National Institute for Health and Care Excellence

Health Technology Evaluation

Crizotinib for treating ROS1-positive advanced non-small-cell lung cancer (MA review of TA529) [ID6289]

Response to stakeholder organisation comments on the draft remit and draft scope

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 and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	British Thoracic Oncology Group	This is an appropriate evaluation to undertake as crizotinib still represents an important therapy for patients with ROS1+ NSCLC.	Thank you for your comment. No action required.
	Pfizer Ltd.	We consider that a cost-comparison approach for this appraisal is the most appropriate and proportionate approach. The cost-comparison analysis will assume equivalence in overall survival and progression free survival between crizotinib and entrectinib as supported by the literature, clinical expert opinion and an indirect treatment analysis.	Thank you for your comment. This topic will be completed using the cost-comparison approach.
Wording	British Thoracic Oncology Group	The wording is satisfactory	Thank you for your comment. No action required.

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	Pfizer Ltd.	Yes	Thank you for your comment. No action required.
Timing Issues	British Thoracic Oncology Group	Crizotinib remains an important drug for patients with ROS1+ NSCLC, hence it's appraisal for access remains important. NICE should consider the timing for this assessment, since repotrectinib which is FDA approved for ROS1+ advanced NSCLC will likely be receiving MHRA approval in 2024 and will need to undergo NICE technology appraisal for the same front-line indication (at least) as crizotinib. There therefore may be efficiency in appraising both drugs concurrently.	Thank you for your comment. Under current timelines, the guidance for repotrectinib is scheduled for publication in 2025.
	Pfizer Ltd.	The timing of the appraisal is appropriate.	Thank you for your comment. No action required.
Additional comments on the draft remit	British Thoracic Oncology Group	No comments	Thank you.
	Pfizer Ltd.	No comments	Thank you.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	British Thoracic Oncology Group	"ROS1 is a rare type of mutation" is factually incorrect as it is a "rare type of gene alteration…" It would be useful to better understand the numbers of patients with stage 3-4 NSCLC that have been shown to be ROS1+ from NHSE genomics unit data, if possible, rather than the total number of NSCLC patients and the	Thank you for your comment. The background section of

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		percentage expected to be ROS1+ as this latter method assumes 100% ROS1 testing penetrance, accuracy, and timeliness of results for decision-making, which are unlikely to occur in reality.	the scope has been updated.
	Pfizer Ltd.	Suggest to the change wording when describing in which patients are more commonly found to have ROS1 rearrangements in paragraph 2, as "significant overlap" suggests co-presentation with ROS1 and ALK rearrangements. This could be clarified by the following alteration - "These rearrangements are more commonly found in patients who have never smoked and who have histologic features of adenocarcinoma, having a similar patient profile to those who have anaplastic lymphoma kinase (ALK)-positive NSCLC.3 ROS1 tends to be mutually exclusive to ALK and other known oncogenic drivers such as EGFR, KRAS, HER-2, RET and MET aberrations.3" In paragraph 1, we suggest to add clarification under stage III (locally advanced) NSCLC. Usually, cancers that are limited to a small area of the chest are considered early-stage lung cancer (Stage I, Stage II, and Stage IIIA). Advanced stage lung cancer, as per the indication for crizotinib, is defined as Stage IIIB and Stage IV. In these stages it is usually not possible to remove all the cancer and the goal of treatment is to control the cancer, minimise symptoms, and extend and improve quality of life.	Thank you for your comment. The background section of the scope has been updated.
Population	British Thoracic Oncology Group	The population should be restricted to stage 3 or 4 ROS1+ NSCLC, as this is the population of interest for treatment with crizotinib.	Thank you for your comment. Stage 3 and 4 are captured under 'advanced' lung cancer.

