National Institute for Health and Care Excellence

Health Technology Evaluation

Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer [ID6368]
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	Roche	The appraisal of alectinib is appropriate.	No action required
	ALK Positive UK	Very appropriate.	No action required
	British Thoracic Oncology Group (BTOG)	Appropriate to evaluate as STA	Thank you for your comment
Wording	Roche	The wording of the remit is appropriate.	No action required
	ALK Positive UK	Yes although it does not focus enough on ALK+NSCLC, whereas carries quite a lot of general information about NSCLC that is not really very relevant to the ALK+ subgroup. I understand it may be necessary to introduce the Case, but it needs to be balanced. Given the figures the company quote at the beginning of this scoping document (31,000pts diagnosed with NSCLC in 2021, estimated 5% have ALK fusion mutation), there should be 1550 new	Thank you for your comment. The prevalence estimate in the scope has been updated in line with recent literature

Section	Stakeholder	Comments [sic]	Action
		diagnoses of ALK+ a year. When you look into the references, one is a CRUK figure and the other uses a 2-5% estimate in a paper from 2007. The lower end of that range would give a figure of 620 new cases/year. Maybe that's nearer the mark. Overall numbers have implications on total cost but given that "The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year", either end of the range shouldn't impact on the decision to use Alectinib as an adjuvant treatment for patients who have had total surgical resection. Our understanding is that studies have shown that 50% of patients with ALK-positive have negative PD-Li expression. Even for the 50% with varying degrees of PD-Li expression, the evidence for the use of immunotherapy is still limited. In relation to the question below, we would have thought the answer is that patients would want to be offered Alectinib with its proven efficacy in advanced disease rather than immunotherapy. • If someone with ALK-positive NSCLC had neo-adjuvant treatment with an immunotherapy and then surgery would clinicians offer alectinib as adjuvant treatment? Or would an adjuvant immunotherapy be preferred?	estimates in light of these comments.
	BTOG	Appropriate	Thank you for your comment

Section	Stakeholder	Comments [sic]	Action
Additional comments on the draft remit	Roche	No additional comments.	No action required
	ALK Positive UK	We would hope that the appraisal committee also takes into consideration the FDA Priority Review outcome.	Thank you for your comment. The committee will consider the evidence presented in the submissions.
	BTOG	The proposed license wording is unknown but presumed to reflect the registrational trial dataset.	Thank you for your comment.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Roche	Around 60% of patients diagnosed with NSCLC have advanced or metastatic disease, and approximately 30% are diagnosed with Stage I or II in addition to the scoping document approximately 10% are diagnosed with Stage IIIA (Xing et al., Can Med, 2019). There is a typo in the last sentence in the second paragraph. It is recommended that this is changed from “ALK fusions can occur in type of NSCLC”to “ALK fusions can occur in any type of NSCLC”.	Thank you for your comment the scope has been amended to include stage 3A disease and correct the typo.
	ALK Positive UK	We feel that there is a lack of due diligence in providing the necessary important background information (peer reviewed and " grey literature"). There is a growing body of reports supporting the utility of ALK TKIs (Alectinib in particular) in the adjuvant [and neo-adjuvant] setting[s], and	Thank you for your comment. The scope is only intended to give a general background to the condition and

Section	Consultee/ Commentator	Comments [sic]	Action
		there are ongoing clinical trials testing those aspects. There is no mention of them in the Case.	treatment pathway. The committee will consider the evidence on efficacy that is presented in the submissions.
	BTOG	No major comments	Thank you for your comment
Population	Roche	The population defined in the scoping document is appropriate.	Thanks for your comment. Following the consultation, the population in the final scope has been amended as "adults with ALK-positive NSCLC who have undergone surgical resection" to keep it broad at this stage.
	ALK Positive UK	Yes	Thanks for your comment. Following the consultation, the population in the final scope has been amended as "adults with ALK-positive NSCLC who have undergone surgical

