National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Crizotinib for untreated ROS1-positive advanced non-small-cell lung cancer

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Wording	Royal College of Pathologists	OK	Comment noted. No action taken.
	Pfizer	No comments	Comment noted. No action taken.
	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action taken.
Timing Issues	Royal College of Pathologists	URGENT	Comment noted. No action taken.
	Pfizer	Crizotinib was approved by the EMA for use in patients with ROS1+ advanced NSCLC in August 2016. There are no currently reimbursed targeted therapies available for this patient group. Chemotherapy offers the only first line option of therapy, and clinicians have been clear that immunotherapy would not be a treatment of choice in a patient with advanced	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
		NSCLC who presents with a specific oncogenic driver. Patients with ROS1+advanced NSCLC therefore represent an area of high unmet need, meaning that is appropriate to appraise this indication as soon as possible.	
	NCRI-ACP-RCP-RCR	Crirozinib is licensed for use in this indication so an early outcome from NICE is important for equality of access.	Comment noted. No action taken.
Additional comments on the draft remit	Pfizer	None.	Comment noted. No action taken.
	NCRI-ACP-RCP-RCR	No	Comment noted. No action taken.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	1. "In England, there were 37,453 people newly diagnosed with lung cancer in 2014, of whom 75% had stage III or IV disease." • There is a more up-to-date NLCA 2016 publication, which states that there were 36,025 lung cancer cases in England, in 2015. • This figure is changed to "36,025" as opposed to "37,453". 2. "It is estimated that ROS1 rearrangements occur in 2% of patients with NSCLC.4" • Clinical expert opinion in the UK indicates the ROS1+ incidence in NSCLC to be around 0.9-1%, rather than 2%.	Comment noted. The figures in the final scope have been changed to include the most up to date information.

Section	Consultee/ Commentator	Comments [sic]	Action
		• This figure is changed to “around 1%” as opposed to “2%”. 3. “However, for the majority of people with NSCLC, the aims of treatment are to prolong survival and improve quality of life.” • This is an incomplete characterisation of the aims of treatment. Patients and clinicians consistently report that the aims of treatment are also to delay progression, and to control or improve lung cancer symptoms. Royal college of Physicians, National Lung Cancer Audit annual report 2016. Available at: https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2016. Accessed 8th March 2017.	
	NCRI-ACP-RCP-RCR	Appropriate	Comment noted. No action taken.
The technology/ intervention	Pfizer	Yes, it is accurate.	Comment noted. No action taken.
	NCRI-ACP-RCP-RCR	Appropriate	Comment noted. No action taken.
Population	Pfizer	Yes, it is accurate. Given the rarity of the patient population already, there are no subgroups that need to be considered separately.	Comment noted. No action taken.
	NCRI-ACP-RCP-RCR	Appropriate	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Royal College of Pathologists	No comparators in relation to the drug that I am aware of currently. Screening of lung cancer cases fro ROS1 will be however be required in a similar fashion to assessing patients in relation to crizotinib therapy for lung cancer patients with ALK gene abnormalities	Comment noted. No action taken.
	Pfizer	The expectations of the scope (with respect to the named comparators) are not well aligned to the relevant evidence base. We therefore suggest that the comparator sections amended as described below. It is first important to note that the concept of mutation-rearrangement NSCLC is fundamentally different to the general NSCLC population. Similar to patients with ALK-positive NSCLC, patients with ROS1-positive NSCLC tend to be younger, never /minimal- smokers, with a histological diagnosis of adenocarcinoma, compared to other unselected patients with lung cancer (1;2). In effect, ROS1 NSCLC is a different population than broader NSCLC types, and there is no evidence of the efficacy of many of the suggested comparators in the ROS1 population, suggesting that evidence in the broader NSCLC population is not applicable. However, the relevant similarities between the ALK and ROS-1 histologies suggest that the ALK+ evidence base may prove useful in the consideration of the ROS-1 evidence (discussed further below). It is also important to note that the licence for crizotinib in ROS1+ patients is for 'all lines' XALKORI® is indicated for the treatment of adults with ROS1-positive advanced non-small cell lung cancer (NSCLC)", rather than for any one specific line of treatment. This licence was given in the context of an extremely limited evidence base within the ROS1 population, owing to the extreme rarity of the condition. Indeed, ROS1 gene rearrangements lead to fusions and aberrant expression in approximately 1-2% of patients with NSCLC (1;2), compared to 3-5% of patients with ALK positive NSCLC (3;4). ROS1 gene rearrangement is also usually mutually exclusive to other	Comment noted. Comparators in the final scope are defined by current practice, not by the available evidence base.

