National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Alectinib for untreated anaplastic lymphoma kinase-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	Roche Products	The indication for alectinib is as follows: "Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)." Thus the remit should be reworded to specify adult patients, as opposed to "people"	The remit states that the technology will be appraised within its marketing authorisation and does not specify the relevant age group. No changes to the remit are required. The population on page 2 of the scope has been updated to specify adults.

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	Royal College of Pathologists	YES	Comment noted.
Timing Issues	Roche Products	Alectinib has demonstrated considerable superiority versus crizotinib in the ALEX trial. As a result, the regulatory timelines have been accelerated to ensure patient access at the earliest opportunity. Marketing Authorisation is anticipated [redacted]. In addition, alectinib has been designated PIM status, and Roche are anticipating confirmation of an Early Access to Medicines Scheme (EAMS) scheme by [redacted]. This scheme must close to new patients at the point of Marketing Authorisation. NICE timelines are already delayed for this indication, with final guidance anticipated much later than 90 days after marketing authorisation, as was recommended in the CDF SOP. Therefore, it is critical this appraisal continues without further delay, to prevent patients missing an opportunity of treatment with a significant advance over current standard of care.	Comments noted.
	Royal College of Pathologists	URGENT	Comment noted.

Comment 2: the draft scope

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	Roche Products	The Anaplastic Lymphoma Kinase alteration was first demonstrated as an important prognostic factor in October 2010 when crizotinib demonstrated	Thank you for your comments. The

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Background information		superiority versus chemotherapy in the second line setting (PROFILE 1007). Since, with the positive recommendation of crizotinib in the first line setting, other ALK-inhibitors in subsequent settings, and ALK testing becoming ingrained in clinical practice, the treatment pathway for ALK-positive NSCLC has become a stand-alone pathway: part of, but distinctly separate from the NSCLC pathway. As such, the fourth paragraph in the background summary needs to be adapted to reflect the ALK-positive NSCLC treatment pathway better, which is followed by most patients, as opposed to the wider NSCLC treatment pathway. As ALK testing is now ingrained within clinical practice, and crizotinib has demonstrated superiority versus chemotherapy, only technology appraisal guidance 406 is applicable to this scope.	background section is intended to provide a brief summary of the disease, on a broad level, to provide context for the positioning of the technology in the pathway. It is understood that the treatment pathway for people with ALK-positive NSCLC is distinct, and that the only other targeted treatment currently available is crizotinib. The population in which alectinib will be appraised and the relevant comparators are specified later in the scope. No changes to the background section are required. Please refer also to the response to comments on the comparators section.

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	Royal College of Pathologists	OK	Noted. No changes to the scope required
The technology/ intervention	Pfizer	Yes, it is accurate	Noted. No changes to the scope required.
	Roche Products	Yes, the description of the technology is accurate.	Noted. No changes to the scope required.
	Royal College of Pathologists	Yes – drug for ALK +ve NSCLC	Noted. No changes to the scope required
Population	Pfizer	Yes, it is accurate	Noted. No changes to the scope required.
	Roche Products	Yes, the population is appropriate. No additional subpopulations are relevant.	Comments noted. No changes to the scope required.
Comparators	Pfizer	Yes, it is accurate	Comments noted. No changes to the scope required.
	Roche Products	ALK testing is now ingrained in clinical practice, and crizotinib has demonstrated superiority over chemotherapy. As such, upon confirmation of the ALK mutation, all patients would be eligible for treatment with crizotinib. Therefore, pemetrexed in combination with a platinum drug, with or without pemetrexed maintenance cannot be considered a standard treatment option, and thus should not be a comparator. It should be noted that the only rationale for ALK testing, is to test suitability for an ALK inhibitor. When	Comments noted. Pemetrexed in combination with a platinum drug has been removed as a comparator.

