National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Entrectinib for treating ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer ID1541

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	NCRI-ACP-RCP-RCR	Yes	Comment noted. No action required.
	Roche	The wording of the remit is accurate.	Comment noted. No action required.
Timing Issues	NCRI-ACP-RCP-RCR	The proposal is timely as there are limited options for patients with ROS1 positive NSCLC. The emerging data are promising in terms of PFS and control of CNS disease compared with crizotinib as main comparator	Comment noted. No action required.
	Roche	Entrectinib is likely to deliver clinical benefits to a group of advanced-stage lung cancer patients who have limited treatment options available. As such, the appraisal should be treated as urgent.	Comment noted. The aim of the STA process is to provide guidance close to the marketing authorisation being granted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	NCRI-ACP-RCP-RCR	Background is adequate although brief. There are no data included in the draft on effectiveness of entrectinib	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how it is managed, and is not designed to be exhaustive. No change required.
	Roche	The review of systemic treatments that aim to prolong survival and increase quality of life lacks a number of significant treatment options that are now available to NHS patients through NICE baseline and CDF funding. First line treatment now includes single agent pembrolizumab for patients whose PD-L1 expression is ≥50%, and pembrolizumab in combination with chemotherapy for non-squamous NSCLC regardless of PD-L1 expression. In second line, atezolizumab is available for all patients regardless of PD-L1 expression, pembrolizumab is available for patients with ≥1% PD-L1 expression and nivolumab is available in all squamous patients and non-squamous patients with ≥1% PD-L1 expression. While these immunotherapies are now part of the treatment pathway, it is important to note that they are unlikely to be used in a ROS1 positive NSCLC patient.	Comment noted. The background section of the scope aims to provide a brief summary of the disease and how the disease is managed in the population defined within the remit. No change required.
The technology/ intervention	NCRI-ACP-RCP-RCR	The description is accurate.	Comment noted. No action required.

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	Roche	Please note that entrectinib is currently being studied in adults in three trials (ALKA, STARTRK-1, and STARTRK-2) which are likely to inform the regulatory approval in this indication	Comment noted. The technology section has been amended to include the phase I trials.
Population	NCRI-ACP-RCP-RCR	Yes, the target population is ROS1 fusion positive NSCLC. It may be of value to consider separately patients with and without brain metastases	Comment noted. The scope has been amended to include subgroups by the presence and absence of Brain metastases.
	Roche	The population is appropriately defined.	Comment noted. No action required.
Comparators	NCRI-ACP-RCP-RCR	If ROS1 status is known then comparator should be crizotinib as TKI would be the preferable option over chemo or chemo-IO. When ROS1 status is unknown at the time of the initial treatment decision (majority in current UK practice?) the standard chemotherapy pemetrexed-platinum for non-squamous NSCLC patients (ROS1 very unlikely occur in squamous cell carcinoma) OR pemetrexed-platinum-pembrolizumab OR pembrolizumab (depending on PD-L1 status) would be given and hence would be a potential comparator	Comment noted. Treatments available via the CDF are not considered to represent 'established NHS practice', and are therefore not included as comparators in the scope. See NICE's Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. No change required.

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	Roche	Crizotinib is a key comparator that is missing from the scope, as crizotinib is licensed and reimbursed in ROS1 positive NSCLC patients. Furthermore, discussion with UK-practicing clinicians has confirmed that crizotinib is a clinically relevant comparator. We are aware that several recent draft scopes from NICE have included treatments currently only available on the CDF as relevant comparators. Given that crizotinib is currently the only targeted therapy in this area we would recommend its inclusion.	Comment noted. Treatments available via the CDF are not considered to represent 'established NHS practice', and are therefore not included as comparators in the scope. See NICE's Position statement: consideration of products recommended for use in the Cancer Drugs Fund as comparators, or in a treatment sequence, in the appraisal of a new cancer product. No change required.
		Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) is not commonly used in patients with non-squamous histology (where ROS1 arises most frequently); pemetrexed with a platinum drug is the most frequently used chemotherapy regimen in these patients.	Comment noted. Whilst chemotherapy in combination with a platinum drug is not commonly used, NICE needs to consider all drugs used in clinical practice as possible comparators. No change required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Single agent chemotherapy is rarely used and is mostly in ECOG PS ≥2, a population that is typically excluded by CDF criteria. Best supportive care is not an appropriate comparator patients must be fit for active treatment to receive entrectinib.	Comment noted. Whilst Single agent chemotherapy is not commonly used, NICE needs to consider all drugs used in clinical practice as possible comparators. No change required Comment noted. Best supportive care has been removed from the list of comparators.

