

6.02 CRIZOTINIB, 250 mg capsule, 200 mg capsule, Xalkori®, Pfizer Australia Pty Ltd

1 Purpose of Application

- 1.1 The submission requested a new Section 85 Authority Required 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.
- 1.2 The codependent integrated submission also requested that a new Medical Benefits Schedule (MBS) item number for *ROS* proto-oncogene 1 (*ROS1*) fluorescent in-situ hybridisation (FISH) testing as a co-dependent medical service that is performed to inform eligibility for crizotinib treatment in patients with *ROS1*-positive 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 anaplastic lymphoma kinase (*ALK*) gene rearrangement. This aspect is being considered by the Medical Services Advisory Committee (MSAC).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description for medicine	Description for test
Population	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-squamous NSCLC with evidence of a <i>ROS1</i> gene rearrangement ^a	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-squamous or histology NOS specified NSCLC without both <i>EGFR</i> activating mutations and <i>ALK</i> gene rearrangements and have demonstrated 2+ or 3+ staining intensity for the <i>ROS1</i> protein by IHC
Intervention	Crizotinib 200 mg or 250 mg twice daily	FISH testing for <i>ROS1</i> gene rearrangement after positive IHC testing ^b for <i>ROS1</i>
Comparator	Standard of care: pemetrexed	No <i>ROS1</i> gene rearrangement testing
Outcomes	Progression-free survival, overall survival and adverse events	Analytic performance: sensitivity, specificity, NPV, PPV Comparative performance: concordance with evidentiary standard, ROC, reclassification index Rates of re-testing and rates of re-biopsy
Clinical claim	The overall claim was for superior efficacy and safety over standard care (no testing for <i>ROS1</i> rearrangements and standard of care treatments).	

Source: Table 1.1.1, p4 of the submission

ALK = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; NPV = negative predictive value; NSCLC = non-small cell lung cancer; NOS = not otherwise specified; PPV = positive predictive value; ROC = receiver operating characteristic; *ROS1* = *ROS* proto-oncogene 1; WHO = World Health Organisation

^a Defined as 15% (or greater) positive cells by FISH

^b IHC to be performed as a pre-test as basis to decide whether to perform confirmatory FISH testing

2 Requested listing

2.1 The submission requested a new Section 85 Authority Required 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.

2.2 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Crizotinib capsule, 250 mg, 60	1	1	\$7,276.18 (Published) \$ (Effective)	Xalkori Pfizer Australia Pty Ltd
Crizotinib capsule, 200 mg, 60	1	1	\$7,276.18 (Published) \$ (Effective)	Xalkori Pfizer Australia Pty Ltd
Category / Program:	Section 85 – General Schedule			
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)			
Condition:	non-small cell lung cancer			
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer			
Treatment phase:	Initial treatment			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed on or after prior platinum based chemotherapy AND Patient must have a WHO performance status of 2 or less			
Population criteria:	Patient must have evidence of <i>ROS1</i> gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.			
Administrative advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			
Prescriber Instructions	<i>The authority application must be made in writing and must include:</i> (1) a completed authority prescription form; and (2) a completed <i>ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form</i> , which includes details of <i>ROS1</i> gene rearrangement in tumour material.			

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Crizotinib capsule, 250 mg, 60	1	1	\$7,276.18 (Published) \$ [REDACTED] (Effective)	Xalkori Pfizer Australia Pty Ltd
Crizotinib, capsule 200 mg, 60	1	1	\$7,276.18 (Published) \$ [REDACTED] (Effective)	Xalkori Pfizer Australia Pty Ltd
Category / Program:	Section 85 – General Schedule			
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)			
Condition:	non-small cell lung cancer			
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer			
Treatment phase:	Continuing treatment			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	The treatment must be the sole PBS-subsidised therapy for this condition AND Patient must have previously been issued with an authority prescription for this drug <i>received PBS-subsidised treatment with this drug for this condition</i> AND Patient must not have progressive disease <i>while receiving PBS-subsidised treatment with this drug for this condition.</i>			
Administrative advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			
Prescriber Instructions	<i>Authority applications for continuing treatment may be made by telephone to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).</i>			

Name, Restriction, Manner of administration and form	Max. Qty (packs)	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
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Crizotinib capsule, 200 mg, 60	1	1	\$7,276.18 (Published) \$ [REDACTED] (Effective)	Xalkori Pfizer Australia Pty Ltd
Category / Program:	Section 85 – General Schedule			
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)			
Condition:	non-small cell lung cancer			
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer			
Treatment phase:	Grandfathering treatment			
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined			
Clinical criteria:	<i>Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to [PBS listing date]</i> AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC AND The treatment must be the sole PBS-subsidised therapy for this condition AND The condition must have progressed on or after prior platinum based chemotherapy AND <i>Patients may qualify for PBS-subsidised treatment under this restriction once only. Patient must have a WHO performance status of 2 or less</i>			
Population criteria:	Patient must have evidence of <i>ROS1</i> gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing.			
Administrative advice:	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.			
Prescriber Instructions	<i>The authority application must be made in writing and must include:</i> (1) a completed authority prescription form; and (2) a completed <i>ROS1-Positive Non-Small-Cell Lung Cancer Authority Application - Supporting Information Form</i> , which includes details of <i>ROS1</i> gene rearrangement in tumour material.			

2.3 Crizotinib tablets are taken at a dose of 250 mg twice daily orally until disease progression. The lower dose of 200 mg twice daily can be used when patients experience certain adverse events (AEs) with the standard dose.

2.4 The requested restriction was for a second-line listing after platinum-based chemotherapy. This was stricter than the proposed TGA indication which was for the treatment of patients with *ROS1*-positive advanced NSCLC. However, the submission also proposed that a crizotinib restriction that is not restricted to a particular line of therapy may be appropriate. At its November 2014 consideration of crizotinib for anaplastic lymphoma kinase (*ALK*)-positive NSCLC, the PBAC noted that, with a second-line listing, there may be a reluctance to use first-line platinum-based chemotherapy in some patients before starting crizotinib. This would be particularly true if *ROS1* status was known at diagnosis. The Pre-Sub-Committee Response

(PSCR) (p3) concurred that there would likely be a reluctance to use first-line platinum-based chemotherapy before starting crizotinib once a patient's *ROS1* status is known, and requested the PBAC to consider a listing that is agnostic of line of therapy.