Section	Consultee/ Commentator	Comments [sic]	Action
		oncogenic drivers (1). There are no randomised studies to provide comparative analysis for PFS and OS for the ROS1-positive patient population. Both the FDA and EMA felt that given the rarity of ROS1-positive NSCLC and the magnitude of effect of the ORR in this patient population, a randomised controlled trial would likely be unfeasible and lack clinical equipoise (5;6). The supporting clinical trial (PROFILE 1001) therefore includes only 7 patients in first line, and 44 patients in second and later lines, with no comparator arm. On the basis of the above, division of the population first by line of therapy, and then again by histology, for the purpose of nuanced comparison requires an evidence base which is therefore not available. Furthermore, comparator evidence in unselected NSCLC is deemed not applicable to the patient population at hand, due to the differences in patient characteristics (as stated above). Comparisons defined by line of therapy, and especially by histologic subgroup, therefore cannot be made and should therefore be excluded from the scope. In place of the excluded comparators, comparisons should be made with pemetrexed (with or without cisplatin/carboplatin), and docetaxel, through use of the ALK+ data. There is understood to be similar clinical behaviour in ROS1+ and ALK+ advanced NSCLC patients due to the homology of the genetic translocation (7). The ORR seen in patients with ROS1-positive advanced NSCLC are similar to those seen in patients with ALK-positive advanced NSCLC. In ALK-positive NSCLC, the high ORR translated to a PFS benefit compared to standard chemotherapy in either first or second line treatment. Further, it is also suggested that ROS1+ sensitivity to pemetrexed is similar to that seen in ALK+ patients (8-14).	

Section	Consultee/ Commentator	Comments [sic]	Action
		In summary, the scope should not require comparison to gemcitabine, paclitaxel, vinorelbine, pemetrexed maintenance treatment, docetaxel with nintedanib and single agent chemotherapy with a third generation drug in ROS+1 patients. Instead, comparison to non-crizotinib treated patients in the ALK+ population should be considered a reasonable proxy to facilitate the appropriate assessment of crizotinib's relative effectiveness.	
	Merck Sharp and Dohme	After the sub-heading "After previous chemotherapy treatments", we suggest pembrolizumab should be included as a relevant comparator, specifically for patients who are PD-L1-positive and who have had at least one chemotherapy (and targeted treatment if they have an EGFR or ALK positive tumour), in line with the recommendations in TA428.	Comment noted. The final scope does not include other targeted treatments for NSCLC.
	NCRI-ACP-RCP-RCR	These patients are generally adenocarcinomas. In the untreated setting, if receiving doublet chemotherapy, the appropriate comparator is platinum chemotherapy with pemetrexed with or without maintenance pemetrexed as they would usually receive this in preference to other platinum doublet combinations.	Comment noted. No action taken.
Outcomes	Pfizer	Yes.	Comment noted. No action taken.
	NCRI-ACP-RCP-RCR	Appropriate	Comment noted. No action taken.
Economic analysis	Pfizer	No comments	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
	NCRI-ACP-RCP-RCR	The term 'ROS1 mutation' is inappropriate as the genetic event is not a mutation. The preferred term is 'ROS1 fusion'	Comment noted. The final scope has been updated accordingly.
Equality and Diversity	Royal College of Pathologists	a	N/A
	Pfizer	• ROS1 diagnostic testing is not yet established in England and is not routinely conducted, given there is no currently reimbursed medicine. Many laboratories are, however, establishing the testing paradigm they would introduce, if crizotinib is approved. • Previously, a potential inequality in the consideration for the treatment of ALK+ NSCLC was raised in the appraisal of crizotinib as a second-line therapy: "…testing could be restricted to patients with a diagnosis of adenocarcinoma." (NICE, 2013) • Patients with ROS1+ advanced disease fulfil a similar demographic profile to those with ALK+ advanced disease, and recommendation has been made to apply the same testing algorithms. Patients with adenocarcinoma or non-squamous advanced lung cancer and selected squamous tumours for non-smokers would be considered appropriate for ROS1 testing (Virchows Arch (2016) 469:489–503). This testing protocol would support equitable access to patients who would potentially benefit from Crizotinib therapy. . NICE TA296: Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. 2013. Available at: http://www.nice.org.uk/guidance/ta296/chapter/1-Guidance	Comment noted. The committee will consider inequalities which could be introduced at the diagnostic testing stage.

