or after prior platinum-based chemotherapy. MSAC noted that the sequential testing of *EGFR*, *ALK* and *ROS1* yield mutually exclusive treatment pathways and that sequential testing wastes tissue sample, time and is more expensive than a single panel of tests. MSAC recommended that the Department conduct a cost-utility review of gene panel and/or next generation sequencing (NGS) test options to inform these first-line therapy options, at which time the MBS item for *ROS1* FISH testing may need to be revised. MSAC advised that any MBS funding should be based on a gene panel or NGS test of equivalent or better analytical performance to sequential IHC and FISH testing and assurance that the average gene panel or NGS test is no more costly than the average cost of the sequential testing that it would replace. MSAC noted that overall testing may still require more than one gene panel test due to differences in lung cancer gene aberrations as somatic mutations are tested in genomic DNA, whereas gene fusions (such as *ROS1*) are usually tested in cDNA prepared from RNA. MSAC noted that the availability of suitable ctDNA testing in the future may address some of these challenges.

MSAC considered the rationale presented for inclusion of patients with squamous histology and advised that while it is biologically plausible that these patients may benefit from treatment with crizotinib, *ROS1* rearrangements are rare in these patients and only 2/180 patients in the studies had squamous NSCLC. MSAC advised that at this time testing and thus treatment should be limited to patients with non-squamous or NOS NSCLC. Inclusion of testing and treatment in patients with squamous NSCLC would require presentation and assessment of pre-clinical and clinical data.

MSAC noted that overall the linked evidence presented supports the safety and clinical effectiveness for *ROS1* FISH testing for access to crizotinib, though the magnitude of incremental treatment effect for crizotinib in *ROS1*-positive NSCLC over *ROS1*-negative NSCLC is uncertain. MSAC also noted that there were no directly comparative randomised trials of crizotinib in *ROS1*-positive NSCLC and the naïve indirect comparisons presented were compromised by a number of factors including stage, histology, prior chemotherapy and ethnicity. MSAC noted that these data are the best available and further trials are unlikely.

MSAC noted that FISH testing is the reference method for *ROS1* testing and as such its analytical validity has been assumed. MSAC considered that although its reproducibility was not reported, this is assumed to be high.

MSAC noted that ESC accepted the ROS1 IHC sensitivity and specificity as presented in the pooled analyses was adequate for triage, although the trials showed variable performance. MSAC recommended that the IHC and FISH testing of a sample should be conducted in the same specialised central laboratory to ensure optimal test performance overall.

MSAC noted that the evidence for the clinical utility of *ROS1* FISH testing is mostly pre-clinical. This evidence is supported by the improved outcomes observed in non-comparative studies of *ROS1*-positive NSCLC patients treated with crizotinib. MSAC concluded that there is a strong biological plausibility for codependence of *ROS1* testing and crizotinib treatment, which supports targeting crizotinib treatment to *ROS1*-positive patients.

MSAC noted that the model was conducted over a time horizon of 10 years, which it considered was overly optimistic given the limited average survival in this patient population. However, MSAC noted that this aspect of the model was primarily within the remit of PBAC assessment.

MSAC noted that the overall uptake assumed in the model was low (**redacted**%), however this assumption had little impact on the overall cost. MSAC noted that the patient population who would be eligible for treatment with crizotinib under the proposed listing is small. MSAC noted that the estimated annual cost to the MBS was $**redacted** to $**redacted**. MSAC recognised that, in comparison to the estimated annual cost to the PBS of crizotinib (around $ **redacted** to $**redacted**), the cost of testing is modest and makes little difference to the overall cost impact.

4. Background

MSAC considered Application 1454 at its November 2017 meeting. MSAC deferred its advice until the PBAC recommended the PBS listing of crizotinib for this population.

ALK FISH testing was considered by MSAC at its November 2013 and November 2014 meetings. At the November 2014 MSAC consideration, *ALK* FISH testing was supported for

patients with locally advanced or metastatic, non-squamous or histology NOS NSCLC with a documented absence of *EGFR* activating mutations and ALK immunoreactivity by IHC.

The Public Summary Documents (PSDs) for these applications can be found on the MSAC website at www.msac.gov.au.

5. Prerequisites to implementation of any funding advice

Currently, there are no TGA approved tests for *ROS1* gene rearrangement. *ROS1* FISH testing items would be regulated by the TGA as in-vitro diagnostic medical devices (IVDs).

The application stated that there were no commercially available FISH test kits for *ROS1* testing in Australia. However, *ROS1* Break Apart FISH probes are commercially available.