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	Pfizer Ltd.	The population is defined appropriately.	Thank you for your comment. No action required.
Subgroups	British Thoracic Oncology Group	Patients with CNS metastases at baseline may have differential activity of crizotinib compared with those without CNS metastases at baseline, which may impact on cost effectiveness. However, unlike current practice and clinical recommendations, NICE does not recommend CNS imaging in patients with stage 4 NSCLC (including those with ROS1+ NSCLC) so to evaluate this subgroup separately may impact on NICEs current recommendations for staging of lung cancer (CG122).	Thank you for your comment. Crizotinib will be assessed as a cost-comparison appraisal. As such, it will be appraised in the same population as was entrectinib.
	Pfizer Ltd.	None.	Thank you for your comment.
Comparators	British Thoracic Oncology Group	Functionally, the current comparator is entrectinib, as no clinician would recommend chemotherapy based on clinical evidence. However, when crizotinib was initially appraised entrectinib did not exist and the cost effectiveness was appraised relative to chemotherapy- the standard at the time.	Thank you for your comment. No action required.
	Pfizer Ltd.	The comparator listed (entrectinib) is the only relevant comparator.	Thank you for your comment. No action required.
Outcomes	British Thoracic Oncology Group	These are appropriate.	Thank you for your comment. No action required.

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	Pfizer Ltd.	The outcomes listed are appropriate.	Thank you for your comment. No action required.
Equality	British Thoracic Oncology Group	No changes are recommended	Thank you for your comment. No action required.
	Pfizer Ltd.	Though testing for ROS1 genetic rearrangement is routinely performed, there is still a small population of patients who have a delay in receiving ROS1 test results prior to the need to initiate first line therapy in advanced NSCLC. As indicated in the CDF, we would request that a pragmatic approach be applied allowing treatment with crizotinib if a patient received a positive ROS1 diagnosis after treatment was commenced on platinum-based chemotherapy &/or immunotherapy, providing equality of access to targeted therapy in this small population. Examples of this situation: 1) TaT (Turnaround Time) for testing may be too long, such as if centres have moved from traditional IHC/FISH testing to NGS panel testing, so a patient is initiated on chemo +/- immunotherapy prior to return of results. 2) The move to liquid biopsies has also been raised by a Clinical Lead at one of the 7 English Genomic Laboratory Hubs that as the service moves to the NGS panel analyses of ctDNA, there will be a period where due to issues in pre-analytic preparation of samples and the processing steps, false-negative or inconclusive results may initially obtained in a proportion of patients.	Thank you for your comment. NICE will appraise crizotinib within its marketing authorisation and based on the available evidence. NHS England will be responsible for access to crizotinib in practice, if approved by NICE.
Other considerations	British Thoracic Oncology Group	The current appraisal limits patients evaluated in the trials with ECOG performance status 0-1. However, ROS1+ patients are routinely identified	Thank you for your comment. NICE will

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		with performance status 2 or 3 due to disease burden due to the lengthy time taken for suspected lung cancer GP referrals, delays in diagnostics and molecular testing, and are candidates for crizotinib and should not be excluded from the appraisal, due to NHS systems inadequacies outside their control.	appraise crizotinib within its marketing authorisation. This does not specifically exclude patients with worse performance status.
	Pfizer Ltd.	No comments.	Thank you.
Questions for consultation	British Thoracic Oncology Group	**Is entrectinib the most appropriate comparator?** Yes, although crizotinib was initially appraised against chemotherapy. **Where do you consider crizotinib will fit into the existing care pathway for ROS1-positive advanced NSCLC?** Crizotinib should fit into the treatment algorithm for stage 3/4 NSCLC that are ROS1 TKI naïve. This is usually 1st line but genotyping for ROS1 is poorly implemented and some cases are identified to be ROS1+ during 1st line chemotherapy or thereafter on subsequent testing- as patients could not wait for the lengthy time needed for FISH or RNA NGS and needed to start chemotherapy+/-immunotherapy or immunotherapy alone, or were erroneously labelled as ROS1 negative and re-biopsy and re-testing subsequently identified them as ROS1 positive- and should not be excluded from crizotinib access due to problems with tissue sampling/genotyping/NHS delays. **Would crizotinib ever be used before, after, or as an alternative to, entrectinib?**	Thank you for your comment. No action required. Thank you for your comment. NICE will appraise crizotinib within its marketing authorisation. NHS England will be responsible for access to crizotinib in practice, if approved by NICE.