- 2.5 The submission proposed a Special Pricing Arrangement (SPA). Crizotinib currently has an SPA for the ALK-positive NSCLC listing.
- 2.6 The submission sought a grandfathering restriction for patients accessing crizotinib through a compassionate access programs and on private prescription.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

- 3.1 TGA registration status: The submission was made under TGA/PBAC Parallel Process. The Clinical Evaluation Report and TGA Delegate's overview were available at the time of PBAC consideration.
- 3.2 Crizotinib for advanced *ROS1*-positive NSCLC has not been considered previously by the PBAC, however the ESCs noted that this submission was the result of an invitation from the PBAC to the sponsor for a submission for this rare cancer population. Crizotinib for *ALK*-positive Stage IIIB or Stage IV non-squamous or histology NOS specified NSCLC was listed on the PBS on 1 July 2015. The PBAC recommended the listing of crizotinib for the treatment of patients with *ALK*-positive, advanced NSCLC at its November 2014 meeting under a Managed Entry Scheme (MES). At its March 2017 meeting, the PBAC considered that the requirements of the MES had been satisfied.

4 Population and disease

- 4.1 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 takes place 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 ESCs noted that a very small group of NSCLCs are *ROS1* positive, with an estimated prevalence of 1.6%.
- 4.2 The proposed population for crizotinib treatment was patients in whom Stage IIIB or IV, non-squamous or histology NOS NSCLC is confirmed to have *ROS1* rearrangements by FISH testing, and whose NSCLC has progressed on or after platinum based chemotherapy. For brevity, the treatment population is referred to as advanced *ROS1*-positive NSCLC.
- 4.3 The current treatment options for patients with advanced *EGFR*-negative, *ALK*-negative NSCLC are first-line platinum-based chemotherapy or best supportive care for patients with poor performance status. Patients who progress to second-line treatment are treated with pemetrexed, the preferred treatment for patients with non-squamous NSCLC, or docetaxel.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated pemetrexed as the main comparator. This was the appropriate comparator. The submission stated that nivolumab was not considered a comparator because it would be used after crizotinib as recommended by the nivolumab Product Information (PI) for patients with *EGFR* or *ALK* genomic aberrations. The ESCs and PBAC considered that pemetrexed, as a representative of single-agent chemotherapy, was the appropriate comparator.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. At the hearing, a clinician presented data highlighting the benefits of crizotinib treatment in a small population with high unmet clinical need. The clinician also stated that the effects of crizotinib in the *ALK*-positive and *ROS1*-positive NSCLC populations were similar, and advised that the two biomarkers are similar oncogene drivers, resistance to crizotinib eventually develops in both settings, and the tolerability profile of crizotinib is independent of the choice of biomarker. The clinician also noted that while crizotinib can also be administered in the treatment-naïve *ALK*-positive population, the available evidence in the *ROS1*-positive population was in the relapsed/refractory setting. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating *ROS1*-positive NSCLC patients, and provided a qualitative insight into the comparative profile of crizotinib in *ALK*- and *ROS1*-positive populations.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (7) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with crizotinib, and emphasized its effectiveness in reducing tumour burden and improving quality of life.
- 6.3 A comment from Rare Cancers Australia noted that the PBS listing of crizotinib would make a meaningful difference in the lives of the small population of *ROS1*-positive NSCLC patients by slowing disease progression and extending survival.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the crizotinib submission, noting that the PBS listing of crizotinib in this population would fill a significant area of unmet need. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for crizotinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)¹, based on single

¹ Cherny NI, Sullivan R, Dafni U, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26:1547-73, 2015

arm studies.

Clinical trials

6.5 The submission was based on a naïve comparison of two single-arm studies of crizotinib in the second-line treatment of NSCLC (n = 180) with the pemetrexed arm of one randomised controlled trial that compared pemetrexed to docetaxel in the second-line treatment of NSCLC (Hanna et al 2004, n = 283 in the pemetrexed arm). Scagliotti et al. 2009: a retrospective analysis of Hanna et al. 2004 by NSCLC histology (squamous and non-squamous), was included during the evaluation. The submission also presented four supportive studies of the clinical effectiveness of crizotinib.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Primary evidence for crizotinib		
A8081001 (PROFILE 1001)	Pfizer Inc. Internal study report title. Phase 1 Safety, Pharmacokinetic and Pharmacodynamic Study of PF-02341066, a c-Met/HGFR Selective Tyrosine Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer.	01 April 2016 CSR
	Shaw A.T, et al. Crizotinib in <i>ROS1</i> -rearranged Non-Small-Cell Lung Cancer.	N Engl J Med (2014); 371(21): 1963-1971.
	Shaw A.T, et al. Crizotinib in advanced <i>ROS1</i> -rearranged non-small cell lung cancer (NSCLC): updated results from PROFILE 1001	Ann Oncol (2016) 27 (suppl_6): 1206PD.
OO12-01	OxOnc Development, LP and Pfizer, Inc. Phase 2, open-label, single-arm study of the efficacy and safety of crizotinib in East Asian patients with advanced <i>ALK</i> -negative non-small cell lung cancer (NSCLC) harbouring a translocation or inversion involving the <i>c-ros</i> oncogene (<i>ROS1</i>) locus	26 January 2017
	Goto, K., et al. Phase II study of crizotinib in east Asian patients (pts) with <i>ROS1</i> -positive advanced non-small cell lung cancer (NSCLC).	J Clin Oncol (2016); 34: suppl; abstr 9022
Supportive evidence for crizotinib		
Mazières 2015 (EUROS1)	Mazières, J., et al. Crizotinib Therapy for Advanced Lung Adenocarcinoma and a <i>ROS1</i> Rearrangement: Results from the EUROS1 Cohort.	J Clin Oncol (2015); 33 (9): 992 – 999.
Moro-Sibilot 2015 (ACSé)	Moro-Sibilot, D., et al. Crizotinib in patients with advanced <i>ROS1</i> -rearranged non-small cell lung cancer (NSCLC). Preliminary results of the ACSé phase II trial.	J Clin Oncol (2015); 33 (15)_suppl (May 2015)
Michels 2016 (EUCROSS)	Michels S., et al. A European phase II trial to evaluate efficacy and safety of crizotinib treatment in advanced adenocarcinoma of the lung harbouring <i>ROS1</i> translocations-Preliminary results.	Oncology Research and Treatment (2016); 39: 209 -210.
Zhang 2016	Zhang, L., et al. Efficacy of crizotinib and pemetrexed-based chemotherapy in Chinese NSCLC patients with <i>ROS1</i> rearrangement.	Oncotarget (2016); 7(46):75145-75154.
Evidence for comparator treatments		
Hanna et al. 2004	Hanna, N. et al. Randomised Phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy.	J of Clin Oncol (2004); 22(9): 1589-1597.
Scagliotti 2009	Scagliotti G, Hanna, N, Fossella, F et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies.	The Oncologist 2009; 14: 253-263.