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		clinicians test for ALK positivity they only do so to enable treatment with an ALK inhibitor, as a better alternative to chemotherapy.	
Outcomes	Pfizer	Yes	Noted, no changes to the scope required.
	Roche Products	Yes, the listed outcomes capture the most important health related benefits and harms.	Noted, no changes to the scope required.
Economic analysis	Roche Products	Alectinib has demonstrated considerable benefit over crizotinib, thus a cost effectiveness analysis is the most appropriate economic analysis. This will be expressed in terms of incremental cost per quality-adjusted life year. The time horizon should be sufficient to capture all health related benefits and costs of treatment: a lifetime horizon that captures the full expected overall survival of patients is the appropriate time horizon.	Comments noted. No changes to the scope required.
Equality and Diversity	Roche Products	No equality issues have been identified.	Noted.
Other considerations	Royal College of Pathologists	The implications for RCPath are in the testing for ALK gene rearrangements, but this has essentially been addressed for the NHS in relation to usage of crizotinib. As this is for untreated disease, then the testing will essentially be the same as is currently in place.	Comments noted.
Innovation	Roche Products	Promising Innovative Medicine (PIM) Designation was issued for alectinib for the first line treatment of adult patients with anaplastic lymphoma kinase positive advanced non-small cell lung cancer on the 26th April 2017, with a subsequent submission for EAMS in process. PIM/EAMS status indicates that Alecensa could be available to UK patients to meet a high unmet clinical need.	Comments noted. The company and other consultees will be able to fully describe why they consider alectinib to be innovative in their

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		Alectinib has demonstrated significantly superior efficacy and a better tolerability profile than crizotinib in primary treatment of ALK-positive NSCLC. The ALEX trial reported significantly longer progression free survival of alectinib versus crizotinib in both the: • Independent review committee-assessed endpoint (25.7 months [95% CI, 19.9 to not estimable] vs. 10.4 months [95% CI, 7.7 to 14.6]; hazard ratio, 0.50 [95% CI, 0.36 to 0.70]; P<0.001), and • Investigator assessed endpoint (not reached [95% CI, 17.7-not estimable] vs. 11.1 months [95% CI, 9.1-13.1]; hazard ratio, 0.47 [95% CI, 0.34-0.65]; P<0.0001). • In addition, alectinib was shown to effectively protect against and treat CNS metastases. • The tolerability of alectinib compared favourably to crizotinib, despite longer treatment duration, with fewer dose reductions and interruptions than crizotinib. The prognosis for ALK-positive NSCLC patients is poor, thus alectinib is considered a significant step change for the management of this condition.	evidence submissions. This will be considered by the appraisal committee, focussing on substantial health benefits that are not captured in the model.
Questions for consultation	Pfizer	**Are non-squamous tumours routinely tested for the ALK mutation in current NHS practice?** Yes **Is the same test used throughout the NHS?** There is a variation in testing approach which include upfront IHC screen and FISH confirmation, FISH screen, IHC alone **Would a different test be used depending on the treatment being considered (that is, do alectinib and crizotinib have specific companion diagnostics)?**	Comments noted.

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		No. A validated ALK assay is necessary for the selection of ALK-positive NSCLC patients for both drugs **Would alectinib be used in people with ALK-positive squamous NSCLC?** There are rare cases of advanced squamous NSCLC which have been identified to be ALK positive and could therefore have the potential to be treated with alectinib **Would alectinib be suitable for people who are unable to tolerate a platinum combination (for whom the NICE clinical guideline recommends single-agent chemotherapy with a third-generation chemotherapy drug)?** Yes **The NICE clinical guideline recommends platinum plus a third-generation drug (docetaxel, gemcitabine, paclitaxel, or vinorelbine) as first line treatment for advanced NSCLC. Are these combinations still used in clinical practice for untreated ALK-positive NSCLC?** • Clinical expert opinion suggests that it is it is uncommon for docetaxel, paclitaxel or vinorelbine with platinum-based chemotherapy to be used in non-squamous patients in the first line setting. These are instead comparators more commonly used to treat squamous patients. • It is also understood that gemcitabine is not commonly used in non-squamous patients, however it may be an alternative therapy offered to a small number of non-squamous patients who are not be able tolerate pemetrexed-platinum doublet therapy. **Are they used for squamous and non-squamous NSCLC?** Yes	