Section	Consultee/ Commentator	Comments [sic]	Action
			resection" to keep it broad at this stage.
	BTOG	The population should be restricted to those with ALK+ NSCLC with stage that underwent resection as per the ALINA trial data (ie UICC v7 stage 1B (>=4cm)-IIIA, rather than all ALK+ NSCLCs that underwent resection.	Thank you for your comment. The population in the scope is kept broad at this stage in case of any changes. The committee will consider the population covered by the marketing authorisation during the appraisal.
Subgroups	Roche	Patients in the trial are stratified by disease stage (IB - IIIA) and race (Asian vs non- Asian). No difference is expected to be seen in terms of cost-effectiveness or clinical efficacy for patients of Asian or non-Asian descent.	Thank you for your comments. The scope has been amended to allow the committee to consider clinical- and cost-effectiveness in any subgroups allowed by the evidence.
	ALK Positive UK	Not in our opinion	Thank you for your comment.
	BTOG	No	No action required

Section	Consultee/ Commentator	Comments [sic]	Action
Comparators	Roche	As there are now several options for effective treatment in the adjuvant setting (i.e. chemotherapy and immunotherapy), active monitoring would no longer be an acceptable clinical or ethical choice for this group of patients. Pembrolizumab (ID: GID-TA10784) has not received a recommendation from NICE at this time, therefore would not be deemed a relevant comparator. Atezolizumab has received a positive recommendation for use within the cancer drugs fund as an option for adjuvant treatment after complete tumour resection in adults with stage 2 to 3a non-small cell lung cancer (NSCLC) (TA823). It should be noted that ALK was not specifically looked at in this appraisal" It is generally recognised that treatment with immunotherapy has shown significantly reduced or no efficacy in ALK+ NSCLC. ALK+ patients are either excluded from trials or the number enrolled is too small to provide a clinically meaningful assessment of immunotherapy in ALK positive early-stage NSCLC. The IMpower010 study of atezolizumab included ALK+ patients; however, results should be interpreted with caution due to small numbers of patients; a high percentage with unknown status (~40%) and large confidence intervals. No significant benefit has been observed in the metastatic setting to date with immunotherapies for patients with ALK-positive NSCLC, even among patients with high PD-L1 expression. Atezolizumab is not a suitable comparator for this appraisal.	Thank you for your comments. The comparators have been kept inclusive at this stage to allow the committee to discuss and consider any potentially relevant comparators or evidence including clinical expert opinions during the appraisal. However, atezolizumab has been removed as a comparator as it is only recommended within the CDF.
	ALK Positive UK	Yes in our opinion.	Thank you for your comment.
	BTOG	The appropriate comparators are platinum-based chemotherapy and active monitoring. Whilst pembrolizumab does have marketing authorization for adjuvant use including ALK+ NSCLC, this is not yet NICE approved, and	Thanks you for your comments. The comparators have been

Section	Consultee/ Commentator	Comments [sic]	Action
		pembrolizumab has little, if any, activity in ALK+ NSCLCs. Hence, pembrolizumab should not be a comparator as it would (should) not be used as an adjuvant therapy for ALK+ NSCLC	kept inclusive at this stage to allow the committee to discuss and consider any potentially relevant comparators or evidence including clinical expert opinions during the appraisal.
Outcomes	Roche	Both event-free survival and pathological complete response are endpoints associated with neoadjuvant therapy and are therefore not included in this adjuvant trial. Response rates are only used in trials where there is evaluable tumour in situ i.e. metastatic disease. This is an adjuvant trial looking at fully resected disease and therefore there are no response rates to collect. Although overall survival was collected in the trial, the data is immature for this clinical data cut-off, it is unlikely that the data will be available for some time due to expected treatment effect. The other listed outcomes capture the most important health-related benefits and harms for people with adjuvant ALK positive NSCLC.	Thank you for your comment. The outcomes have been amended to reflect the adjuvant decision space.
	ALK Positive UK	Yes in our opinion	Thank you for your comment.