Outcomes	NCRI-ACP-RCP-RCR	Yes, although 'time to treatment discontinuation' could also be considered as a novel endpoint. Some patients may continue beyond progression if they have maintained clinical benefit or if, for example, patients develop small volume oligometastatic progression that could be managed by stereotactic radiotherapy then the patient continues on the TKI with ongoing further benefit. (This concept is being tested in the context of the HALT study for other mutation driven NSCLC).	Comment noted. Time to treatment discontinuation has been added as an outcome.
	Roche	The outcomes stated are expected to represent the key benefits and harms of a cancer medicine such as entrectinib.	Comment noted. No action required.
Economic analysis	NCRI-ACP-RCP-RCR	Limited information has been provided in relation to economic analysis	Comment noted. No action required.

	Roche	No comment	Comment noted. No action required.
Equality and Diversity	NCRI-ACP-RCP-RCR	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 entrectinib will be licensed; No • 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; No. The only issue will be access to ROS1 testing which may not currently be equitable across the country (this is impartial to protected characteristics) although this should be resolved with introduction of the test directory and the new Genomics laboratory hubs and commissioning for molecular tests by 2020. • could have any adverse impact on people with a particular disability or disabilities. No	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.
	Roche	No equality concerns noted	Comment noted. No action required.
Other Considerations	NCRI-ACP-RCP-RCR	I*s testing for ROS1 fusion-positive non-small-cell lung cancer established routine clinical practice in the NHS?* ROS1 testing is likely to have been adopted in most academic centres but may not currently be routine practice across all centres in the UK.	Comment noted. ROS1 testing is not considered to be established routine clinical in the NHS as crizotinib is only

		This is an important test and should be accessible to all non-squamous NSCLC patients. Access to testing should become equitable with the new Genomic Laboratory Hubs and adoption/implementation of the test directory but it may also be worth considering within this appraisal.	available through the Cancer Drugs Fund for ROS1 fusion non-small-cell lung cancer. The economic analysis section of the scope has been amended accordingly.
Innovation	NCRI-ACP-RCP-RCR	• Do you consider entrectinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)? Yes, ROS1 fusion is a key genomic driver of disease for around 1-2% of patients with non-squamous NSCLC and selective inhibitors of this pathway are needed Entrectinib is a highly selective ROS/ALK/TRK inhibitor. Data suggest longer PFS for ROS1 positive disease compared with crizotinib (a less selective ROS1 inhibitor). Randomized data are very challenging to obtain in this setting due to rarity of the population. Control of brain mets appears to be better with entrectinib and this is an important unmet need in the management of patients with NSCLC. • Do you consider that the use of entrectinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No although control of brain mets would be of interest to include in the model if not already covered in the QALY calculation.	Comments noted. The extent to which the technology is innovative will be considered in the appraisal of crizotinib. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. The scope has been amended to include subgroups by the presence and absence of Brain metastases.

		• Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. Three Phase 1/2 entrectinib trials (ALKA-372-001, EudraCT 2012-000148-88; STARTRK-1, NCT02097810; STARTRK-2, NCT02568267)	Comment noted. Technology section has been amended accordingly.
	Roche	Entrectinib has been granted Promising Innovative Medicine designation by the MHRA for "Treatment of patients with ROS-1 positive locally advanced or metastatic non-small cell lung cancer with brain metastases". This was granted on the basis of the high unmet need in ROS1 patients with CNS metastases, and entrectinib's ability to improve outcomes in a clinically meaningful way in patients with and without CNS disease at baseline, which is representative of the drug's ability to address active CNS disease and delay both systemic and CNS progression. This was deemed to be a therapeutic advantage over currently available therapies. Roche therefore considers that entrectinib is innovative in its potential to make a significant and substantial impact on health-related benefits, particularly in those patients who have CNS metastases, who typically have a much poorer prognosis than those without.	Comments noted. The extent to which the technology is innovative will be considered in the appraisal of crizotinib. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required.
Questions for consultation	NCRI-ACP-RCP-RCR	Where in the treatment pathway for treating ROS1 fusion-positive NSCLC is entrectinib likely to be used in practice? First-line or second-line? 1st line treatment if the ROS1 status is known upfront. Second (or subsequent) line setting should also be considered where ROS1 results become available during first-line (or subsequent line) treatment with chemo or chemo-IO. The unknown may be whether entrectinib is advantageous in patients who have failed on crizotinib	Comment noted. No action required.