6. Proposal for public funding

Table 1: Proposed MBS item descriptor

Category 6 – Pathology Service
MBS item number: to be advised Fluorescence in situ hybridization (FISH) test of tumour tissue from a patient: - with locally advanced or metastatic non-small-cell lung cancer (NSCLC), which is of non-squamous histology or histology not otherwise specified, - with documented evidence of *ROS1* immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+, and - with documented absence of either activating mutations of the epidermal growth factor receptor (*EGFR*) gene or anaplastic lymphoma kinase (*ALK*) gene rearrangement, requested by a specialist or consultant physician - to determine if requirements relating to *ROS1* gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. Fee: $400.00 Benefit: 75% = $300.00; 85% = $340.00

Consistent with the related current item for *ALK* testing, the proposed MBS item descriptor was not limited to use following failure of first-line NSCLC treatment and was specific to *ROS1* gene rearrangement testing by FISH.

The critique noted the advice from Royal College of Pathologists of Australasia (RCPA) that "testing for *ROS1* should not be restricted to a specific technology (e.g. FISH) in any new MBS item number as other methodologies are available and continue to be developed."

The application presented evidence for *ROS1* gene rearrangement testing using next generation sequencing (NGS), also known as massively parallel sequencing technologies, and using real-time polymerase chain reaction (qRT-PCR). This was referred to as reverse-transcriptase polymerase chain reaction (RT-PCR) in the application. The critique noted that, although the application considers NGS and RT-PCR, it does not propose either be included in the item descriptor for either the purpose of pre-testing or determining *ROS1* gene rearrangement status, and it does not consider the comparative costs of these alternative test options against IHC or FISH testing. A broader item descriptor that includes NGS would mean that *ROS1* testing may not occur sequentially because NGS allows multiple genes to be tested at once.

Consistent with the related current item for *ALK* testing, the proposed MBS item descriptor was for patients with non-squamous or histology NOS NSCLC. However, the critique noted that the crizotinib studies included two patients (1%) with *ROS1*-positive squamous NSCLC.

Although *ROS1* gene rearrangements are rarer in squamous NSCLC, inclusion of squamous NSCLC may increase testing costs.

7. Summary of public consultation feedback/consumer issues

Public consultation feedback provided one response from a professional body.

The response was positive overall, highlighting the benefits to the affected individual, their family and the community (in an effort to provide Australian patients with the best practice pathology and clinical treatment). The key issues raised were that:

- testing for *ROS1* rearrangement may require repeat biopsy due to the amount of prior testing (sequential testing);
- repeat biopsies increase both the cost and risk of harm to the patient;
- cytology and/or cell-free DNA specimens may need to be considered for testing samples;
- there is uncertainty regarding the sensitivity of ROS1 IHC testing;
- there would be an effect on utilisation of MBS items, with regard to other, more efficient molecular techniques used in assessment of lung cancer.

The response suggested:

- not restricting the item descriptor to sequential testing, but instead do multi panel testing;
- anticipating the potential for using RT-PCR or massively parallel sequencing (MPS) as intervention; and
- providing a table of *EGFR* and *ALK* costs in comparison to *ROS1* tests.

8. Proposed intervention's place in clinical management

Approximately 90% of lung cancer cancers are classified as NSCLC. Advanced lung cancer has poor survival outcomes with only 10-15% of diagnosed patients alive after five years. *ROS1*-positive lung cancer occurs when a chromosomal rearrangement happens and a part of the *ROS1* gene, including its entire tyrosine kinase domain, fuses with a partner gene. This results in *ROS1* fusion kinases that are active and drive cellular transformation.

The proposed population for *ROS1* FISH testing was 'patients with locally advanced or metastatic, non-squamous or histology NOS NSCLC whose tumours do not have either *EGFR* activating mutations or *ALK* gene rearrangements, and who have undergone *ROS1* IHC testing that resulted in a staining intensity of 2+ or 3+ (positive test)'.

The application stated that the *ROS1* gene rearrangement is stable and not effected by prior treatment, based on the biological understanding of *ROS1* as an oncogene driver. The critique noted that two studies included in the application that examined re-biopsies in patients with NSCLC found *ROS1* gene rearrangements occurred more frequently in recurrent tumours, however these studies were limited by either small numbers or lack of *ROS1* FISH confirmation. If *ROS1* gene rearrangements occur more frequently at NSCLC recurrence, previous biopsy samples may incorrectly classify patients as having *ROS1*-negative disease.

ROS1 gene rearrangement testing is intended to be used in addition to pathology tests currently performed on NSCLC tumour samples, after *EGFR* testing and *ALK* testing. Patients would first undergo ROS1 IHC testing, followed by confirmatory *ROS1* FISH testing if a positive IHC result was obtained.

9. Comparator

The nominated comparator for *ROS1* gene rearrangement testing was no testing. This was appropriate.

10. Comparative safety

Adverse events from testing

ROS1 gene rearrangement testing will be performed on a biopsy specimen obtained as part of standard diagnostic work-up and would not incur any direct risks to patients. The main risk to the patient would occur if an additional biopsy is required in order to obtain tissue to perform the test. This could result in complications such as pneumothorax and haemorrhage.

Adverse events from changes in management

The change in management expected to arise due to *ROS1* gene rearrangement testing, is the use of crizotinib, rather than pemetrexed, in those who have *ROS1* gene rearrangements in their tumour tissue.

