National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Lorlatinib for previously treated 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	Pfizer suggests the following wording: "To appraise the clinical and cost effectiveness of lorlatinib within its expected marketing authorisation which is for treating ALK-positive advanced NSCLC previously treated with one or more ALK TKIs, except for patients previously treated with crizotinib as the only ALK TKI".	Thank you for your comment. The population has been changed to reflect lorlatinib's anticipated marketing authorisation. To maintain flexibility the remit is broader than the population, but now specifies that the appraisal should focus on people with previously treated ALK-positive NSCLC.

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	Roche	No comments	Thank you for your comment.
Timing Issues	Pfizer	No comment.	Thank you for your comment.
	Roche	No comments	Thank you for your comment.
Additional comments on the draft remit	Pfizer	Considering a license for previously treated patients is anticipated prior to a license for previously untreated patients, Pfizer suggests rewording the title of the appraisal to the following “Lorlatinib for treating ALK-positive advanced non-small-cell lung cancer previously treated with one or more ALK TKI, except for patients treated with crizotinib as the only ALK TKI”.	Thank you for your comment. The proposed title has been changed to ‘Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer’ to reflect the update to the population. The title is broader than the population included in the scope to maintain flexibility.

Comment 2: the draft scope

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Background information	Pfizer	"Approximately 5% of people with NSCLC have ALK fusion genes". • A genomics classification study analysing 1255 lung cancer tumours found the ALK alteration rate to be 3.4% in adenocarcinomas (Thomas, 2013). • Pfizer understands from clinical expert opinion in the UK that the real-world ALK+ incidence in NSCLC is closer to 3% than 5%. • Pfizer suggests the figure is changed to "3%" as opposed to "5%". *Thomas, A genomics-based classification of human lung tumors. CLCGP and NGM. Sci Transl Med 2013. 5, 2019ra153.*	Thank you for your comment. The prevalence statistic has been updated.
	Pfizer	"For adults with untreated ALK-positive advanced NSCLC, NICE recommends ceritinib (NICE TA500) and crizotinib (NICE TA406) as treatment options. NICE is also currently appraising alectinib for untreated ALK-positive advanced NSCLC (NICE technology appraisal guidance ID925)" • The final appraisal determination for alectinib was published on 28th June 2018, recommending alectinib as an option for untreated anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults. • Pfizer suggests the following wording: "For adults with untreated ALK-positive advanced NSCLC, NICE recommends alectinib (NICE ID925), ceritinib (NICE TA500) and crizotinib (NICE TA406) as treatment options."	Thank you for your comment. The scope now focuses on people with previously treated ALK-positive NSCLC. Because of this, the description of the current treatment options has been updated to reflect treatment options for this population.
	Roche	Roche agrees with all treatment options listed, however one appears to be missing: nivolumab for previously treated non-squamous (PDL1 expression >1%) and squamous NSCLC is recommended by NICE for use in the CDF.	Thank you for your comment. For this indication, nivolumab is only available through the Cancer Drugs Fund. Because it is not

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			available through routine commissioning, it is not considered to be established NHS practice in England, and so has not been included in this scope.
The technology/ intervention	Pfizer	The brand name for lorlatinib will be Lorviqua®.	Thank you for your comment. The description of the technology has been updated.
	Roche	No comments	Thank you for your comment.
Population	Pfizer	Pfizer suggests the following wording to align the population with the expected license, which includes removing the previously untreated population from this appraisal: “People with ALK-positive advanced NSCLC previously treated with one or more ALK TKIs, except for patients treated with crizotinib as the only ALK TKI”.	Thank you for your comment. The population has been updated to reflect the anticipated marketing authorisation. The wording has been changed to: ‘people with advanced ALK-positive NSCLC that has:

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			been previously treated with crizotinib and at least one other ALK-tyrosine kinase inhibitor, or, has been previously treated with at least one ALK- tyrosine kinase inhibitor other than crizotinib.'
	Royal College of Pathologists	The pathology community have procedures in place for the assessment of both ALK and ROS1 status in relation to previous appraisals so, unless there is a different methodology to be assessed, there is little to comment on from our perspective.	Thank you for your comment.
	Roche	No comments	Thank you for your comment.
Comparators	Pfizer	People with untreated ALK-positive advanced NSCLC should not be included within the scope of the submission as the license for lorlatinib is not expected to include the untreated population at this time. Therefore, "For people with untreated ALK-positive advanced NSCLC" and all the associated comparators should be removed. <u>Pfizer considers the following comparator relevant for people with ALK-positive advanced NSCLC treated with one or more ALK TKIs, except for patients treated with crizotinib as the only ALK TKI</u> • <u>Pemetrexed with cisplatin/carboplatin</u>	Thank you for your comment. The population in the scope has been updated to reflect lorlatinib's anticipated marketing authorisation. The remit for the appraisal now focuses on people with previously treated ALK-