		and whether it should be considered in this setting. Data exist in relation to CNS penetration and uncontrolled brain mets may be one indication where entrectinib could be considered in crizotinib-failed patients if sufficient data to support.	
	Roche	Is testing for ROS1 fusion-positive non-small-cell lung cancer established routine clinical practice in the NHS? Roche response: Feedback from 9 consultant oncologists based throughout the UK suggest that ROS1 testing by IHC is largely established in routine clinical practice, with many centres conducting reflex testing. However, not all centres have local testing in place. Where do you consider entrectinib will fit into the existing NICE pathway, Lung Cancer? • Where in the treatment pathway for treating ROS1 fusion-positive NSCLC is entrectinib likely to be used in practice? First-line or second-line? Roche response: The anticipated licence for entrectinib is for ROS1 positive NSCLC patients, and does not specify a line of therapy. Roche expects that where treatment-naïve patients are identified as	Comment noted. Comment noted. ROS1 testing is not considered to be established routine clinical in the NHS as crizotinib is only available through the Cancer Drugs Fund for ROS1 fusion non-small-cell lung cancer. The economic analysis section of the scope has been amended accordingly.

		ROS1 positive, ROS1 TKIs such as entrectinib and crizotinib would be the preferred treatment option. However, some patients, particularly those already in the treatment pathway, may be identified as ROS1 positive at a later line of treatment, at which point a ROS1 TKI may also be used. • Have all relevant comparators for entrectinib been included in the scope? Roche response: please refer to comments in comparator section. Which treatments are considered to be established clinical practice in the NHS for ROS1 fusion-positive locally advanced or metastatic non-small-cell lung cancer? Roche response: Based on consultant oncologist feedback, the treatments currently used for ROS1 positive NSCLC patients would be crizotinib in 1L, followed by pemetrexed + platinum chemotherapy in 2L, then docetaxel ± nintedanib, potentially followed by	Comment noted. No action required. Comment noted. Please see NICE's response to comments on the comparator section. No action required. Comment noted. Please see NICE's response to comments

		immunotherapy. The order of treatments is dependent on the stage at which a patient is identified as ROS1 positive. In particular, should the following be included for untreated disease: • Chemotherapy (docetaxel, gemcitabine, paclitaxel or vinorelbine) in combination with a platinum drug (carboplatin or cisplatin) ○ with (for people with non-squamous NSCLC only) or without pemetrexed maintenance treatment. • Single agent chemotherapy with a third generation drug for people who cannot tolerate platinum-based therapy. Roche response: Please refer to comments in comparator section. Roche believes that these chemotherapy regimens should not be included due to very limited use in ROS1 positive NSCLC patients. • How should best supportive care be defined?'	on the comparator section. No action required. Comment noted. Please see NICE's response to comments on the comparator section. No action required.

		Roche response: NA as best supportive care is not an appropriate comparator.	Comment noted. Please see NICE's response to comments on the comparator section. No action required.
		• Are the outcomes listed appropriate? Roche response: Yes.	Comment noted. No action required.
		• Are there any subgroups of people in whom entrectinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? Roche response: While entrectinib has a PIM designation in ROS1 positive NSCLC with CNS metastases due to compelling data in these patients, Roche believes the limited overall size of the trial population and the smaller CNS population prohibits separate comparative effectiveness and cost-effectiveness analysis of this group.	Comment noted. The scope has been amended to include subgroup by the presence and absence of brain metastases.

The following consultees/commentators endorsed NCRI-ACP-RCP-RCR submission

The Christie NHS Foundation Trust

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

Department of Health and Social Care