Source: Table 2.2.1, pp85-7 of the submission and compiled during the evaluation

c-Met/HGFR = tyrosine-protein kinase Met or hepatocyte growth factor receptor; CSR = clinical study report; NSCLC = non-small cell lung cancer; *ROS1* = *ROS* proto-oncogene 1

6.7 The key features of the studies included for the naïve comparison of the efficacy of crizotinib in patients with *ROS1*-positive advanced NSCLC versus pemetrexed in a broader population of NSCLC with an unknown prevalence of genetic aberrations are summarised in the table below.

Table 3: Key features of the included evidence, crizotinib vs. pemetrexed (naïve comparison)

Trial	Trial/study design	N	Risk of bias	Patient population	Key outcomes	Model use
Primary studies						
Crizotinib						
A8081001	Phase I, MC, OL (AU, S.Korea, USA)	53	High	<i>ROS1</i> -pos (FISH, RT-PCR) Stage III or IV NSCLC	ORR ^a , PFS, OS, AEs	Pooled results ^c
OO12-01	Phase II, MC, OL (East Asia) ^b	127	High	<i>ROS1</i> -pos, <i>ALK</i> -neg (FISH, IHC, RT-PCR); adv NSCLC	ORR ^a , PFS, OS, AEs	
Pemetrexed						
Hanna et al. 2004	Phase III, MC, R, OL	283	Low	Stage IIIB or IV NSCLC (unselected pts)	OS ^a , ORR, PFS, AEs	Yes
Scagliotti 2009 ^d	Retro	283	High	Stage IIIB or IV NS NSCLC	OS, PFS by histology	No
Supportive studies						
Crizotinib						
Michels 2016	Phase II, OL (Spain, Germany)	33	Unclear	<i>ROS1</i> -pos (FISH); adv NSCLC	PFS ^a , ORR	No
Moro-Sibilot 2015	Phase II, OL (France)	34	Unclear	<i>ROS1</i> -pos (FISH); adv NSCLC	ORR ^a , OS, AEs	
Mazières 2015 ^e	Retro, MC, OL (Europe) ^f	32	High	<i>ROS1</i> -pos (FISH); Stage IV NSCLC (adeno)	ORR ^a , PFS, OS, AEs	
Zhang 2016 ^g	Retro, OL (China)	51 ^g	High	<i>ROS1</i> -pos (RT-PCR); adv NSCLC	PFS ^a , ORR	

Source: Compiled during the evaluation from pp101-127 of the submission, A8081001 CSR, OO12-01 CSR, Hanna et al. 2004, Scagliotti et al. 2009, Michels et al 2016, Moro-Sibilot 2015, Mazières 2015 and Zhang 2016

Adeno = adenocarcinoma; Adv = advanced (not further defined); AE = adverse events; AU = Australia; MC = multi centre; FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; neg = negative; NS = non-squamous; NSCLC = non-small cell lung cancer OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; pos = positive; Retro = retrospective; R = randomised; RT-PCR = reverse transcription polymerase chain reaction; S.Korea = South Korea; USA = United States of America; vs. = versus

^a Primary outcome

^b China, Japan, Taiwan and South Korea

^c Combined Kaplan-Meier data from restricted cohort (OS and PFS restricted at last event)

^d Retrospective analysis of Hanna et al. 2004 by NSCLC histology (squamous and non-squamous)

^e A total of 26 (81%) patients received pemetrexed (either alone or in combination with platinum-based chemotherapy and either before or after crizotinib)

^f France, Switzerland, Italy, Germany, Poland, and the Netherlands

^g A total of 15 (29%) patients received crizotinib in $\geq 2^{\text{nd}}$ line, 49 (96%) patients received pemetrexed (1st line: n=28; $\geq 2^{\text{nd}}$ line: n=21) and 44 (86%) patients received non-pemetrexed-based chemotherapy (1st line: n=19; $\geq 2^{\text{nd}}$ line: n=25)

6.8 There were a number of transitivity issues across the crizotinib studies and Hanna et al (2004). These included:

- the comparison of a *ROS1*-positive NSCLC population in the crizotinib studies compared with an unselected pemetrexed population in Hanna et al 2004;
- larger proportion of patients with a performance status of 2 in Hanna et al (2004) (2% in A8081001, none in OO12-01 vs. 11.4% in Hanna et al (2004));

- larger proportion of patients with metastatic disease at baseline in the crizotinib studies (>87% in A8081001 and 95% in OO12-01 vs. 75% in Hanna et al (2004));
- inclusion of patients with squamous NSCLC in Hanna et al 2004 (28%) who have poorer outcomes with pemetrexed;
- prior use of chemotherapy at baseline (>80% in crizotinib studies vs. 100% in Hanna et al (2004));
- differences in treatment practices due to Hanna et al. 2004 being conducted in 2001 to 2003. The clinician survey of health service utilisation (HSU) presented in the submission reported that 22 oncologists estimated Australian patients received a median of six cycles of pemetrexed, compared with four in Hanna et al (2004); and
- predominantly patients of East Asian ethnicity, who have better NSCLC prognosis (Zhou and Cristiani, 2011): in crizotinib studies (40% in A8081001 and 100% in OO12-01); unknown in Hanna et al (2004).

6.9 The ESCs considered that transitivity issues were inherent to most indirect comparisons, and advised that these issues should be interpreted in the light of the rarity of the patient population, noting that it was unlikely that direct randomised trials would be available for this patient population in the near future.

Comparative effectiveness

6.10 The pooled results for overall survival (OS) for crizotinib from A8081001 and OO12-01 compared to pemetrexed are presented in the table below. The Kaplan-Meier plots for OS for crizotinib and pemetrexed are presented in Figures 1 and 2.

Table 4: Crizotinib pooled OS outcomes (Studies A8081001^a and OO12-01)

	Crizotinib Pooled A8081001 & OO12-01 (N=53)	Pemetrexed Hanna et al (2004) (N=283)
Median follow-up for OS	-	7.5 months ^b
Deaths n/N (%)	██████████	409/501 (71.6%)
Median OS, months (95% CI)	██████████	8.3 months