Section	Consultee/ Commentator	Comments [sic]	Action
Other considerations	Royal College of Pathologists	Any potential appraisal needs to take in the cost implications for ROS1 testing (either FISH or immunohistochemistry) and the staffing issues in terms of consultant pathologist and biomedical scientist time.	Comment noted. No action taken.
	Pfizer	No other considerations.	Comment noted. No action taken.
Innovation	Pfizer	<u>Step-change in disease management</u> • There is a high unmet need in patients who have ROS1+ NSCLC as there are no current targeted therapies available. Crizotinib presents the first targeted treatment option for these patients. • Crizotinib is an oral therapy which offers an alternative to the standard of care which is intravenously administered, which is invasive, requires additional hospital visits and day case time for treatment. <u>Not captured by the QALY</u> • Advanced NSCLC is associated with considerable indirect costs due to loss of productivity from patients and carers (Stanisic, 2010). However, the alleviation of carer burden as a result of this benefit would not be captured in the QALY. • Younger patients with progression-free disease may be able to return to work and thus reduce costs associated with loss of productivity (Stanisic, 2010). At presentation, ROS1+ patients are typically younger than the typical NSCLC patient and are commonly still of working age. This, combined with crizotinib's ability to alleviate symptoms, can lead to wider societal benefits less commonly seen with chemotherapy.	Comment noted. No action taken. Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
		Stanisic S et al. (2010) Societal cost savings through bevacizumab-based treatment in non-small cell lung cancer (NSCLC). Lung Cancer. 2010 Aug;69 Suppl 1:S24-30	
	NCRI-ACP-RCP-RCR	Yes, crizotinib is a revolutionary drug for patients with ROS1+ disease with markedly improved outcomes (responses; progression-free survival) compared to historical series of patients treated with chemotherapy	Comment noted. No action taken.
Questions for consultation	Pfizer	<u>Where in the treatment pathway for treating ROS1-positive NSCLC is crizotinib likely to be used in practice? First-line or second-line?</u> • As per the licensed indication, we anticipate that once ROS1 testing is in place, all patients who test positive will be treated with crizotinib as soon as possible. <u>Have all relevant comparators for crizotinib been included in the scope?</u> • Please see above comments in 'Comparators' <u>Which treatments are considered to be established clinical practice in the NHS for ROS1-positive advanced non-small-cell lung cancer?</u> • Pemetrexed in combination with cisplatin/carboplatin is considered to be the established standard of care in UK clinical practice for non-squamous NSCLC. <u>Should nivolumab and atezolizumab be included as comparators in the previously chemotherapy-treated population?</u>	Comment noted. No action taken. Comment noted. No action taken. Comment noted. Please see the comparators section.