The common adverse events that occurred with crizotinib were vision disorders, elevated transaminases, oedema, and gastrointestinal adverse events.

11. Comparative effectiveness

The application used a linked evidence approach to link the:

- prognostic evidence of *ROS1*-positive, advanced NSCLC;
- analytical performance of *ROS1* testing; and
- the clinical evidence for crizotinib in patients with *ROS1*-positive, advanced NSCLC.

Table 2: Linked evidence (Level 5)

Prognostic evidence	Comparison of outcomes (OS) in patients receiving standard care conditioned on the presence or absence of biomarker positive status.	☒ k = 15 n = 182 [a]
Test accuracy	Studies that compared IHC, RT-PCR or NGS with the evidentiary standard FISH determine analytical validity	☒ k = 18 n = 3,872
Change in patient management	Evidence to show that biomarker determination guides treatment with the drug was not presented in the application	☐ k = 0 n = 0
Treatment effectiveness	Two single-arm, non-randomised studies of crizotinib in NSCLC patients with *ROS1* gene rearrangements and the pemetrexed arm of a RCT that compared pemetrexed and docetaxel for second-line treatment of NSCLC. Four supporting studies of crizotinib in *ROS1*-positive NSCLC were also presented	☒ k = 7 n = 609

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; NGS = next-generation sequencing; NSCLC = non-small cell lung cancer; OS = overall survival; RCT = randomised controlled trial; *ROS1* = *ROS* proto-oncogene 1; RT-PCR = reverse transcription polymerase chain reaction

[a] Number of *ROS1*-positive patients

Prognostic evidence

The prognostic evidence presented in the application, from the nine studies that included ten or more *ROS1*-positive patients, is presented in the table below.

Table 3: Prognostic evidence for *ROS1*-positive NSCLC

Study	*ROS1* n (%) N	Testing method	Population: NSCLC	Risk of bias	Treatments *ROS1*-pos	Treatments *ROS1*-neg	Outcome
Prospective							
Scheffler 2015 [a]	19 (1.8%) 1,035	FISH, NGS [b]	2nd line ≥, Stage I-IV 84% Stage IIIB/IV	High [c]	Crizotinib [c] or chemo	Targeted and non-targeted [d]	OS
Wiesweg 2017	11 (2%) [e] 805	IHC, FISH	Any line; Stage IIA-IV 96% Stage IIIB/IV	High [f]	Crizotinib/Pemetrexed/ doublet chemo	NR	OS
Chen 2014	12 (2.4%) 492	IHC, RT-PCR	Any line, Stage I-IV 58% Stage IV	Unclear	Pemetrexed/ doublet chemo/EGFR TKI	Similar	OS
Retrospective							
Drilon 2016	10 (10%) 104	FISH, MSMM	1st line, Stage IIIB, IV 100% Stage IIIB/IV	Low	Pemetrexed/doublet or non-doublet chemo [g]	Similar	OS
Bergethon 2012	18 (1.7%) 1,073	FISH, RT-PCR	1st line, Stage IA-IV 72% Stage IIIB/IV	Low	Not stated Crizotinib (in vitro)	Similar	OS
Yoshida 2013	15 (2.6%) 570	IHC FISH	NR, Stage I-III 53% Stage IIIB/IV	Unclear	NR	NR	OS
Lee 2013	33 (6.7%) 491	IHC FISH [h]	NR, Stage I-III 58% Stage IV	Unclear	NR	NR	OS
Jin 2015	10 (1.3%) 754	IHC FISH	NR, Stage I-IV NR Stage IIIB/IV	Unclear	NR	NR	OS
Pan 2014	11 (1.0%) 1,128	IHC FISH RT-PCR	1st line, Stage I-IV 55% Stage II/-V	Unclear	NR	NR	OS

ALK = anaplastic lymphoma kinase; chemo = chemotherapy; EGFR = epidermal growth factor receptor; *KRAS* = Kirsten rat sarcoma proto-oncogene; m = months; MSMM = mass spectrometry multiplex mutation; neg = negative; NSCLC = non-small cell lung cancer; NR = not reported; OS=overall survival; PFS=progression-free survival; pos = positive; pts = patients; R=randomised; RET = rearranged during transfection proto-oncogene; RT-PCR = reverse transcription polymerase chain reaction =; *ROS1* = *ROS* proto-oncogene; TKI = tyrosine kinase inhibitor; vs = versus; yr = year

[a] Phase II trial

[b] NGS was used in co-occurring mutations

[c] A total of 5 (26%) *ROS1*-positive patients received crizotinib

[d] A mix of mutations in *ROS1*-negative patients including: *EGFR* mutations, treated with erlotinib and/or gefitinib and/or afatinib (±cetuximab); *ALK* rearrangement, treated with crizotinib and/or certinib; patients with *KRAS* mutations (treatment unspecified)