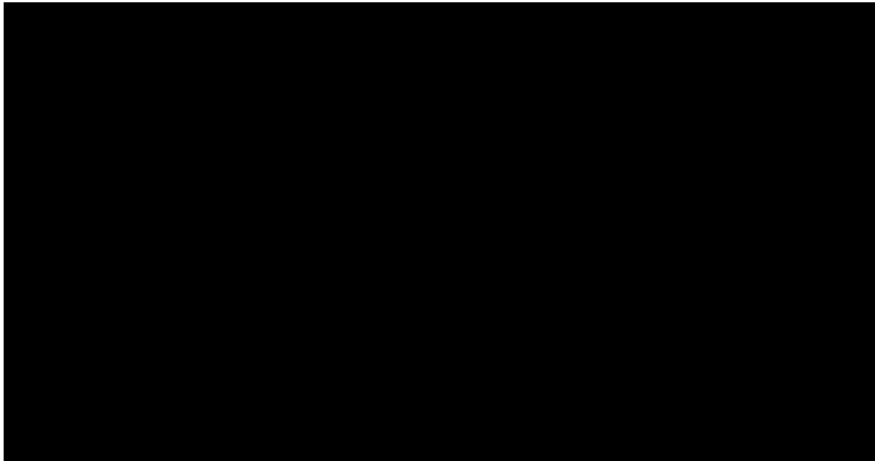
Source: Table 2.6.2, p180 of the submission

CI = confidence interval; NR = not reached; OS = overall survival

^a Safety analysis population

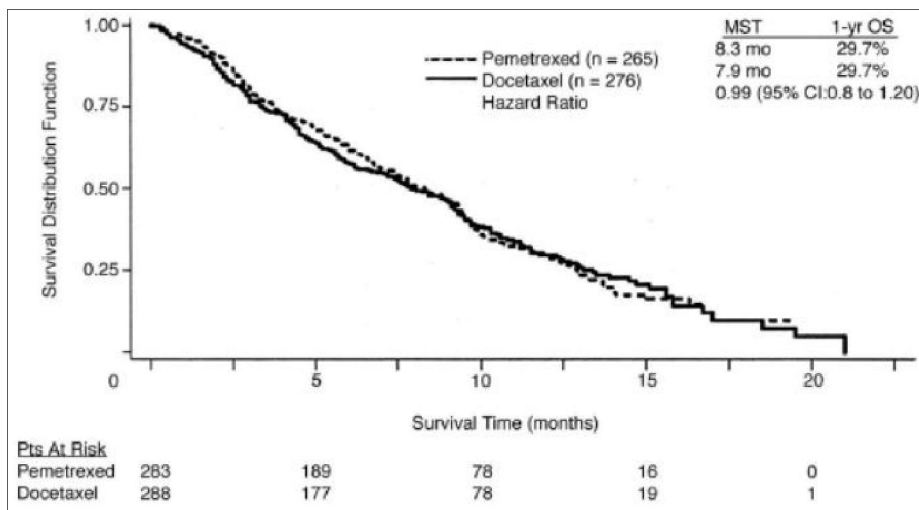
^b For both pemetrexed and docetaxel arms

Figure 1: Crizotinib pooled OS Kaplan-Meier curve (N = 180)



Source: Figure 2.6.2, p181 of the submission
OS = overall survival

Figure 2: Kaplan-Meier plot of OS for pemetrexed from Hanna et al (2004)



Source: Figure 2.5.9, p149 of the submission
CI = confidence interval; MST = median survival time; OS = overall survival

- 6.11 Median overall survival was not reached in the pooled analysis for crizotinib. Crizotinib showed a trend towards a substantial improvement in OS compared to the results for pemetrexed. However, this may have been overestimated due to the inclusion of patients with possible poorer outcomes in the pemetrexed study (Hanna et al (2004)), worse performance status, and squamous NSCLC) compared to the crizotinib studies that included patients of East Asian ethnicity (who have better NSCLC prognosis); and which employed censoring practices resulting in patients being censored for reasons other than loss to follow-up.
- 6.12 The ESCs noted that, although median OS was not reached in the pooled analysis for crizotinib, the crizotinib arm showed a trend towards an improvement in OS compared to the results for pemetrexed.
- 6.13 The ESCs considered that incremental OS was likely to be overestimated, as (i) crizotinib studies employed censoring practices resulting in patients being censored for reasons other than loss to follow-up; and (ii) the magnitude of OS benefit with

crizotinib was unknown as only 31% of patients had died in the pooled crizotinib analysis. As such, the ESCs also advised that the magnitude of incremental overall survival, if any, with crizotinib treatment over pemetrexed treatment was difficult to determine from the evidence presented in the submission.

6.14 Table 5 presents the naïve comparison of PFS outcomes with crizotinib compared with pemetrexed. Figure 3 presents the Kaplan-Meier plot for crizotinib PFS.

Table 5: Crizotinib pooled PFS outcomes (Studies A8081001 and OO12-01)

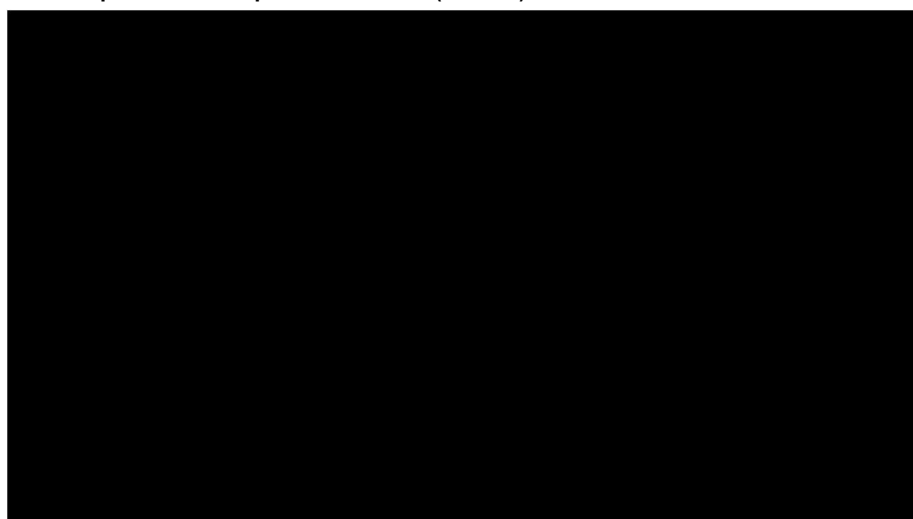
Study and intervention	Crizotinib Pooled A8081001 & OO12-01 (N=180)	Pemetrexed Hanna et al. 2004 (n=283)
Median follow-up for PFS	NR	7.5 months
Patients with events n/N (%)	██████████	—
Censored n/N (%)	██████████	18 (6.4%)
Median PFS, months	██████████	2.9 (-, -)

Source: Table 2.6.1, p179 of the submission

Note: PFS, quartiles, and probability of survival were presented with the Kaplan-Meier estimates calculated using the log cumulative hazard transformation.

