National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Alectinib for previously treated anaplastic lymphoma kinase-positive non-small-cell lung cancer

Response to consultee and commentator comments for the second consultation on the draft remit and draft scope (post-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 scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Novartis Pharmaceuticals	None	Comment noted.
	Roche	No comment	Comment noted.
The technology/ intervention	Novartis Pharmaceuticals	None	Comment noted.
	Roche	It is accurate	Comment noted.
Population	Novartis Pharmaceuticals	None	Comment noted.
	Roche	It is appropriate	Comment noted.
Comparators	Novartis Pharmaceuticals	No, the comparator should only be ceritinib, because, by the time of this appraisal, ceritinib will be the standard of care for ALK+ NSCLC previously	Thank you for your comment.

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		treated with crizotinib. It is extremely unlikely that any patient would be suitable to receive chemotherapy (pemetrexed +/- platinum or docetaxel) but would not be suitable for ceritinib. Therefore, platinum doublet chemotherapy or docetaxel are not appropriate comparators. Comparators for alectinib if crizotinib is recommended as a treatment for untreated ALK-positive NSCLC? Ceritinib only, because, by the time of this appraisal, ceritinib will be the standard of care for ALK+ NSCLC previously treated with crizotinib, irrespective of whether crizotinib is given to patients previously untreated or previously treated with chemotherapy. Furthermore, It is extremely unlikely that any patient would be suitable to receive platinum doublet chemotherapy (alternative in this setting) but would not be suitable for ceritinib. Therefore, platinum doublet chemotherapy is not an appropriate comparator in patients previously only treated with crizotinib. Is it appropriate to split the comparators for alectinib according to line of treatment? No, because the appropriate comparator is only ceritinib in any line of treatment for ALK+ NSCLC previously treated with crizotinib.	At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy setting only. Therefore best supportive care was considered to be the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been

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			kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the scope needed.
	Roche	Ceritinib (appraisal ID729) has been recommended for use within the final appraisal determination (FAD). It is therefore anticipated this therapy will become a treatment option for patients who have progressed following treatment with crizotinib. As such ceritinib is likely to be a relevant comparator for alectinib. The anticipated marketing authorisation for alectinib is identical to that of ceritinib. As such, the comparators for alectinib should be consistent with those defined for ceritinib, in addition to ceritinib itself (subject to appraisal ID729). Within the FAD, the committee concluded that the only relevant comparator for ceritinib was best supportive care (BSC), which would not include any active chemotherapy [platinum doublet chemotherapy or docetaxel] (paragraph 4.2, page 18). This was consistent with advice provided to the committee from clinical experts, and it is unclear why this same advice is not accounted for in this scope. The appropriate comparators for this appraisal, in order to be consistent with the recently published FAD for ID729, are ceritinib and BSC	Thank you for your comment. At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy setting only. Therefore best supportive care was considered to be the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel

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			could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the scope needed.
	British Thoracic Oncology Group (BTOG)	The potential licensed indication for alectinib is intolerant of or relapse on crizotinib. NICE do not currently approved 1st line crizotinib in their ACD (ID865). This may change. Assuming ACD for ID865 remains and becomes a FAD, then alectinib could not be used after 1st line crizotinib due to lack of access to 1st line crizotinib. For 2nd and 3rd line ALK+ NSCLC, access for crozotinib in England is via the CDF. This is being reappraised by NICE. If crizotinib access in this setting is not supported then alectinib could not be used after 3rd and 4th line setting after 2nd line crizotinib due to lack of access to 2nd line crizotinib. Assuming 1st line crizotinib (ID865) is approved for funding, ceritinib is the	Thank you for your comment. At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy setting only. Therefore best supportive care was considered to be

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		correct comparator as this is now approved [ACD, ID729]. The other comparator for patients not fit for ceritinib is best supportive care. Assuming ceritinib is becomes approved in the FAD, chemotherapy is no longer a comparator.	the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the scope needed. In addition, alectinib will

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			be appraised within its marketing authorisation and any impact of ongoing relevant appraisals will be taken into account by the appraisal committee.
Outcomes	Novartis Pharmaceuticals	None	Comment noted.
	Roche	Yes	Comment noted.
Economic analysis	Novartis Pharmaceuticals	None	Comment noted.
	Roche	The time horizon will be appropriate to capture differences in costs and outcomes	Comment noted.
Equality and Diversity	Novartis Pharmaceuticals	None	Comment noted.
	Roche	No equality issues identified	Comment noted.
	NCRI-ACP-RCP-RCR	There are no equality issues.	Comment noted.
	British Thoracic Oncology Group	There are no equality issues.	Comment noted.
Other	Novartis	None	Comment noted.