[e] 25 patients ROS1 IHC positive. 11 patients *ROS1* FISH positive

[f] A total of 9 (36%) *ROS1*-positive patients received crizotinib

[g] With or without bevacizumab

[h] RT-PCR, DNA extract and pyrosequencing

Overall, the application suggested that *ROS1* positivity was unlikely to be a favourable prognostic factor. The critique considered that the independent prognostic impact of *ROS1* gene rearrangements was difficult to determine due to (i) the potential confounding from differences in disease stage between *ROS1*-positive and broader NSCLC groups; (ii) limited information on the treatments used by *ROS1*-negative patients and (iii) use of crizotinib by *ROS1*-positive patients (eg in Scheffler 2015 and in Wiesweg 2017). As a result, the prognostic impact of *ROS1* gene rearrangements in advanced NSCLC could not be determined.

Predictive evidence

The application did not present evidence comparing crizotinib and pemetrexed in both *ROS1*-positive and *ROS1*-negative patients. The crizotinib studies were in patients with *ROS1*-positive NSCLC and the pemetrexed trial was in a broad NSCLC population with an unknown prevalence of genetic aberrations.

Comparative analytical performance

The analytical performance of ROS1 IHC using staining intensity criteria is presented in the table below.

Table 4: IHC analytic performance outcomes using staining intensity criteria of 2+ or 3+

Study	N[a]	*ROS1*-positive n/N (%)	Sensitivity	Specificity	PPV	NPV
Selinger 2016	**278** [b]	**1/278 (0.4%)**	**100%**	**96.8%**	**10%**	**100%**
Cha 2014	330	13/330 (4.1%)	100%	95%	45%	100%
Jin 2015	**754**	**10/754 (1.3%)**	**80%**	**89.5%**	**9.3%**	**100%**
Wu 2016	238	10/238 (4.2%)	100%	99.6%	91%	100%
Zhou 2016	349	27/349 (7.7%)	100%	34.4%	60%	100%
Cao 2016	**183**	**3/183 (1.6%)**	**100%**	**97.8%**	**43%**	**100%**
Scholl 2013	56	8/56 (14.3%)	100%	91.7%	67%	100%
Mescam-Mancini 2014	121	98/107 (8.4%)	100%	98.0%	82%	100%
Yoshida 2014	270	17/270 (6.3%)	94.1%	87.0%	32.7%	100%
Shan 2015	60	13/60 (21.7%)	76.9%	95.7%	83%	94%
Kao 2016	205	5/199 (2.5%)	100%	96.0%	33%	100%
Rogers 2015	**362**	**3/303 (1.0%)**	**33.3%**	**100%**	**100%**	**99%**

Bold = studies with *ROS1* prevalence less than 2%.

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; NPV = negative predictive value; PPV = positive predictive value; *ROS1* = *ROS* proto-oncogene 1

[a] May be higher than the denominator in the results due to failed tests, inadequate tumour samples or some tests carried out on a subset of total samples.

[b] Retrospective cohort only because prospective cohort was reported as ROS1 IHC positive with any staining.

The sensitivity and specificity of IHC ranged from 33-100% and 34-100%, respectively with most studies reporting sensitivity of 100% where a staining intensity of 2+ or 3+ was considered positive. Rogers et al (2015), (one of two Australian studies) reported a sensitivity of 33%, which was substantially lower than the other studies. The study authors noted the reasons for the difference in results were unclear, and implied that the use of whole tissue blocks may have had an effect on the IHC testing. It was unclear whether the IHC testing practices in some Australian pathology laboratories may result in a higher level of false negative results for ROS1 IHC tests.

The pooled results of IHC analytical performance and meta-analysis performed during the evaluation are presented in the table below.

Table 5: Pooled results of IHC analytic performance outcomes across the studies

Analysis	Sensitivity [95% CI]	Specificity [95% CI]	Likelihood ratios [95% CI]
Pooled (excluding Rogers 2015)	95.1%	93.8%	-
Pooled (including Rogers 2015)	90%	94%	-
Pooled (excluding Rogers 2015)[a]	96.4% [84.5%, 99.2%]	95.5% [92.9%, 97.2%]	Positive LR: 21.5 [13.3, 34.9]
	1-sensitivity (false negative) = 3.6%	1-specificity (false positive) = 4.5%	Negative LR: 0.0 [0.0, 0.2]
Pooled (including Rogers 2015)[a]	94.4% [81.0%, 98.5%]	96.7% [93.7%, 98.3%]	Positive LR: 28.4 [15.0, 53.6]
	1-sensitivity (false negative) = 5.6%	1-specificity (false positive) = 3.3%	Negative LR: 0.1[0.0, 0.2]

CI = confidence interval; IHC = immunohistochemistry; LR = likelihood ratio.