CI = confidence interval; KM = Kaplan-Meier; NR = not reached; PFS = progression-free survival

Figure 3: Crizotinib pooled PFS Kaplan-Meier curve (N = 180)



Source: Figure 2.6.1, p179 of the submission

PFS = progression-free survival

6.15 Crizotinib showed superior median progression-free survival at ██████ months, compared with pemetrexed at 2.9 months. This was likely overestimated due to:

- patients treated with pemetrexed in Hanna et al 2004 having worse prognostic factors such as worse performance status, squamous NSCLC, and prior use of chemotherapy at baseline (favoured crizotinib);
- use of fewer doses of pemetrexed than Australian practice (favoured crizotinib);
- the results of Hanna et al 2004 not capturing improvements in clinical practice that have occurred since the trial was conducted; and
- the predominantly East Asian ethnicity of patients who have better NSCLC prognosis in the crizotinib studies.

- 6.16 The PSCR (p3) argued that the differences in prognosis from the number of prior treatments was unlikely to have favoured crizotinib, noting that a large proportion of patients in the crizotinib studies were more heavily pre-treated than the pemetrexed patients in Hanna et al 2004.
- 6.17 The comparison of a *ROS1*-positive NSCLC population in the crizotinib studies compared with an unselected pemetrexed population in Hanna et al 2004 was a substantial transitivity issue. The direction of this bias is unknown. The prognostic impact of *ROS1* gene rearrangements was unknown. In addition, it was unknown whether *ROS1* gene rearrangements are a treatment effect modifier for pemetrexed.
- 6.18 Scagliotti et al 2009 reported median progression-free survival of 3.1 months and overall survival of 9.3 months for patients with non-squamous NSCLC treated with pemetrexed in Hanna et al 2004.
- 6.19 The submission did not present a comparison of crizotinib with first line treatment to support a PBS listing that was agnostic to the line of treatment. In A8081001, median progression-free survival and overall survival were not reached for the seven patients with no prior therapies. OO12-01 reported median progression-free survival of [REDACTED] months for 24 patients not previously treated with chemotherapy. Overall survival by number of prior treatments was not presented for OO12-01.

Comparative harms

- 6.20 Table 6 presents the naïve comparison of safety data from the two crizotinib studies and Hanna et al (2004).

Table 6: Summary of all causality adverse events across primary evidence

	A8081001 Crizotinib n (%) N=53	OO12-01 Crizotinib n (%) N=127	Hanna et al. 2004 Pemetrexed (%) N=265
Any grade	53 (100%)	████████	-
Grade 3-4	28 (53%)	████████	-
Fatal AE	9 (17%)	████████	3 (1%)
Treatment-related AE leading to discontinuation			
Permanent discontinuation	4 (8%)	████████	-
Dose reduction	6 (11%)	████████	-
Temporary discontinuation	24 (45%)	████████	-
Grade 3 or 4 AE occurring ≥ 5% of patients			
Hypophosphataemia	8 (15%)	████████	-
Neutropenia	5 (9%)	████████	14 (5.3%)
Elevated transaminases	2 (4%)	████████	21 (8%) ^a
Vomiting	3 (6%)	█	4 (1.5%)
Fatigue	-	█	14 (5.3%)
Most frequent AEs of any grade (≥ 30% of patients)			
Vision Disorder	46 (87%)	████████	-
Elevated Transaminases	19 (36%)	████████	21 (8%) ^a
Nausea	31 (59%)	████████	82 (31%)
Diarrhoea	24 (45%)	████████	34 (13%)
Vomiting	27 (51%)	████████	-
Constipation	23 (43%)	████████	42 (16%)
Oedema	29 (55%)	████████	13 (5%)
Upper Respiratory Infection	21 (40%)	████████	-
Neutropenia	9 (17%)	████████	-
Dizziness	21 (40%)	████████	-
Fatigue	17 (32%)	████████	90 (34%)
Neuropathy	16 (30%)	████████	-

Source: Table 2.5.25, p155, Tables 2.5.30-2.5.34, pp 161-164 of the submission, Table 25, p88 of the OO12-01 CSR and Hanna et al. 2004

AE = adverse event; ALT = alanine aminotransferase; NR = not reached

^a Elevated ALT only

- 6.21 The common adverse events that occurred with crizotinib were vision disorders, elevated transaminases, oedema, and gastrointestinal adverse events. Based on a naïve comparison, the rates of Grade 3 or 4 neutropenia, hypophosphataemia, and vomiting showed a trend towards occurring more frequently in crizotinib. Grade 3 or 4 fatigue showed a trend towards occurring more frequently with pemetrexed.
- 6.22 Notwithstanding the inherent biases of indirect comparisons, the ESCs considered that the fatal adverse event rate in the crizotinib studies (17% and █%) appeared to be greater than for pemetrexed (1%).

Benefits and harms

- 6.23 The naïve comparison presented in the submission did not allow for a comparison of the benefits and harms of crizotinib and pemetrexed. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.24 The submission claimed that crizotinib had superior effectiveness over its main comparator, pemetrexed, in patients with *ROS1*-positive advanced NSCLC who have progressed on prior platinum-based chemotherapy.
- 6.25 The ESCs considered that, although crizotinib was likely to be more effective than pemetrexed, the magnitude of incremental effectiveness was difficult to estimate. Overall, the ESCs and PBAC advised that the biases in the indirect comparison along with the transitivity issues indicated that the incremental effectiveness of crizotinib over pemetrexed was overestimated in the submission; however, the PBAC was satisfied that the incremental effectiveness of crizotinib treatment in the *ROS1*-positive NSCLC population would be similar to that in the *ALK*-positive NSCLC population.
- 6.26 The submission claimed crizotinib's adverse event profile was no worse than standard care single agent chemotherapy (pemetrexed). The ESCs noted that the PBAC previously accepted that crizotinib had non-inferior safety compared to pemetrexed and docetaxel at its November 2013 consideration of crizotinib for *ALK*-positive NSCLC (paragraph 9, November 2013 PBAC public summary document (PSD)).
- 6.27 The ESCs considered that the submission's claim of non-inferior safety compared to standard care single agent chemotherapy (pemetrexed) was reasonable.
- 6.28 The PBAC considered that the submission's claim of non-inferior safety compared with pemetrexed was reasonable, but noted that the fatal adverse event rate in the crizotinib studies (17% and █%) appeared to be greater than for pemetrexed (1%).

Economic analysis

- 6.29 The submission presented a modelled cost-utility analysis based on the superiority claim of the proposed scenario (*ROS1* testing and crizotinib) with the current scenario (no *ROS1* testing and single agent chemotherapy with pemetrexed).

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 █████ 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).

Source: Table 3.1.1, p192 and Table 3.5.3, p217 of the submission

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

6.30 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).

6.31 In the treatment stage, patients were assumed to receive either █████ months of crizotinib treatment or six cycles of pemetrexed, irrespective of disease progression. This was not consistent with the clinical evidence for pemetrexed where a median of four cycles was used. Median duration of treatment in the crizotinib studies was longer than median progression-free survival. Exponential models for the probability of remaining alive (OS) or progression-free (PFS) were used for both the crizotinib and pemetrexed treatment arms. The model did not attribute a higher risk of death for the post-progression state. This might not reflect the disease process. Table 8 presents the key drivers of the model.