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		○ There are currently three NICE recommended ALK inhibitors: crizotinib, ceritinib and alectinib. All three are recommended for use in previously untreated patients. Ceritinib is recommended for use post-crizotinib. Crizotinib is recommended for use in previously treated patients, based upon evidence post-chemotherapy. ○ As such, currently pathways are: ▪ crizotinib → ceritinib ▪ chemotherapy → crizotinib → ceritinib ▪ ceritinib ▪ alectinib ○ The expected license for lorlatinib is for use in patients treated with one or more ALK TKIs, except for patients treated with crizotinib as the only ALK TKI. Lorlatinib will thus be used after all 4 of the above pathways. ○ Clinical expert opinion has confirmed that currently pemetrexed in combination with platinum-based chemotherapy is the standard of care following all of the above 4 pathways in the UK. ○ Carboplatin and cisplatin are equally used in combination with pemetrexed in UK clinical practice according to expert opinion. ○ In order to accurately reflect UK practice, Pfizer requests pemetrexed with cisplatin/carboplatin is added as the only relevant comparator, which is in line with expert opinion and NICE recommendations for current ALK inhibitors. <u>The following comparators are deemed not relevant for the proposed indication:</u> • <u>Crizotinib</u>	positive NSCLC. Because of this, the treatment options for first-line treatment (alectinib, ceritinib and crizotinib) have been removed as comparators. Brigatinib has been removed as a comparator because it is unlikely to be established care at the time of the proposed appraisal (because brigatinib is currently being appraised). Following confirmation with clinical experts about the current treatment pathway for previously treated ALK-positive NSCLC, crizotinib and ceritinib have been removed as comparators. Pemetrexed is not recommended for the treatment of locally

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		○ Crizotinib is only used in ALK+ NSCLC patients who are untreated with an ALK inhibitor in the UK. There is currently no data for crizotinib use post ceritinib or alectinib. • <u>Ceritinib</u> ○ Ceritinib has a market authorisation for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib (EMA SmPC July 2018). As such, ceritinib is not a relevant comparator, as lorlatinib will not be indicated for those previously treated with crizotinib alone. • <u>Brigatinib</u> ○ Brigatinib is awaiting CHMP opinion and is subject to an ongoing NICE appraisal with publication expected in December 2018, therefore cannot be considered a relevant comparator as it is not standard of care. • <u>Atezolizumab and pembrolizumab</u> ○ The final appraisal determination for both treatments recommends them for patients who have previously had chemotherapy and targeted treatment if ALK-positive (TA520 and TA428). Hence, neither are appropriate comparators as patients would receive chemotherapy after ALK targeted treatments prior to receiving atezolizumab or pembrolizumab. Clinical expert opinion has confirmed these are not standard of care. • <u>Best supportive care (BSC)</u> ○ Patients receiving BSC are unable to tolerate or are unwilling to receive any further active treatment; therefore BSC is not considered an appropriate comparator for lorlatinib.	advanced or metastatic NSCLC in people who have had previous chemotherapy (NICE TA124). Clinical experts have confirmed that they would expect some people with confirmed ALK+ NSCLC to have had previous chemotherapy (reflecting possible problems with the testing of ALK- status). Because of this, pemetrexed with cisplatin/carboplatin has been added as a comparator for people who had not had previous chemotherapy. Clinical experts have confirmed that atezolizumab and pembrolizumab may be used to treat ALK+ NSCLC when other treatment options have been exhausted. These treatments have been

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			included as comparators for people who have had previous chemotherapy (and are therefore ineligible for treatment with pemetrexed). Best supportive care has been included as a comparator for people who have had previous chemotherapy, as an alternative to immunotherapy.
	Roche	Please see comment on background information for missing comparator. In addition, alectinib guidance will be finalised on 8th August, therefore will no longer be subject to an ongoing appraisal.	Thank you for your comment. For this indication, nivolumab is only available through the Cancer Drugs Fund. Because it is not available through routine commissioning, it is not considered to be established NHS practice in England, and so has not been included in this scope.

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			The remit for the appraisal now focuses on people with previously treated ALK-positive NSCLC. Because of this, the treatment options for first-line treatment (including alectinib) have been removed as comparators.
Outcomes	Pfizer	Yes, these outcomes are sufficient to capture the health related benefits of the technology.	Thank you for your comment.
	Roche	No comments	Thank you for your comment.
Economic analysis	Pfizer	Pfizer does not believe it necessary to include the costs associated with diagnostic testing for ALK mutation, as patients have already received ALK targeted therapy under the proposed indication.	Thank you for your comment. To ensure the scope is comprehensive, it specifies that costs associated with ALK-status testing are included. However, the scope specifies that this only applies for people who would not otherwise have been

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			tested. If the population does not include patients with unknown ALK-status, this requirement is unlikely to affect the cost-effectiveness estimates.
	Roche	No comments	Thank you for your comment.
Equality and Diversity	Pfizer	No comment.	Thank you for your comment.
	Roche	No comments	Thank you for your comment.
Other considerations	Pfizer	None.	Thank you for your comment.
	Roche	No comments	Thank you for your comment.
Innovation	Pfizer	Lorlatinib was specifically designed to meet the unmet need for a CNS-active, potent ALK inhibitor with efficacy against tumours bearing ALK-resistant mutations and addresses a clear medical need by advancing outcomes for patients with ALK-positive NSCLC who have progressed despite treatment with second-generation ALK TKIs. For these patients, no other treatment options exist aside from chemotherapy, which is associated with poor outcomes (Novello 2017). In the Phase I/II Study 1001, lorlatinib	Thank you for your comment. The appraisal committee will consider any innovative benefits of lorlatinib during the appraisal.