[a] Calculated during the evaluation using STATA metandi command. Metandi fits a hierarchical logistic regression model for meta-analysis of diagnostic test accuracy

The application used the 95.1% sensitivity and 93.8% specificity for ROS1 IHC testing in the economic evaluation (excluding Rogers et al 2015). The meta-analyses conducted during the

evaluation resulted in higher sensitivity and specificity results of 96.4% and 95.5%, respectively excluding Rogers et al (2015) and 94.4% and 96.7% including Rogers et al (2015).

The critique noted that the application implicitly claimed that IHC with a staining intensity of 2+ or greater was an adequate pre-test to identify patients for further determinative testing for those whose NSCLC tumours have *ROS1* gene rearrangements. This was broadly supported by evidence presented in the application. However, one Australian study reported a substantially lower sensitivity than the other studies of 33%, raising concerns about whether the high sensitivity for detecting *ROS1* gene rearrangements reported in the evidence presented in the application would occur in Australian practice. Poor sensitivity is of concern for this test given that its purpose would be to pre-test to decide whether the subsequent determinative test should be used. The application considered that FISH, as the reference standard, would correctly identify all patients with *ROS1* gene rearrangements without false positives. This would be appropriate if accredited pathology laboratories perform *ROS1* FISH testing with accepted quality assurance programs to minimise false results. At its November 2013 consideration, MSAC previously considered that 100% sensitivity and specificity was only true for FISH testing of *ALK* gene rearrangements in ideal circumstances.

The application considered NGS to be highly concordant with *ROS1* FISH testing. However, the application considered that IHC would still be a preferred pre-test. The critique noted that NGS is likely to be performed as a single test to ascertain *ROS1* status alongside other clinically relevant genetic aberrations, and not as a pre-test as proposed in the application. NGS, when conducted with robust methodology, would likely be a highly sensitive and specific test.

The application considered RT-PCR to be unsuitable as a pre-test to detect *ROS1* gene rearrangements because it can only detect known *ROS1* rearrangements. The critique considered that this was appropriate because there are a large number of *ROS1* fusion partners and RT-PCR would incorrectly classify some *ROS1*-positive samples as *ROS1*-negative. MSAC considered that this could be reviewed when these alternative options are of sufficient accuracy to not compromise the overall clinical utility of testing when compared with IHC/FISH testing.

The comparative analytical performance of NGS against FISH testing is presented below.

Table 6: Results of NGS analytic performance outcomes across the studies

Study	N [a]	NGS	FISH	*ROS1* pos n (%)	Sensitivity	Specificity
Pfarr 2016	159	Ion Torrent AmpliSeq™ (ThermoFisher) with RNA Lung Cancer Fusion Panel	ZytoLight SPEC *ROS1* probe	8/135 (6%)	100%[b]	100% [b]
Lira 2014	295	Custom *ROS1* target sequence (NanoString Technologies)	ZytoLight SPEC *ROS1* probe	4/46 (9%)	100%	100%
Reguart 2017	108	nCounter Prep Station™ and Digital Analyzer™	ZytoLight SPEC *ROS1* probe	27/79 (35%)	70%	96%

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; NGS = next-generation sequencing; NPV = negative predictive value; pos = positive; PCR = polymerase chain reaction; PPV = positive predictive value; RNA = ribonucleic acid; *ROS1* = *ROS* proto-oncogene 1; RT-PCR = reverse transcription polymerase chain reaction.

[a] May be higher than the denominator in the results due to failed tests, inadequate tumour samples or some tests carried out on a subset of total samples.

[b] Only a subset of positive and negative cases were verified using FISH.

The application claimed that NGS technologies were highly concordant with *ROS1* FISH testing. The critique considered that this was appropriate and that, if NGS is used to detect *ROS1* gene rearrangements in NSCLC, it is likely to be utilised as the main test to identify *ROS1* rearrangements and other lung cancer genetic aberrations, not as a pre-test as implied in the application.

The application considered that RT-PCR was less reliable than FISH as a diagnostic test to detect *ROS1* gene rearrangements, because RT-PCR is unable to detect *ROS1* fusions that are beyond the range of the primers used. The critique considered that this was appropriate because there are numerous *ROS1* fusion partners which would be missed resulting in more false negative test results, and is consistent with MSAC's November 2013 consideration of RT-PCR for *ALK* testing.

Prevalence

The application performed a systematic literature review to estimate the prevalence of *ROS1* gene rearrangements in non-squamous NSCLC or pulmonary adenocarcinoma. The identified studies reported prevalence of *ROS1* gene rearrangements ranging from 0.4% to 2.9%. The application estimated a prevalence of 1.6% based on the pooled analysis of the studies. Two Australian studies reported prevalence of 0.4% (Selinger et al. 2016) and 0.5% (Rogers et al. 2015).

The critique considered that the studies used to estimate the prevalence of *ROS1* gene rearrangements had a number of issues including:

- use of specimens from patients who had undergone surgical resection resulting in patients with predominantly earlier stage NSCLC. This was not reflective of Australian NSCLC patients who are usually diagnosed with unresectable disease;
- 12 of 20 included studies were in East Asian countries. The prevalence of *ROS1* gene rearrangements might differ in East Asian populations;
- the heterogeneity in the proportion of patients who were female or non-smokers across included studies. (females and non-smokers are more likely to have *ROS1* gene rearrangements); and
- the timing and source of the biopsy sample tested. *ROS1* gene rearrangements may be more frequent in recurrent tumours. The majority of included studies did not provide sufficient detail to determine whether specimens were sourced from primary or recurrent tumours.