Section	Consultee/ Commentator	Comments [sic]	Action
		• Clincal experts do not support the use of immunotherapy agents, including nivolumab, atezolizumab and pembrolizumab,in preference to targeted therapy for patients with ROS1 positive advanced NSCLC	Comment noted. No action taken.
		<u>Is the ROS1 rearrangement mutually exclusive from other NSCLC mutations or can it be present in people with other mutations?</u> • Evidence to date supports that ROS1 gene rearrangement is mutually exclusive with other NSCLC gene rearrangements / mutations which are commonly tested i.e. EGFR and ALK.	Comment noted. No action taken.
		<u>Should NSCLC treatments targeted at other mutations be included as comparators?</u> • There are no other current medicines, within licence, that have activity in treatment patients with ROS1 positive advanced NSCLC.	Comment noted. No action taken.
		<u>Are the outcomes listed appropriate?</u> • Yes	Comment noted. No action taken.
		<u>Are there any subgroups of people in whom crizotinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?</u> • No	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which crizotinib is licensed; could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology; could have any adverse impact on people with a particular disability or disabilities. • The European licence for crizotinib requires that an accurate and validated assay for ROS1 is performed for the selection of patients for treatment with Crizotinib (SPC).If regional variations exist, this could lead to inequitable access (http://www.medicines.org.uk/emc/medicine/27168). Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. • Existing levels of ROS1 testing (where testing is currently taking place) may suggest what testing rate could be expected across the UK. Do you consider crizotinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might	Comment noted. No action taken. Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
		<u>improve the way that current need is met (is this a 'step-change' in the management of the condition)?</u> • Yes, see 'Innovation' above. <u>Do you consider that the use of crizotinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?</u> • The wider societal impact of patients returning to work is an outcome unlikely to be included in the QALY calculation, along with care burden alleviation. See 'Innovation' above. <u>Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.</u> • Crizotinib's ALK-positive Phase III trial (Solomon, 2014). Innovation is demonstrated through the significant improvement in the response rate vs. standard of care, the speed of response vs. standard of care, the reversal of symptom progression on treatment, significant improvement in global quality of life compared to chemotherapy and the availability of an oral administration optional. *Solomon et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.*	Comment noted. No action taken. Comment noted. No action taken. Comment noted. No action taken.
	Merck Sharp and Dohme	Question: Have all relevant comparators for crizotinib been included in the scope?	Comment noted. The final scope does not include other targeted treatments for NSCLC.

Section	Consultee/ Commentator	Comments [sic]	Action
		Answer: No – pembrolizumab should be included. As per the recommendations in TA428, it could be a potential comparator in the population of interest covered by this submission.	
	NCRI-ACP-RCP-RCR	Where do you consider crizotinib will fit into the existing NICE pathway, Lung Cancer? ROS1 testing should be implemented at time of diagnosis for non-squamous NSCLC. If ROS1+ patients should ideally receive crizotinib as 1st line therapy. However, there will be a sizeable proportion of patients in whom systemic therapy (usually chemotherapy) will need to be commenced before ROS1 results are returned. For these patients crizotinib will be appropriate for the second line setting. There will be a small number of patients who have technical ROS1 genotpying failures or tumour sample insufficient for molecular analysis that may be ROS1 identified for the second or third line setting. NICE should use the proportion of these patients as evaluated in their recent review of crizotinib (TA406)	Comment noted. The scope considers crizotinib as a first, second and third-line treatment option.
		Have all relevant comparators for crizotinib been included in the scope? For the first line setting, most patients will usually normally receive cisplatin / carboplatin-pemetrexed with maintenance pemetrexed in the responders. A small number will be unfit for platinum-doublet chemo and for them the single agent chemos identified are appropriate. These patients would be unlikely to be treated with first-line immune checkpoint inhibitors.	Comment noted. Please refer to the comparators section.
		In the second-line setting pembrolizumab is NICE approved for patients with PD-L1 expression and nivolumab is currently under review. Therefore, pembrolizumab (immune checkpoint inhibitors) would be a standard 2nd line treatment in PD-L1 expressors where it is likely to be used ahead of	Comment noted. The final scope does not