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		demonstrated a clinically meaningful benefit in patients with ALK-positive advanced NSCLC, with rapid, deep and durable systemic and IC responses, and a manageable AE profile. Lorlatinib is the only ALK TKI with robust clinical evidence for efficacy in ALK-positive NSCLC patients harbouring the G1202R mutation, which is the most common ALK mutation among patients who have progressed following treatment with second-generation ALK TKIs (Gainor 2016). Lorlatinib's ability to cross the blood-brain barrier, along with the rapid and durable IC response, means that it is expected to provide therapeutic benefit to patients with brain metastases, a common cause of disease progression following treatment with current ALK TKIs. Lorlatinib therefore offers the opportunity to delay subsequent chemotherapy, and the associated toxicities and reduced QoL. Due to the poor outcomes associated with chemotherapy, only single arm studies are appropriate within this indication, therefore comparator data is reliant on external data sources. However, initial searches suggest there are a limited number of studies reporting outcomes which do not directly match the indication and no data on overall survival has been identified. In addition, given the positive improvement in outcomes of patients on the new first line standard of care (alectinib), outcomes beyond progression on alectinib are still unknown. Therefore, the clinical uncertainty within the initial analysis will reduce over time while further evidence is collected. *Novello S, Mazieres J, Oh I, de Castro J, Migliorino MR, Helland A, et al. Primary results from the phase III ALUR study of alectinib versus chemotherapy in previously treated ALK+ non-small-cell lung cancer (NSCLC). Ann Oncol. 2017;28(Suppl 5):v605-49.* *Gainor JF, Dardaei L, Yoda S, Friboulet L, Leshchiner I, Katayama R, et al. Molecular Mechanisms of Resistance to First- and Second-Generation ALK*	

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		Inhibitors in ALK-Rearranged Lung Cancer. Cancer Discov. 2016;6(10):1118-33.	
	Roche	No comments	Thank you for your comment.
Questions for consultation	Pfizer	No further comments.	Thank you for your comment.
	NCRI-ACP-RCP-RCR	*Which treatments are considered to be established clinical practice in the NHS for ALK-positive advanced NSCLC?* • Alectinib and Ceritinib are likely to gradually replace crizotinib in the first line setting. • 2nd line ceritinib (brigantinib) for patients progressing on crizotinib. • No established treatment for patients progressing on Alectinib and Ceritinib options will include chemotherapy, immunotherapy and other TKIs. *How should best supportive care be defined?* To include palliative radiotherapy but not chemotherapy. *Would best supportive care include chemotherapy? If so, which treatment regimens? Would nintedanib be used in combination with chemotherapy?* Platinum based doublets with pemetrexed most commonly considered for non-squam NSCLC, second line chemotherapy would be docetaxel – nintendinib *Are the outcomes listed appropriate?* Yes	Thank you for your comment. The remit for the appraisal now focuses on people with previously treated ALK-positive NSCLC. Because of this, the treatment options for first-line treatment (alectinib, ceritinib and crizotinib) have been removed as comparators. Brigatinib has been removed as a comparator because it is unlikely to be established care at the time of the proposed appraisal (because

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		Are there any subgroups of people in whom lorlatinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No *Do you consider lorlatinib 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)?* Lorlatinib is a third generation TKI targeting the ALK rearrangement, evidence suggests significant benefits (step change) cf first generation inhibitors but evidence against other third generation inhibitors that are going through NICE assessment is lacking. *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.* None the process of identifying and treating these patients with oral TKIs is well established.	brigatinib is currently being appraised). Following clinical expert advice, the comparators in the scope now include chemotherapy (pemetrexed with cisplatin/carboplatin) and immunotherapy options (atezolizumab and pembrolizumab) for people who have progressed after ALK-inhibitors. Choice of comparators depends on treatment with prior chemotherapy, in line with NICE TA124.
Additional comments on the draft scope	Roche	*Have all relevant comparators for lorlatinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for ALK-positive advanced NSCLC?* See comment on background information for missing comparator, and comparators for details of the alectinib appraisal. *Which treatments are people with ALK-positive advanced NSCLC likely to receive after initial treatment with crizotinib?*	Thank you for your comment. For this indication, nivolumab is only available through the Cancer Drugs Fund. Because it is not available through routine commissioning, it is not considered to be established NHS

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		In the appraisal of alectinib, it was deemed 70-80% of people who progressed on crizotinib would be treated with certinib *Which treatments are people with ALK-positive advanced NSCLC likely to receive after initial treatment with alectinib?* In the appraisal of alectinib, it was estimates 50% of people who progressed taking alectinib would have subsequent chemotherapy *Other questions:* No comment	practice in England, and so has not been included in this scope.

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

Merck Sharp & Dohme UK Ltd.