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		Have all relevant comparators for alectinib been included in the scope? Yes **Which treatments are considered to be established clinical practice in the NHS for untreated ALK-positive non-small-cell lung cancer?** The comparators stated in the draft scope **Are the outcomes listed appropriate?** Yes **Are there any subgroups of people in whom alectinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?** No **Where do you consider alectinib will fit into the existing NICE pathway for Lung Cancer?** Patients who are diagnosed with ALK+ advanced NSCLC and who have not received systemic anti-cancer treatment in the palliative setting **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No	
	Roche Products	1. Are non-squamous tumours routinely tested for the ALK mutation in current NHS practice? Is the same test used throughout the NHS? Would a different test be used depending on the treatment being considered (that is, do alectinib and crizotinib have specific companion diagnostics)?	Comments noted.

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		Testing is conducted irrespective of tumour type. Rather, it is based on patient characteristics, as the baseline characteristics of ALK-positive patients are distinct from other NSCLC patients. There are no specific companion diagnostics for either alectinib or crizotinib: the same test would be used irrespective of treatment. The two most common tests are FISH and IHC. 2. Would alectinib be used in people with ALK-positive squamous NSCLC? Yes, whilst the ALK mutation is most common in non-squamous NSCLC, the ALEX trial recruited a small number of squamous NSCLC patients, thus was able to demonstrate efficacy within this population as well. 3. Would alectinib be suitable for people who are unable to tolerate a platinum combination (for whom the NICE clinical guideline recommends single-agent chemotherapy with a third-generation chemotherapy drug)? ALK inhibitors are standard of care within this indication. It is unlikely a patient would receive a platinum combination, whether they are tolerant or not. As stated above – by testing a patient for the ALK status of their tumour a clinician is, in effect committing to starting ALK inhibitor therapy where the test is positive: as a better alternative to chemotherapy. Thus, a patients suitability for chemotherapy is not relevant 4. The NICE clinical guideline recommends platinum plus a third-generation drug (docetaxel, gemcitabine, paclitaxel, or vinorelbine) as first line treatment for advanced NSCLC. Are these combinations still used in clinical practice for untreated ALK-positive NSCLC? Are they used for squamous and non-squamous NSCLC? No. The standard of care for ALK-positive NSCLC is crizotinib. Chemotherapy is used in patients who are ALK-negative.	

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		5. Have all relevant comparators for alectinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for untreated ALK-positive non-small-cell lung cancer? Pemetrexed in combination with a platinum drug, with or without pemetrexed maintenance treatment is not an appropriate comparator. The only used treatment for ALK-positive NSCLC is crizotinib. 6. Are the outcomes listed appropriate? Yes, the outcomes are appropriate 7. Are there any subgroups of people in whom alectinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No further subgroups can be identified 8. Where do you consider alectinib will fit into the existing NICE pathway for Lung Cancer? Alectinib would replace crizotinib as a first line treatment for ALK-positive NSCLC 9. Could the proposed remit and scope: exclude from full consideration any people protected by the equality legislation who fall within the patient population for which alectinib will be licensed? No 10. Could the proposed remit and scope: 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	

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		No 11. Could the proposed remit and scope: have any adverse impact on people with a particular disability or disabilities. No 12. Do you consider alectinib 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, alectinib has demonstrated considerable superiority in this setting, thus is considered a step change in the management of this condition. As detailed above, PIM status has been designated to alectinib for this indication, and an EAMS program is anticipated. 13. Do you consider that the use of alectinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? No comment 14. To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly. No: ALK testing is already routine clinical practice, and given both products are orally administered, there are no drug administration concerns for alectinib replacing crizotinib in clinical practice. Thus there are no barriers to adoption of this medicine 15. Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?	

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		Alectinib has demonstrated significant superiority versus crizotinib, thus cannot be considered similar in clinical efficacy. However, both treatments are oral, thus there will be a similar resource use between the comparators. Chemotherapy cannot be considered an appropriate comparator. 16. Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant? Yes. The primary endpoint was progression free survival: a key endpoint for both economic appraisals, and within clinical practice. 17. Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year? Roche are not aware of any new evidence for crizotinib.	

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

Department of Health