As a result, there was some uncertainty associated with the likely prevalence of *ROS1* gene rearrangements in the Australian non-squamous NSCLC population. However, the application appropriately tested the financial impact of using the lower and upper estimates of prevalence of *ROS1* gene rearrangements in sensitivity analyses.

Clinical claim

The overall clinical claim is for superior efficacy and safety over the current scenario (i.e. no genetic testing for *ROS1* rearrangements and standard of care treatments).

12. Economic evaluation

The application presented a modelled cost-utility analysis.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	10 years in the model base case versus 25.4 months in A8081001 and **redacted** months in OO12-01 and 7.5 months in Hanna et al (2004)
Outcomes	LYG and QALYs
Methods used to generate results	Cohort expected value analysis
Health states	Partitioned survival state-transition model with three health states: pre-progression, post-progression and dead.
Utilities	EORTC QLQ-C30 from OO12-01 mapped to EQ-5D-5L. Same for crizotinib and pemetrexed.
Cycle length	8 weeks
Transition probabilities	Modelled using exponential function from pooled crizotinib KM PFS and OS curves and pemetrexed KM PFS and OS curves from Hanna et al. 2004. Modelled throughout (KM not used in base case).

EORTC = European Organisation for Research and Treatment of Cancer; QLQ-C30 = EORTC core quality of life questionnaire; EQ-5D-5l = Euroqol 5-dimension 5-level instrument; KM = Kaplan-Meier; LY = life year; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year

The modelled evaluation was divided into two phases: testing and treatment. For the testing phase, a simple decision analytic was used to determine the proportion of patients who would qualify for crizotinib treatment on the basis of the underlying prevalence of *ROS1* positivity (estimated at 1.61%) and the analytical performance of IHC (95.1% sensitivity and 93.8% specificity) as a pre-test with FISH confirmation (100% sensitivity and specificity). This resulted in 7.7% of ROS1 IHC tested patients having a positive result and receiving FISH testing. The cost per *ROS1*-positive patient was $5,914.

13. Financial/budgetary impacts

The cost of the *ROS1* test per *ROS1*-positive patient was estimated to be around $**redacted** over the first six years of listing. This was based on a *ROS1* gene rearrangement prevalence of 1.6%, assuming all patients undergoing at least one ROS1 IHC testing, of whom **redacted**% have a positive IHC result and **redacted**% undergo *ROS1* FISH testing based on the uptake assumptions in the application. This differed from the economic evaluation because the financial impact assumed that some patients would not undergo *ROS1* FISH. Additionally, it was assumed that *ROS1* FISH testing was repeated in **redacted**% of patients. The proposed MBS fee for *ROS1* FISH testing was $400.

The utilisation of ROS1 IHC testing and patients eligible for *ROS1* FISH testing is presented in the table below.

Table 8: Estimated number of patients receiving the proposed MBS item for *ROS1* FISH testing

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
Patients with advanced or metastatic *EGFR* and *ALK*-negative NSCLC	redacted	redacted	redacted	redacted	redacted	redacted
IHC true positive patients eligible for *ROS1* FISH testing	redacted	redacted	redacted	redacted	redacted	redacted
IHC false positive patients eligible for *ROS1* FISH testing	redacted	redacted	redacted	redacted	redacted	redacted
Estimated uptake of *ROS1* diagnostic testing in eligible patients	redacted%	redacted%	redacted%	redacted%	redacted%	redacted%
Patients receiving proposed ROS1 IHC testing	redacted	redacted	redacted	redacted	redacted	redacted
Patients receiving proposed *ROS1* FISH testing	redacted	redacted	redacted	redacted	redacted	redacted
ROS1-positive patients confirmed by FISH testing	redacted	redacted	redacted	redacted	redacted	redacted

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; FISH = fluorescent *in situ* hybridisation; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; NSCLC = non-small cell lung cancer; *ROS1* = *c-ROS* proto-oncogene 1
Prevalence of *ROS1* gene rearrangement in *EGFR* and *ALK*-negative advanced NSCLC patients = (1/(100%-15%-4.9%))x1.6% = 2%, where: 15% = % of patients with an *EGFR* activating mutation; 4.9% = % patients with *ALK* gene rearrangement; and 1.6% = prevalence of *ROS1* gene rearrangement in non-squamous NSCLC patients

The application estimated that **redacted** patients would receive ROS1 IHC testing in Year 1, increasing to **redacted** patients in Year 6. The critique considered that this may be underestimated due to the low uptake assumed in the application and potential underestimation of the incidence of lung cancer.