Table 8: Key drivers of the model

Description	Method/Value	Impact
Extrapolation	Exponential extrapolation of PFS and OS for both crizotinib and pemetrexed for 10 years	High, favours crizotinib
Time horizon	10 years	High, favours crizotinib
Utilities	EORTC QLQ-C30 mapped to EQ-5D-5L from OO12-01	Moderate, favours crizotinib
Duration of crizotinib treatment	█████ months (weighted median from crizotinib studies)	Moderate, favours crizotinib
Prevalence of <i>ROS1</i> positive	1.61%	Moderate (unclear bias)
Exclusion of re-biopsy costs	No patients require re-biopsy	Low, favours crizotinib

Source: compiled during the evaluation (reference sections/tables/spreadsheets within the submission)

EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol-5 dimension-5 level instrument; OS = overall survival; PFS = progression-free survival; *ROS1* = ROS proto-oncogene 1

6.32 The ESCs noted that the submission had presented four goodness-of-fit scenarios for extrapolating OS in the crizotinib arm and had claimed that exponential distribution

had the best fit. Although the goodness-of-fit statistics were similar for all the distributions presented, the ESCs considered that exponential distribution was the most conservative option, given the observed data sets used as an initial basis.

- 6.33 For the pemetrexed arm, the ESCs noted that the submission extrapolated PFS and OS from Hanna et al. 2004 from 20 months to 10 years using exponential distribution. Further, the extrapolated survival curves were not externally validated. The ESCs considered that improvements in clinical practice since Hanna et al. 2004 was conducted would have resulted in improvements in NSCLC survival in the chemotherapy arm.
- 6.34 The key driver of the model was the extrapolation of crizotinib outcomes and the 10-year time horizon. The submission estimated that, at five years (60.7 months), 35% of patients treated with crizotinib would be alive and 9% would be progression free. This was not supported by post-progression survival data from crizotinib studies involving the *ALK* biomarker. A Canadian observational study (Kayaniyil et al., 2016) of 49 *ALK*-positive patients treated with crizotinib reported 0% one-year survival after crizotinib discontinuation for patients who did not use ceritinib (another *ALK* inhibitor).
- 6.35 Table 9 presents the results of the economic evaluation.

Table 9: Results of the economic evaluation (per patient undergoing ROS1 IHC testing)

Component	Crizotinib	Pemetrexed	Increment
Costs	\$████	\$████	\$████
QALYs	0.58	0.54	0.03
Incremental cost/extra QALY gained			\$████

Source: Table 3.8.1, p227 of the submission

IHC = immunohistochemistry; QALY = quality-adjusted life year; ROS1 = ROS proto-oncogene 1

- 6.36 The ICER of QALY\$45,000/QALY - \$75,000/QALY from the economic model was likely overestimated because:
- the extrapolated PFS and OS for crizotinib were overestimated because substantial post-progression survival was assumed. The PSCR (p4) argued that, even in the absence of a formal analysis of post-progression survival time, it was clear from reviewing of the reported outcomes of study OO12-01 that the majority of patients treated with crizotinib must have experienced post-progression survival of over █████ months, since the median PFS was █████ months (95% CI: █████) and the lower bound of the confidence interval for median overall survival was █████ months (95% CI: █████);
 - the crizotinib studies overestimated the likely survival gain in the PBS population because it included patients with better prognostic factors (performance status of 0 or 1, younger age, and East Asian ethnicity); and
 - the effectiveness of pemetrexed was underestimated due to the inclusion of patients with squamous NSCLC in the trial (worse outcomes with pemetrexed) and the use of fewer pemetrexed cycles. The PSCR (p6) presented additional sensitivity analyses that increased the progression-free survival and overall survival of pemetrexed by improvements of 10%, 20% and 30%. This resulted in ICERs of between \$45,000 - \$75,000/QALY.

6.37 The ESCs considered that the use of historical data for the chemotherapy arm confounded the analysis; however, the ESCs also acknowledged that Hanna et al 2004 was the best available dataset for estimating survival with chemotherapy treatment in this small patient population.

6.38 Overall, the ESCs considered that the economic evaluation was informed by a naïve clinical comparison that likely overestimated the effectiveness of crizotinib and underestimated the effectiveness of pemetrexed. The extrapolated incremental effectiveness was therefore likely overestimated.

6.39 Table 10 presents the key sensitivity analyses of the economic evaluation.

Table 10: Results of univariate sensitivity analyses (per 10,000 patients tested)

Univariate analyses	Δ costs	Δ QALYs	ICER
Base case	\$ [REDACTED]	318	\$ [REDACTED]
Lower range of pooled prevalence of ROS1 positive = 0.4% (base case = 1.61%)	\$ [REDACTED]	79	\$ [REDACTED]
Time horizon (base case = 10 years)			
5.1 years (33 cycles)	\$ [REDACTED]	241	\$ [REDACTED]
7.5 years (49 cycles)	\$ [REDACTED]	292	\$ [REDACTED]
Treatment duration of crizotinib: weighted average (base case = [REDACTED] months)			
Duration of treatment = [REDACTED] months (mean modelled PFS)	\$ [REDACTED]	318	\$ [REDACTED]
Multivariate analysis:			
• Meta-analysis sensitivity (96.4%) and specificity (95.5%) excluding Rogers 2015 (base case: sensitivity = 95.1%, specificity = 93.8%)			
• Time horizon = 5.1 years (33 cycles) (base case = 10 years)			
• Treatment duration of crizotinib 23.2 months (base case = [REDACTED] months)	\$ [REDACTED]	189	\$ [REDACTED]
• Utilities from Chouaid 2012: PFS = 0.700, progression = 0.580 (base case: PFS = [REDACTED], progression [REDACTED])			
• Crizotinib OS: Weibull with worse OS outcomes (base case exponential) ^a			
• Pemetrexed PFS and OS adjusted using Scagliotti et al. 2009 ^{a,b}			
Multivariate analysis: as above except time horizon = 7.5 years	\$ [REDACTED]	223	\$ [REDACTED]

Source: Table 3.9.2, p230 of the submission and constructed during the evaluation

ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; OS = overall survival; QALY = quality-adjusted life year; ROS1 = ROS proto-oncogene 1; Δ = incremental

^a derived using 'nl' command in Stata (version 13.0) for non-linear regression

^b Based on longer PFS for non-squamous NSCLC patients in Scagliotti et al. 2009 which did not provide a Kaplan-Meier curve for PFS

The redacted table shows ICERs in the range \$45,000/QALY - \$105,000/QALY.