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considerations	Pharmaceuticals		
	Roche	No additional issues to be considered	Comment noted.
Innovation	Novartis Pharmaceuticals	None	Comment noted.
	Roche	Despite introduction of ALK inhibitor therapies, there is a continued and significant unmet need in patients with ALK positive, advanced NSCLC. J-ALEX is an ongoing phase III study, randomised, head-to-head study comparing two ALK inhibitors (alectinib vs, crizotinib) for the treatment of ALK+ NSCLC. In February 2016, an independent data monitoring committee recommended that the data from the J-ALEX study are released early after the study met its primary endpoint at a preplanned interim analysis (50% PFS events), demonstrating superiority of alectinib over crizotinib. Alectinib, and its future indications, offers significant and substantial health-related benefits, and has the potential to be a step change in the management of patients with ALK positive NSCLC. Central nervous system (CNS) metastases are a common site of disease progression in patients with ALK positive, advanced NSCLC. Development of brain metastases is associated with a reduction in quality of life, and estimated life expectancy. Existing ALK targeted therapies; crizotinib and ceritinib; are substrates for P-gp, which may result in poor CNS penetration. Preclinical data have shown alectinib is not a substrate for the P-gp efflux transporter, indicating alectinib can penetrate the CNS and elicit clinical activity. Alectinib phase II data have shown comparable efficacy against systemic disease and CNS metastases.	Thank you for your comments. The appraisal committee will discuss the potential innovative nature of this technology. No changes to the scope needed.
Questions for consultation	Novartis Pharmaceuticals	Have all relevant comparators for alectinib been included in the scope?	Thank you for your comment.

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		As mentioned earlier, we don't believe that chemotherapy and BSC are appropriate comparators. Please refer to the comparators section for more details. Crizotinib for untreated ALK-positive NSCLC is currently subject to ongoing NICE appraisal. What would be the relevant comparators for alectinib if crizotinib is recommended as a treatment for untreated ALK-positive NSCLC? In our view the only relevant comparator is ceritinib as that will be the standard of care by the time of this appraisal. Please refer to the comparators section for further details. Is it appropriate to split the comparators for alectinib according to line of treatment? As we mentioned in earlier sections, we do not believe that it is appropriate to split comparators by line of treatment. Ceritinib will be the standard of care in both lines of treatment and therefore should be the comparator for this appraisal	At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy setting only. Therefore best supportive care was considered to be the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been

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			kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the scope needed.
	Roche	Alectinib is anticipated to enter the patient pathway at the same point as the recently FAD recommended ceritinib. As such, the comparators for alectinib should be consistent with those defined for ceritinib, in addition to ceritinib itself (subject to appraisal ID729). It is not appropriate to split the comparators for alectinib according to line of treatment given the current UK standard of care is treatment with platinum-based chemotherapy first line for patients with ALK positive NSCLC. No equality issues identified.	Thank you for your comment. At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy setting only. Therefore best supportive care was considered to be the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel

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			could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the scope needed.
Additional comments on the draft scope	Novartis Pharmaceuticals	None	Comment noted.
	NCRI-ACP-RCP-RCR	The NCRI-ACP-RCP-RCR are grateful for the opportunity to respond to the above consultation. We would like to make the following comments: The potential licensed indication for alectinib is intolerant of or relapse on crizotinib. NICE do not currently approved 1st line crizotinib in their ACD (ID865). This may change. Assuming ACD for ID865 remains and becomes a FAD, then alectinib could not be used after 1st line crizotinib due to lack of	Thank you for your comment. At the time of the ceritinib appraisal (TA395), the marketing authorisation for crizotinib was in the post-chemotherapy

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		access to 1st line crizotinib. For 2nd and 3rd line ALK+ NSCLC, access for crozotinib in England is via the CDF. This is being reappraised by NICE. If crizotinib access in this setting is not supported then alectinib could not be used after 3rd and 4th line setting after 2nd line crizotinib due to lack of access to 2nd line crizotinib. Assuming 1st line crizotinib (ID865) is approved for funding, ceritinib is the correct comparator as this is now approved [ACD, ID729]. The other comparator for patients not fit for ceritinib is best supportive care. Assuming ceritinib is becomes approved in the FAD, chemotherapy is no longer a comparator.	setting only. Therefore best supportive care was considered to be the relevant comparator for ceritinib in that setting. However, clinicians advised that if crizotinib is given as a 1st line treatment, platinum doublet chemotherapy would be a 2nd line treatment option. They also advised that docetaxel could be a treatment option after treatment with crizotinib fails. Therefore in line with the Guide to the methods of technology appraisal, which states that identification of comparators should be inclusive, the list of comparators has been kept broad in the scope to avoid excluding potentially relevant comparators during the appraisal. No changes to the

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			scope needed. In addition, alectinib will be appraised within its marketing authorisation and any impact of ongoing relevant appraisals will be taken into account by the appraisal committee.

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

- Department of Health