Section	Consultee/ Commentator	Comments [sic]	Action
	BTOG	Event free survival, response rates, and pathological complete response are not appropriate as this is not a neoadjuvant therapy, but is an adjuvant (post operative) therapy	Thank you for your comment. The outcomes have been amended to reflect the adjuvant decision space.
Equality	Roche	No equality issues have been identified.	No action required
	ALK Positive UK	None	No action required
	BTOG	No changes needed	No action required
Other considerations	Roche	No comments	No action required
	ALK Positive UK	In the Case, there are questions for Discussion. The answers actually may already exist in the published literature. We have provided some references in the "Notes" that may be useful (e.g. Tabbò and Novello, 2019 https://tlcr.amegroups.org/article/view/30691/html)	Thank you for your comment.
	BTOG	No comment	No action required
Questions for consultation	Roche	**Is the population defined appropriately in the scope?** The population is defined appropriately in the scope. **Is testing for ALK gene fusions considered to be standard practice in the adjuvant setting for NSCLC in the NHS?**	Thank you for your responses to the consultation questions and please see responses to comments on population, comparator, and

Section	Consultee/ Commentator	Comments [sic]	Action
		ALK testing for gene fusions is included in the national testing directory regardless of setting. The onset of neoadjuvant nivolumab has made the need for testing in the pre-surgery setting mandatory. Patients initiated on to neoadjuvant nivolumab are required to test negative for ALK gene fusions and EGFR mutations. **Where do you consider alectinib will fit into the existing care pathway for NSCLC?** Alectinib will fit into the existing care pathway in the post-surgery adjuvant setting in place of adjuvant chemotherapy for fully resected early-stage ALK+ NSCLC patients. **Have all relevant comparators been included?** Platinum based chemotherapy is the only relevant comparator for this patient population. **For someone with ALK-positive NSCLC, would a clinician generally offer adjuvant alectinib over an adjuvant immunotherapy?** It is generally recognised that treatment with immunotherapy has shown significantly reduced or no efficacy in ALK+ NSCLC. ALK-positive patients are either excluded from trials or the number enrolled is too small to provide a clinically meaningful assessment of immunotherapy in ALK-positive early-stage NSCLC. **If someone with ALK-positive NSCLC had neo-adjuvant treatment with an immunotherapy and then surgery would clinicians offer alectinib as**	subgroups above and how amends were made in the final scope

Section	Consultee/ Commentator	Comments [sic]	Action
		adjuvant treatment? Or would an adjuvant immunotherapy be preferred? ALK+ NSCLC patients would not receive neoadjuvant immunotherapy. One of the stipulations of the CDF (Cancer Drugs Fund) is that in order for patients to be initiated on to neoadjuvant immunotherapy they have to be negative for ALK and EGFR alterations. The CDF states “Either the patient has been documented as not having a NSCLC which harbours an EGFR 19 or 21 mutation or an ALK gene fusion or the patient has a squamous cell carcinoma and a decision to not test for an EGFR 19 or 21 mutation or an ALK gene fusion and proceed with nivolumab has been discussed with the patient during the consenting process, i.e. the patient has consented to be treated with an unknown EGFR/ ALK status. Please mark below which option applies to this patient:- Documented as NOT having a NSCLC which harbours an EGFR 19 or 21 mutation or an ALK gene fusion.- Patient has squamous NSCLC and a decision to not test for an EGFR 19 or 21 mutation or an ALK gene fusion and proceed with nivolumab has been discussed with the patient during the consenting process” **If recommended, would alectinib use depend on whether there was complete or incomplete resection of the locally advanced NSCLC?** The ALINA study evaluated the efficacy and safety of adjuvant alectinib compared with platinum based chemotherapy in patients with completely resected *ALK*+ NSCLC **Have all relevant subgroups been included in the scope?** Patients in the trial are stratified by disease stage (IB - IIIA) and race (Asian vs non- Asian).	