The application estimated that **redacted** patients would receive *ROS1* FISH testing in Year 1, increasing to **redacted** patients in Year 6. The critique considered that this was substantially underestimated given the superior comparative effectiveness of crizotinib, clinicians would be very likely to request *ROS1* FISH testing. The size of the population eligible for *ROS1* FISH testing was also dependant on the sensitivity and specificity of ROS1 IHC in Australian practice. There was some variation in ROS1 IHC sensitivity and specificity in the Australian studies presented in the application.

The estimated cost implications to the MBS of *ROS1* testing are presented in the table below.

Table 9: Estimated cost implications to the MBS

	Year 1 2018	Year 2 2019	Year 3 2020	Year 4 2021	Year 5 2022	Year 6 2023
Cost of IHC testing (Item 72846)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Patients receiving proposed *ROS1* FISH testing	redacted	redacted	redacted	redacted	redacted	redacted
Cost of *ROS1* FISH testing	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost of *ROS1* testing	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Cost of ophthalmological examinations (Items 10910, 10913)	$redacted	$redacted	$redacted	$redacted	$redacted	$redacted
Total cost to MBS	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

FISH = fluorescent *in situ* hybridisation; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; *ROS1* = *c-ROS* proto-oncogene 1
- Crizotinib patients have 2 eye tests per year

The application estimated the total cost to the MBS of *ROS1* gene rearrangement testing and ophthalmological examination treatment to cost $**redacted** in Year 1, increasing to $**redacted** in Year 6, resulting in a net cost of $**redacted** million over six years. The critique considered that the cost to the MBS may have been underestimated based on the low uptake

of *ROS1* FISH testing assumed in the application. The ESCs noted that the Pre-Sub-Committee Response increased the assumed uptake of *ROS1* gene rearrangement testing, but that this did not materially change the estimated net cost to the MBS.

The application did not consider the additional re-biopsy costs due to additional testing resulting in a larger group of patients having inadequate biopsy tissue. A sensitivity analysis was conducted during the evaluation estimating that an additional 15% of patients who undergo IHC testing would require a re-biopsy. This was estimated to cost $**redacted** (85% fee) based on the utilisation of lung biopsy items 30696, 30710, 38812 in the 12 months to June 2017. This did not have a very large impact on net financial implications for government health budgets.

14. Key issues from ESC for MSAC

The proposed item descriptor specifies that, prior to confirmatory fluorescent *in situ* hybridisation (FISH) testing for *ROS1* gene rearrangement status, patients should have immunohistochemical (IHC) examination of tumour tissue for evidence of *ROS1* immunoreactivity with a staining intensity of 2+ or greater. The ESCs noted that the clinical evidence presented for the sensitivity of IHC broadly supports IHC as an adequate pre-test to identify patients whose tumours have *ROS1* gene rearrangements. The ESCs noted that there was one Australian study (Rogers TM et al 2015) that reported a substantially lower sensitivity for ROS1 IHC testing. However, this study was considered to be an outlier and meta-analyses undertaken during the evaluation suggested that inclusion or exclusion of this study had minimal impact on the overall estimated sensitivity and specificity. The ESCs advised that IHC testing in Australian practice is likely to be sufficiently sensitive for use as a pre-test for *ROS1* gene rearrangement.

The ESCs considered whether *ROS1* gene rearrangement should be limited to FISH testing, and considered the cost and relevance of next generation sequencing (NGS) for the proposed service. The ESCs noted the position of the Royal College of Pathologists of Australasia (RCPA), that testing for *ROS1* should not be restricted to a specific technology (i.e. FISH). This is consistent with PASC advice that, if alternative testing methods are shown to have equivalent analytical performance characteristics and incur similar costs, then MSAC may consider broadening MBS funded options beyond FISH. The evaluator's commentary proposed that NGS, if conducted with robust methodology, would likely be a highly sensitive and specific test. The ESCs noted that NGS appears to be less costly to perform, with pathology providers currently testing for several genetic aberrations in NSCLC, colorectal cancer and melanoma for the cost of a single MBS item. However no costing information for NGS is provided in the application, and it has not been considered as part of the economic model or financial estimates.

The ESCs therefore advised that, if MSAC is confident that NGS has at least equivalent sensitivity to IHC + FISH for *ROS1* testing at an equivalent or lower cost, then an item that allows for more than one test methodology might be appropriate. However, as this has not been assessed for clinical and cost effectiveness, an item for one or more NGS gene panels (eg, RNA and DNA panels) in NSCLC may need separate MSAC consideration. The ESCs also considered that listing of an item for one or more NGS gene panels in NSCLC would have implications for the current MBS items for testing for *EGFR* and *ALK* gene rearrangement which also depend on prior IHC-based testing. It would also have implications for the sequence of tests in the proposed clinical algorithm as it is likely that all testing would be completed at the time of the initial diagnostic biopsy. The ESCs advised that MSAC may wish to consider listing the FISH test as proposed until further analysis of the cost-

effectiveness and budget impact of one or more potential gene panel items for NSCLC can be provided.