Section	Consultee/ Commentator	Comments [sic]	Action
		docetaxel / nintendanib which would be the standard chemotherapy combination. Is the ROS1 rearrangement mutually exclusive from other NSCLC mutations or can it be present in people with other mutations? Yes, ROS1 fusions are largely mutually exclusive so no other molecular NSCLC cohorts should be considered. Subgroups: ROS1 +ve patients represent a small subgroup of the total NSCLC population who need to be routinely identified in routine NHS practice. Equality: no obvious issues Innovation: Yes, for ROS1+ patients, crizotinb is a step change therapy and a first-in class treatment for this condition. The rapid nature of benefit, oral therapy, minimal toxicities and long progression-free survival make this a step-change STA process: appropriate	include other targeted treatments for NSCLC. Comment noted. No action taken. Comment noted. No action taken. Comment noted. No action taken. Comment noted. No action taken.
	Merck Sharp and Dohme	Under the section “Related NICE recommendations and NICE Pathways”, we suggest the following should be included: ‘Pembrolizumab for treating PD-L1-	Comment noted. The final scope does not

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope		positive non-small-cell lung cancer after chemotherapy' (Jan 2017) NICE Technology Appraisal 428. Review proposal Date Jan 2019.	include other targeted treatments for NSCLC.
	NCRI-ACP-RCP-RCR	Crizotinib could be used in the first or second line treatment setting two posters presented at ESMO provide further data on the efficacy of crizotinib for ROS-1 rearranged NSCLC. They highlight the impressive response rate and duration of response comparable to crizotinib in ALK mutation positive. These references are currently not listed in the scope and should be included. ESMO 2016 abstract 1191 PD Ou SI, Camidge DR, Engelman JA, Clark JW, Tye L,4 Wilner K et.al Clinical Activity of Crizotinib in Patients with Advanced Non-small Cell Lung Cancer Harboring ROS1 Gene Rearrangement. ESMO 2016 abstract 1206 PD Shaw AT, Riely GJ, Bang YJ, Kim DW, Camidge DR, Varella-Garcia M et.al. Crizotinib in Advanced ROS1-Rearranged Non-Small Cell Lung Cancer (NSCLC): Updated Results From PROFILE 1001	Comment noted. The scope considers crizotinib as a first, second and third-line treatment option.
		NCRI Lung CSG Consumer representative comments Our consumer representatives note the importance of being able to access the right treatment at the right time in the right place.	Comment noted. No action taken.

Section	Consultee/ Commentator	Comments [sic]	Action
		It is their understanding that it is already proven that first line treatment is superior to standard platinum based chemo in chemo naive patients with this tumour mutation/fusion (although patients often progress*) and is available in US and other countries, so this is a timely review. This treatment is allowing some patients to survive using an oral treatment (easier to take at home than visits to hospitals for chemotherapy therefore savings elsewhere within the healthcare budget). Ease of treatment compared to usual chemo (and travel / accompaniment by carer/relative/friend) should afford better QOL/treatment experience at a difficult time. Although this may represent a low percentage of all LC patients, as this is a type that impacts never smokers), it represents a growing interest on the patient forums and a welcome move from the highly heterogeneous tumours of long term smokers so imagine it should be relatively simple to test for. Costs and timelines for such testings need to be factored in at the earliest opportunity so patients can benefit from the most appropriate treatment for their tumour. Quality of life is a patient and carer (where applicable) desired outcome so treatment efficacy, convenience of how and where that treatment is administered should all be noted that these are superior to standard care for this group.	

Section	Consultee/ Commentator	Comments [sic]	Action
		It's important that where such factors are known, that patients are not only able to access such treatments in limited centres but have greater access across the country.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

British Thoracic Society

NHS England

Department of Health