National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lorlatinib for untreated ALK-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	Pfizer	The population does not reflect the proposed marketing authorisation which is: [redacted] While this is dependent on the finally approved wording of MHRA assessment, or consistency we would suggest the wording of the title of this evaluation be changed from: *"Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer",* to: [redacted]	No action needed. The remit of the scope is kept broad, partly so that confidential wording is not shared and partly to align with the clinical trial.
	Novartis	No comment	No action needed.
Timing Issues	Pfizer	In this indication Lorlatinib has achieved an [redacted] as the first 3rd generation ALK inhibitor, designed specifically to penetrate the blood-brain-	Comment noted. No action needed.

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		barrier and in addition to overcome most known resistance mutations that can delay ALK-dependent mechanisms of resistance. This pharmacological rationale has been supported by the significant reported improvement in progression free survival vs crizotinib in this patient group found in the CROWN study. [redacted]	
	Novartis	No comment	No action needed.
Additional comments on the draft remit	Pfizer	[redacted]	Comment noted. No action needed.
	Novartis	No comment	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Pfizer	Typo at end of first paragraph of background section. Should be stage IIIB/C, not as written stage IIB/C	Typo has been corrected.
	Novartis	The following statement is incomplete and not entirely accurate: “Treatment choices are influenced by the presence of biological markers (such as mutations in EGFR-TK, ALK or PD-L1 status)...” There should be much clearer distinction between markers containing mutations compared to those whose expression levels make them a target for therapy.	Comment noted. Sentence has been updated.

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		We suggest the following: "Treatment choices are influenced by the presence of biological markers (such as mutations in EGFR-TK, ALK, ROS-1 or BRAF, or levels of PD-L1 expression)..."	
The technology/ intervention	Pfizer	The only change is that Lorlatinib has a conditional marketing authorisation, therefore suggest the wording is changed to: Lorlatinib as monotherapy has ***conditional*** marketing authorisation for the treatment of adults with ALK-positive advanced NSCLC that has been previously treated by other ALK-positive advanced tyrosine kinase inhibitors, including alectinib, ceritinib and crizotinib.	Comment noted. Since the wording of the marketing authorisation is no longer confidential this sentence has been updated.
	Novartis	No comment	No action needed.
Population	Pfizer	Please modify the description of the population to align with the proposed marketing authorisation more closely. We suggest the wording be changed from: *"Adults with untreated ALK-positive advanced NSCLC"* to: [redacted]	The scope is written with information that is in the public domain. The population is usually left broad to align with the clinical trial. The committee will consider the clinical evidence presented to it and make recommendations based on that. No action required.

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	Novartis	No comment	No action needed.
Comparators	Pfizer	Due to the low market share of Ceritinib (less than 2% as recognised in TA670) we request that it is removed from the assessment as it is not a standard treatment currently used in any significant way in the NHS. Ceritinib was removed from the assessment of Brigatinib for ALK-positive advanced non-small-cell lung cancer that has not been previously treated with an ALK inhibitor [TA670], as it was recognised as not being a relevant comparator. This was supported by Takeda, the Liverpool Reviews and Implementation Group, and the NICE appraisal committee D. In terms of the 'best alternative care', whilst Alectinib is the dominant first line treatment of this population, since the NICE recommendation for Brigatinib in January 2021, we would suggest that both Alectinib and Brigatinib are the relevant first line treatment comparators.	The list of comparators within the scope is kept broad to be inclusive of all potentially relevant comparators. The company can provide explanations within their submission regarding which comparators they consider relevant or not.
	Novartis	No comment	No action needed.
Outcomes	Pfizer	We request the inclusion of outcomes related to Central Nervous System (CNS) efficacy, specifically the inclusion of intracranial progression free survival. Firstly, this is a common site of metastases in ALK+ NSCLC patients. A significant proportion of patients with ALK-positive NSCLC have brain metastases at baseline. – Approximately 25% to 40% of patients with ALK-positive NSCLC who are not treated with an ALK inhibitor have brain metastases at baseline (Toyokawa et al., 2015).	The outcomes listed within the scope are not intended to be exhaustive. Data on additional outcomes, including intracranial progression free survival, can be included within the appraisal submission if relevant.

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		– The central nervous system was a site of disease progression in 70% of patients with brain metastases at baseline and in 20% of patients without brain metastases at baseline (Costa et al., 2015). Secondly, patients with ALK-positive NSCLC with brain metastases have poor prognosis. - Brain metastases in patients with ALK-positive NSCLC are associated with a generally poor survival outcome, low quality of life, and high economic burden (Peters et al., 2016; Walker et al., 2016). - Health care utilisation and costs were reported to substantially increase after diagnosis of brain metastasis (Guérin et al., 2015). The NICE technical team for TA670 recognised in their preliminary judgement; “there may be other specific types of extrapulmonary progressions that could incur very specific costs. However, the technical team believes these are likely to have a small impact on the cost effectiveness results of Brigatinib” The inclusion of intracranial PFS was also supported by the appraisal committee in TA670, as detailed in the FAD; “partitioning disease by central nervous system (CNS) progression to account for the effect of CNS involvement was appropriate” Toyokawa G, Seto T, Takenoyama M, Ichinose Y. Insights into brain metastasis in patients with ALK+ lung cancer: is the brain truly a sanctuary? Cancer Metastasis Rev. 2015 Dec;34(4):797-805 Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol. 2015 Jun;33(17):1881-8.	