Section	Consultee/ Commentator	Comments [sic]	Action
		If someone had alectinib as an adjuvant treatment, would clinicians offer ALK inhibitors later for advanced or metastatic disease? If a patient experiences a relapse after completing the 2-year treatment regimen, it is anticipated that they might be considered for treatment with an ALK inhibitor, including alectinib. If a patient relapses whilst on alectinib for adjuvant treatment of ALK+ NSCLC it would be possible to consider an alternative treatment. **Would alectinib be a candidate for managed access?** Alectinib would not be a suitable candidate for managed access given the evidence already available from the ALINA trial. It is anticipated that future data cut offs will have insufficient data for overall survival due to expected treatment effect. **Do you consider that the use of alectinib can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?** The health-related benefits will be captured within 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. 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:	

Section	Consultee/ Commentator	Comments [sic]	Action
		• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which alectinib will be 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. Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts	
	ALK Positive UK	None	No action required
	BTOG	Is the population defined appropriately in the scope? >> Needs to be better defined as per stage eligible for the ALINA trial Is testing for ALK gene fusions considered to be standard practice in the adjuvant setting for NSCLC in the NHS? >> Yes Where do you consider alectinib will fit into the existing care pathway for NSCLC? >>It will be a new standard care for adjuvant ALK+ resected NSCLC as currently these patients are treated with adjuvant chemotherapy. If approved the NHSE Blueteq form for 1st line metastatic aLK+ NSCLC will need to be adjusted to allow relapse having received prior adjuvant alectinib (in the same	Thank you for your comments. Population in the scope is kept broad at this stage in case of any changes. The committee will consider the population covered by the marketing authorisation during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
		was as the 1st line metastatic osimertinib Blueteq form was changed after the introduction of adjuvant osimertinib) Have all relevant comparators been included? >>Yes, although adjuvant pembrolizumab is not a valid comparator For someone with ALK-positive NSCLC, would a clinician generally offer adjuvant alectinib over an adjuvant immunotherapy? >>Yes. Immunotherapy is not active in ALK+ disease (early stage or metastatic?) If someone with ALK-positive NSCLC had ***neo-adjuvant*** treatment with an immunotherapy and then surgery would clinicians offer alectinib as ***adjuvant*** treatment? Or would an adjuvant immunotherapy be preferred? >>ALK-positive NSCLC should not be offered neoadjuvant immunotherapy as these trials generally excluded this patient group. Hence this population does not exist. There is a remote possibility of a patient not being identified as ALK positive until after having received neoadjuvant chemo-immunotherapy and then undergone surgery. In this remote setting, yes adjuvant alectinib would be recommended (as immunotherapy is an inert drug in ALK+ NSCLC). If recommended, would alectinib use depend on whether there was complete or incomplete resection of the locally advanced NSCLC? >>No, in routine practice alectinib should be used regardless of complete/incomplete resection. In the setting of incomplete resection, patients may need adjuvant chemo-radiotherapy before alectinib Have all relevant subgroups been included in the scope? >>Yes	

Section	Consultee/ Commentator	Comments [sic]	Action
		If someone had alectinib as an adjuvant treatment, would clinicians offer ALK inhibitors later for advanced or metastatic disease? >>Yes, but crizotinib would not be given. The choice of ALK inhibitor for metastatic disease may depend on if the patient relapsed on adjuvant alectinib or after adjuvant alectinib had been discontinued. Would alectinib be a candidate for managed access? >>Yes, adjuvant alectinib has a strong effect and is a novel innovative indication with large clinical impact (albeit for a small absolute number of UK patients, as the number of Stage 1b-3 ALK+ NSCLC is small) Do you consider that the use of alectinib 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	
Additional comments on the draft scope	Roche	No additional comments	No action required
	ALK Positive UK	None	No action required
	BTOG	None	No action required

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

MSD