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		Crizotinib is a very real alternative to entrectinib given that the toxicities of entrectinib are more difficult to tolerate than crizotinib, especially in those without CNS disease at baseline. There is no meaningful clinical data demonstrating efficacy to support using crizotinib directly after entrectinib or vice versa. **In current NHS practice, is testing for ROS1 genetic rearrangement routinely performed for people with advanced NSCLC?** Yes, but it is performed poorly. ROS1 IHC has limited sensitivity and a molecular test is needed. This is either FISH or RNA NGS in the UK currently. Both techniques require well fixed tissue with adequate cells or nucleic acids for analysis, and ROS1 testing lab failure rates are sadly high (up to 45% in some series). Moreover RNA/FISH testing takes additional time that patients may not have before needing to start treatment due to clinical deterioration. ctDNA can go a long way to speed up molecular diagnostics but is not routinely available in the NHS and even if so, has limited sensitivity to identify fusions in the setting of low volume or slowly proliferating disease. Moreover 15% of all advanced NSCLC have non-evaluable ctDNA results. Hence, in reality a sizeable proportion of patients start 1st line platinum-pemetrexed+/-pembrolizumab chemo or pembrolizumab alone and are subsequently identified to be ROS1+. Such patients should not be penalized for NHS systems issues and have the ability to receive a ROS1 inhibitor eg crizotinib. **At what point in the pathway is testing for ROS1 genetic rearrangement usually carried out?** At time of diagnosis of NSCLC	Thank you for your comment. No action required. Thank you for your comment. No action required.

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		Do you consider that the use of crizotinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? No **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** N/A	Thank you for your comment. No action required. Thank you for your comment. No action required.
	Pfizer Ltd.	**Is entrectinib the most appropriate comparator? Where do you consider crizotinib will fit into the existing care pathway for ROS1-positive advanced NSCLC?** Entrectinib is the only relevant comparator, as only crizotinib and entrectinib are recommended as initial ROS1-targeted treatment options for ROS1-positive NSCLC. **Would crizotinib ever be used before, after, or as an alternative to, entrectinib?** Crizotinib and entrectinib are both ROS1 inhibitors, with data suggesting they have similar clinical efficacy. As such, crizotinib is used as an alternative to entrectinib and vice versa. There is no substantial evidence to suggest any benefit from sequencing ROS1 treatments, and this is further supported by clinician opinion. An indirect treatment comparison will be conducted to demonstrate clinical equivalence.	Thank you for your comment. No action required. Thank you for your comment. No action required.

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		In current NHS practice, is testing for ROS1 genetic rearrangement routinely performed for people with advanced NSCLC? Yes, there is reflex testing for ROS1 for all advanced NSCLC patients, which is routinely commissioned. **At what point in the pathway is testing for ROS1 genetic rearrangement usually carried out?** Reflex testing of ROS1 (& other genomic alterations) is undertaken prior to initiating initial treatment for advanced NSCLC patients. **Do you consider that the use of crizotinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** As we are conducting a cost comparison analysis, there will be no QALY calculation. There are no further substantial health-related benefits to be included.	Thank you for your comment. No action required. Thank you for your comment. No action required. Thank you for your comment. No action required.
Additional comments on the draft scope	British Thoracic Oncology Group	None	Thank you.
	Pfizer Ltd.	Under the economic analysis section in the draft scope it states “The use of crizotinib is conditional on ROS1+ status. The economic modelling should include the costs associated with diagnostic testing for ROS1 status in people with advanced non-small-cell lung cancer who would not otherwise have been tested. A sensitivity analysis should be provided without the cost of the	Thank you for your comment. The scope has been updated to reflect the routine

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		diagnostic test." As reflex IHC, FISH and NGS testing for all advanced NSCLC patients is routinely commissioned, there are no additional costs associated with diagnostic testing for ROS1 patients with advanced NSCLC. This will exclude the need to include any ROS1 testing costs in this population in the cost comparison analysis, and negate the need for a sensitivity analysis excluding the cost of the diagnostic test.	diagnostic testing for ROS1.

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

- Roche Products Ltd.