6.40 The ICER was sensitive to the time horizon. The ICER was very high around the end of the trial duration (QALY \$105,000 /QALY - \$200,000/QALY at two years) and stabilises after eight years. This was consistent with the much larger proportion of patients treated with crizotinib being alive between two years and eight years.

- A multivariate sensitivity analysis conducted during the evaluation, with less favourable treatment assumptions, but higher ROS1 IHC test performance, also resulted in a more conservative ICER of \$75,000/QALY - \$105,000/QALY over a five-year time horizon.
- The PSCR (p5) argued that, even though a five-year time horizon was considered appropriate by the PBAC for nivolumab, it was not appropriate for crizotinib, as nivolumab had a two-year survival rate of 29% (CheckMate 057 study), which

was substantially lower than the two-year survival for crizotinib (67%). In addition, the PSCR stated that there was no long-term survival data for crizotinib-treated *ROS1*-positive advanced NSCLC patients, and that a 10-year time horizon captured the expected life-span of the modelled population.

- The PSCR (p7) further contended that applying convergence to modelled survival outcomes would not be appropriate because there was no reliable evidence on the long-term outcomes of patients treated with crizotinib.
- The ESCs noted the PSCR's arguments, but considered that even if a 10-year time horizon was accepted, the lack of convergence was implausible.
- The ESCs considered that a multivariate sensitivity analysis forcing the crizotinib OS curve to 0% alive at 10 years, along with a pemetrexed OS curve which would be more reflective of current treatment practice, would provide further information on the realistic cost-effectiveness of crizotinib.

6.41 The submission assumed crizotinib would be used on average for [REDACTED] months. However, the mean PFS was [REDACTED] months. The PSCR (p5) argued that this difference was due to treatment discontinuations that would be inevitable in clinical practice. The ESCs noted that increasing the mean modelled treatment duration to [REDACTED] months increased the ICER from a base case of QALY\$45,000/QALY - \$75,000/QALY.

Drug cost/patient/course: \$ [REDACTED]

6.42 The estimate of \$ [REDACTED] assumed a cost of \$ [REDACTED] per pack for 30 days treatment at 100% dose intensity for a 19.7 month treatment course. The treatment duration was based on the weighted median treatment duration from the two crizotinib studies. A course of pemetrexed costs \$ [REDACTED] for six 21-day cycles of treatment, excluding chemotherapy administration costs.

Estimated MBS and PBS usage & financial implications

6.43 This submission was not considered by DUSC. The submission appropriately used an incidence-based epidemiological approach to estimate usage and financial implications.

Table 11: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
ROS1 testing						
IHC	■	■	■	■	■	■
FISH	■	■	■	■	■	■
Estimated extent of use						
Number of patients treated	■ ^a	■	■	■	■	■
Number of scripts dispensed	■	■	■	■	■	■
Estimated financial implications of crizotinib						
Cost to PBS/RPBS	■	■	■	■	■	■
Co-payments	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments	■	■	■	■	■	■
Estimated financial implications for pemetrexed						
Cost to PBS/RPBS	■	■	■	■	■	■
Co-payments	■	■	■	■	■	■
Cost to PBS/RPBS less co-payments	■	■	■	■	■	■
Estimated financial implications for the MBS						
IHC testing	■	■	■	■	■	■
FISH testing	■	■	■	■	■	■
Ophthalmological examinations	■	■	■	■	■	■
Net financial implications						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS	■	■	■	■	■	■
Net cost to PBS/RPBS/MBS	■	■	■	■	■	■

Source: Tables 4.2.4-4.5.4 pp243-260 of the submission

FISH = fluorescent in-situ hybridisation; IHC = immunohistochemistry; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a estimates include ■ grandfathered patients

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be less than \$10 million per year.

- 6.44 The estimated net cost to the PBS and RPBS was \$20 - \$30 million over the first six years of listing.
- 6.45 The estimated net cost to the MBS was \$■ over the first six years of listing.
- 6.46 The estimated net cost to government health budgets was \$20 - \$30 million over the first six years of listing.
- 6.47 The ESCs considered that the financial implications of *ROS1* testing and crizotinib treatment were modestly underestimated due to:
 - underestimation of the uptake of *ROS1* FISH testing following *ROS1*-positive IHC;
 - underestimation of the uptake of crizotinib in patients eligible for second line treatment;
 - underestimation of mean duration of treatment with crizotinib;
 - overestimation of pemetrexed cost-offsets; and

- underestimation of the incidence of lung cancer.
- 6.48 The PSCR (p7, 10) presented additional univariate sensitivity analyses assuming (i) higher uptake of *ROS1* testing; (ii) higher uptake of second-line treatment; (iii) higher crizotinib uptake in the eligible population; and (iv) removal of pemetrexed cost offsets. The ESCs noted that making these changes (compared to the five it had identified), changed the estimated net cost to the PBS and RPBS from \$20 - \$30 million to \$20 - \$30 million over the first six years of listing.
- 6.49 The ESCs noted that the financial implications were most sensitive to the prevalence of *ROS1* gene rearrangements and the duration and uptake of crizotinib treatment. The ESCs further noted that the financial estimates were not as sensitive to removing the pemetrexed cost-offsets due to further pemetrexed price reductions.
- 6.50 The ESCs noted that, although the submission (and PSCR) requested a PBS listing agnostic of any line of treatment, the financial estimates presented in the submission did not take into account first-line use of crizotinib in *ROS1*-positive NSCLC patients.

Financial Management – Risk Sharing Arrangements

- 6.51 The submission acknowledged that a risk sharing arrangement (RSA) might be required to address any uncertainties in the financial estimates; however, no further details on the specifics of such an arrangement were included in the submission.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC outcome

- 7.1 The PBAC deferred its decision about whether to recommend listing crizotinib for the treatment of *ROS1*-positive NSCLC, requesting that the sponsor develop an appropriate pricing strategy in response to the Committee's concerns.
- 7.2 In deciding to defer, the PBAC noted that the codependent test for *ROS1* rearrangements would be considered by the Medical Benefits Advisory Committee (MSAC) in late November 2017. The PBAC acknowledged that there is a high unmet clinical need in the small proposed population (approximately ■ patients per year, 1.6% of all patients with NSCLC), and recalled that this submission was the result of an invitation from the PBAC to the sponsor for a submission for this rare cancer population. Further, the PBAC advised that crizotinib's effectiveness and safety profile in the *ROS1*-positive NSCLC population is similar to that in the *ALK*-positive NSCLC population, for which it is already PBS listed.
- 7.3 The PBAC foreshadowed its intention to remove the criterion 'The condition must have progressed on or after prior platinum based chemotherapy' from any recommended initial and grandfathering treatment criteria to allow the PBS listing of crizotinib in the *ROS1*-positive NSCLC population to be agnostic of line of therapy, consistent with its current listing in the *ALK*-positive NSCLC population. The PBAC advised that all other aspects of the restriction requested by the sponsor, with proposed changes by the Secretariat, would be appropriate.