The ESCs also noted that some lung cancer gene aberrations are acquired somatic mutations tested in genomic DNA, and some are gene fusions (eg *ROS1*) usually tested in cDNA prepared from RNA, which would require two distinct platforms for testing.

The ESCs considered whether the stability of *ROS1* gene rearrangements over time would be sufficient to allow *ROS1* testing without re-biopsy. The ESCs noted the sponsor's comment that the assumption of stability is based on the biological understanding of *ROS1* as an oncogenic driver mutation (similar to *ALK* rearrangement stability over time). The ESCs noted that, due to the paucity of available evidence, it is not known whether *ROS1* gene rearrangements are stable or unstable over time or following treatment. Two studies included in the application that examined re-biopsies in patients with NSCLC suggested that *ROS1* gene rearrangements occurred more frequently in recurrent tumours. The ESCs considered that the evidence suggesting higher prevalence in recurrent NSCLC was not strong, due to small numbers in one study and the lack of *ROS1* status confirmation by FISH in the other. The ESCs considered that, if there is no evidence that *ROS1* rearrangements are unstable over time, it may not be in the patients' best interest to undergo potentially unnecessary biopsy, but if evidence emerges that *ROS1* rearrangements are unstable, then a requirement for re-biopsy would need to be considered at that time.

The ESCs considered whether the *ROS1* FISH item should be pathologist determinable. The ESCs noted that *EGFR* and ALK IHC testing are pathologist determinable, while *ALK* FISH testing is not. The ESCs noted that there are concerns about multiple, sequential tests on a limited specimen, but considered that the requirement for IHC pre-testing should minimise the number of additional biopsies performed. The ESCs advised that, if the proposed testing sequence is adopted, the ROS1 IHC test should be pathologist determinable in *EGFR*-negative, *ALK*-negative samples at the time of diagnosis, but *ROS1* FISH testing should not be pathologist determinable.

The ESCs noted the limited clinical evidence for *ROS1* testing and crizotinib treatment makes it difficult to assess the magnitude of benefit for patients, but acknowledged that this is the best available evidence in this small patient population. The ESCs also noted the observation of increased fatal events for patients treated with crizotinib compared with standard treatment based on the naïve comparison presented.

The ESCs considered that, overall, the modelling approach was appropriate while acknowledging it was based on the limited available clinical evidence. The ESCs noted that the ICER was sensitive to the time horizon and that a 5-year time horizon may be more appropriate for the base case. Horizons of 2 or 5 years could be considered in sensitivity analyses. The ESCs noted that quality of life outcomes were mapped to EQ-5D-5L values, which introduces some uncertainty, though it is a reasonable approach given the available evidence. The ESCs questioned the reliability of the resource use applied in the model which was based on a survey with a 6% response rate (22 oncologists with a mean of 15 patients each). The ESCs suggested it may be informative to include patients with squamous histology in a sensitivity analysis as only a small proportion would need treatment but testing all patients may be resource intensive.

The ESCs advised that, overall, the base case ICER may be underestimated as the uptake of the test may be underestimated and time horizon long.

The ESCs considered whether *ROS1* testing and crizotinib treatment should be allowed for patients with squamous NSCLC. The ESCs noted that *ROS1* gene rearrangements are rare in

squamous NSCLC (1% of patients in the crizotinib studies). Allowing access to *ROS1* testing for squamous NSCLC would require separate items for *EGFR* and *ALK* tests in squamous patients as the currently listed MBS items for *EGFR* and *ALK* are limited to non-squamous and "not otherwise specified" (NOS) histology. The ESCs noted that this testing scenario has not been costed or modelled.

The ESCs noted that the sensitivity analyses indicated that there is little difference to the total financial impact resulting from MBS items. The ESCs noted that the overall approach appears reasonable, although the uptake of testing is potentially underestimated due to conservative estimates of the prevalence of lung cancer and the prevalence of *ROS1* gene rearrangements. The ESCs noted that some patients may currently be paying privately for the test, and questioned whether this had been considered in the financial estimates. The ESCs considered that the following additional cost analyses may be informative:

1. The cost for a next-generation sequencing (NGS) panel replacing the current IHC and FISH testing for *EGFR*, *ALK* and *ROS1* status under a single MBS item.
2. An estimate of the cost of testing for *ROS1* gene status at initial diagnosis.
3. An estimate of the cost of expanding the testing to include *EGFR* or *ALK* positive patients (which was considered to occur rarely).

While there was perceived consumer support for access to an effective new treatment in this patient population, the ESCs also noted consumer concern to minimise the potential requirement for additional biopsies.

15. Other significant factors

Nil

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

Pfizer welcomes the MSAC and the PBAC's recommendations to make diagnostic testing for ROS1 rearrangements and crizotinib available for the treatment of advanced ROS1-positive non-small cell lung cancer; a rare disease with high unmet clinical need.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website