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		Peters S, Bexelius C, Munk V, Leighl N. The impact of brain metastasis on quality of life, resource utilization and survival in patients with non-small-cell lung cancer. Cancer Treat Rev. 2016 Apr;45:139-62. Walker MS, Wong W, Ravelo A, Miller PJE, Schwartzberg LS. Effect of brain metastasis on patient-reported outcomes in advanced NSCLC treated in real-world community oncology settings. Clin Lung Cancer. 2018 Mar;19(2):139-47. Guérin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns and economic burden. J Med Econ. 2015 Apr;18(4):312-22	
	Novartis	No comment	No action needed.
Economic analysis	Pfizer	No additional comments	No action needed.
	Novartis	No comment	No action needed.
Equality and Diversity	Pfizer	We do not believe any equality issues are relevant	No action needed.
	Novartis	No comment	No action needed.
Other considerations	Pfizer	None	No action needed.
	Novartis	No comment	No action needed.
Innovation	Pfizer	Lorlatinib has been specifically designed to tackle the existing challenges faced by patients using the currently available ALK inhibitors to treat NSCLC. By penetrating the blood-brain-barrier and in overcoming most known resistance mutations that can delay ALK-dependent mechanisms of	Comment noted. No action needed.

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		resistance, Lorlatinib has quickly established itself as an important option in the long-term management of this condition. In its current indication, in patients who have failed an initial ALK inhibitor, Lorlatinib has been granted designation as a Promising Innovative Medicine by the MHRA (in 2018), as recognition of its innovative nature and its potential to improve the lives of ALK positive NSLC sufferers. In the proposed indication as a first line management therapy, interim analysis of the CROWN phase III study (of Lorlatinib vs Crizotinib) has demonstrated that Lorlatinib has a hazard ratio (HR) of 0.28 (0.19-0.41) for reducing the risk of progression or death at 12 months when compared to Crizotinib (Independent assessed) (Shaw et al. 2020). The equivalent HRs for Alectinib and Brigatinib (vs Crizotinib) were 0.50 (0.36 – 0.70) and 0.49 (0.33-0.74) respectively at the similar stage of analysis of their pivotal clinical trials (ALEX and ALTA-1L) (Peters et al. 2017, Camidge et al, 2018). Even though caution should be made on using cross trial comparisons, the magnitude of the improvement in patient outcomes from the 2nd to the first 3rd generation ALK inhibitor is significant. [redacted] Improvements in progression free survival (and importantly reduced CNS progression) and HRQoL have been demonstrated for lorlatinib in the CROWN study, though there remains uncertainty when considering the long-term comparative efficacy versus alectinib and brigatinib and a flexible approach is required to support the swift patient access and uptake to this technology.	

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		Shaw A. Bauer T. de Marinis F. First-Line Lorlatinib or Crizotinib in Advanced ALK-Positive Lung Cancer. NEJM. 2020 Nov;383(21):2018-2029. Peters S. Camidge D. Shaw A. Alectinib vs Crizotinib in untreated ALK-Positive Non-Small-Cell Lung Cancer. NEJM. 2017 Aug;377(9):829-838 Camidge D. Kim H, Ahn M. Brigatinib vs Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. NEJM. 2018 Nov;379(21):2027-2039	
	Novartis	No comment	No action needed.
Questions for consultation	Pfizer	Specific questions not captured above: Where do you consider lorlatinib will fit into the existing NICE pathway, Lung cancer? *Given the different stages of ALK+ NSCLC patients in their treatment journey we would see Lorlatinib as being added into the options for first line management of ALK+ NSCLC, as well as maintaining its current position in second line therapy.* Do you consider that the use of lorlatinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation? *As ALK+ NSCLC affects relatively younger patients than other forms of lung cancer (with an average age of around 50), impacts on employment, carers and family are important considerations.* NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. [redacted] *the similarities between this submission and the very recent Brigatinib submission and the known challenges with data maturity, while we agree Lorlatinib should be reviewed as a single technology, we*	Comment noted. No action needed.

Section	Consultee/ Commentator	Comments [sic]	Action
		request flexibility in the way this assessment is performed to support the swift patient access and uptake to this technology.	
	Novartis	No comment	No action needed.
Additional comments on the draft scope	Pfizer	None	No action needed.
	Novartis	No comment	No action needed.

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

ALK Positive UK, Takeda