- 7.4 The PBAC advised that the clinical place in therapy as proposed in the submission was otherwise appropriate.
- 7.5 The PBAC considered that pemetrexed, as a widely used representative of single-agent chemotherapy, was the appropriate main comparator, and recalled that it had also considered that pemetrexed was the appropriate comparator for the current listing in the *ALK*-positive NSCLC population.
- 7.6 The PBAC noted that the submission was based on a naïve comparison of two single-arm studies of crizotinib in the second-line treatment of NSCLC (n = 180) with the pemetrexed arm of one randomised controlled trial that compared pemetrexed to docetaxel in the second-line treatment of NSCLC (Hanna et al 2004, n = 283 in the pemetrexed arm).
- 7.7 The PBAC considered that the effectiveness of crizotinib was potentially overestimated in the naïve comparison due to the crizotinib studies having (i) a larger proportion of patients with a performance status of 0 or 1; (ii) patients previously untreated for advanced NSCLC, and (iii) predominantly East Asian patients who have a better prognosis.
- 7.8 The PBAC considered that the effectiveness of pemetrexed was potentially underestimated, as (i) study patients received fewer cycles of treatment than Australian practice (as estimated by Australian clinicians); (ii) its supporting study included patients with squamous NSCLC who have worse outcomes with pemetrexed, and (iii) other treatment practices may have improved since the study was conducted (2001 to 2003).
- 7.9 The PBAC noted ESC's advice that, although crizotinib was likely to be more effective than pemetrexed, the magnitude of incremental effectiveness was difficult to estimate from the evidence provided in the submission. Overall, the PBAC advised that the biases and the transitivity issues with the indirect comparison indicated that the incremental effectiveness of crizotinib over pemetrexed was overestimated in the submission; however, as confirmed during the sponsor hearing, the Committee was satisfied that the incremental effectiveness of crizotinib treatment in the *ROS1*-positive NSCLC population would be similar to that in the *ALK*-positive NSCLC population.
- 7.10 The PBAC considered that the submission's claim of non-inferior safety compared with pemetrexed was reasonable, but noted that the fatal adverse event rate in the crizotinib studies (17% and █%) appeared to be greater than for pemetrexed (1%).
- 7.11 The PBAC considered that the uncertainties in the incremental clinical benefit consequently affected the economic analysis presented in the submission, which was further confounded by the use of historical data for the chemotherapy arm. Overall, the PBAC considered that the resultant extrapolated incremental cost-effectiveness ratio (base case of \$45,000/QALY - \$75,000/QALY) was therefore uncertain and overly optimistic.
- 7.12 The PBAC recalled that it had recommended the PBS listing for crizotinib in the *ALK* population based on evidence from a direct randomised controlled trial (A8081007) of crizotinib versus chemotherapy (n=343) with a 4.7 months' gain in median PFS

with crizotinib treatment (7.7 vs 3.0 months; [4.2 months in pemetrexed subgroup]) and a hazard ratio of 0.487 (95% confidence interval: 0.371, 0.638) (crizotinib PSD, November 2013 PBAC meeting). As such, the PBAC advised that in the absence of similar robust evidence to determine the incremental benefit and therefore the cost-effectiveness of crizotinib in the *ROS1*-positive NSCLC setting, and assuming a similar effectiveness across these two biomarker-defined populations, the cost of treating a *ROS1*-positive patient should be the same as treating an *ALK*-positive patient. The PBAC considered that this conclusion of similarity was generous from the perspective of biological plausibility, because (i) although the *ROS1* and *ALK* genes are evolutionarily related, the kinase domains of *ROS1* and *ALK* show only about 49% amino acid sequence homology²; and (ii) *ALK* inhibitors have lower affinity (IC₅₀) for *ALK* than *ROS1* *in vitro* indicating that *ALK* inhibitors are better at inhibiting *ALK* expression than at inhibiting *ROS1* expression. PBAC acknowledged that this data is not based on observations of clinically meaningful outcomes, however it is important nonetheless in the context of rare cancers where the availability of high level evidence is necessarily limited.

- 7.13 Therefore, the PBAC deferred its decision in order to consider any proposal that would maintain parity of *ALK* inhibition costs across the two populations. To achieve this, the PBAC advised that the cost per patient of crizotinib in the *ROS1*-positive setting should be the same as that in the *ALK*-positive setting, that is, after adjusting the effective DPMQ in the *ROS1*-positive setting to account for the difference in observed treatment durations in each setting (■ months and 7.7 months, respectively). A weighted average effective DPMQ could then be calculated across the two settings.
- 7.14 In providing this advice, the PBAC also noted the results of a phase II study (n=32) demonstrated that ceritinib, a second generation *ALK* inhibitor also listed on the PBS for *ALK*-positive NSCLC, was an effective agent in *ROS1*-positive NSCLC, with a median progression-free survival of 9.3 months in crizotinib-naïve patients³. The PBAC considered that this was relevant, because ceritinib is already PBS-listed in the *ALK*-positive setting at without the requirement for a written authority. The PBAC recalled that it had requested a minor submission from the sponsor of crizotinib in order to assess the comparative efficacy, safety and cost-effectiveness of crizotinib and ceritinib in *ALK*-positive NSCLC (paragraph 6.4, March 2017 crizotinib PSD).
- 7.15 The PBAC advised that the utilisation assumptions supporting the financial estimates were reasonable from a PBS perspective after adjusting the estimate of eligible patients in the first year to include patients who would receive treatment under the proposed grandfathering arrangement.
- 7.16 The PBAC considered that given the modest financial estimates in a relatively small population, a risk sharing arrangement would not be necessary, provided MSAC was

² Expert Rev Anticancer Ther. 2012 Apr;12(4):447-56. doi: 10.1586/era.12.17

³ Open-Label, Multicenter, Phase II Study of Ceritinib in Patients With Non-Small-Cell Lung Cancer Harboring *ROS1* Rearrangement. Journal of Clinical Oncology 2017 35:23, 2613-2618

satisfied with the financial estimates and crizotinib was listed at the DPMQ determined by the approach outlined above (paragraph 7.13).

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

9 Sponsor's Comment

The Sponsor is committed to working with the PBAC and the Department of Health to make crizotinib available for the treatment of advanced ROS1-positive non-small cell lung cancer; a rare disease with high unmet clinical need.