National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

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

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Pfizer	We consider it appropriate for this topic to be referred to NICE for appraisal. However, we are not aware of any existing or planned evidence for LDK378 in the treatment of patients with ALK-positive non-small-cell lung cancer (NSCLC) who have received chemotherapy only, as is the case with crizotinib. There are only two ongoing Phase 3 clinical trials for LDK378 registered in Clinicaltrials.gov (NCT01828099 and NCT01828112) [accessed 31st March 2014], of which only one focuses on previously treated patients (NCT01828112) and is therefore relevant for this appraisal. Clinical trial NCT01828112 compares LDK378 versus chemotherapy in ALK rearranged (ALK positive) patients previously treated with chemotherapy (platinum doublet) and crizotinib. The inclusion criteria of this study is as follows: #1.Patient has a histologically or cytologically confirmed diagnosis of non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK) positive as assessed by the Abbott FISH Test. #2.Patient has stage IIIB or IV diagnosis and must have received previous treatment with crizotinib and one regimen of platinum doublet cytotoxic chemotherapy for the treatment of locally advanced or metastatic NSCLC. #3.Patient has at least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation The inclusion criteria (point #2) for this trial requires that patients receive previous treatment with crizotinib and one regimen of platinum doublet cytotoxic chemotherapy.	Comment noted. Given the uncertainty around the wording of the final marketing authorisation for ceritinib, scoping workshop attendees agreed to keep the remit broad to encompass all the potential licensed indications for ceritinib. No action required.

Section	Consultees	Comments	Action
Appropriateness (cont.)	Pfizer (cont.)	We therefore believe that the only relevant population to this appraisal should include people with ALK-positive NSCLC who have received prior treatment with platinum doublet, cytotoxic chemotherapy and crizotinib.	
Wording	Pfizer	We do not think that the current wording fully reflects the planned clinical trial evidence for LDK378, whereby LDK378 is appraised for ALK positive NSCLC in patients who have previously been treated with platinum doublet cytotoxic chemotherapy and crizotinib. We would suggest the following revised wording to the remit for this proposed technology appraisal: "LDK378 for treating anaplastic lymphoma kinase-positive non-small-cell lung cancer that has progressed following prior treatment with chemotherapy and crizotinib".	Comment noted. Given the uncertainty around the wording of the final marketing authorisation for ceritinib, scoping workshop attendees agreed to keep the remit broad to encompass all the potential licensed indications for ceritinib. No action required.
Timing Issues	Pfizer	No comments	No action required.
Additional comments on the draft remit	Pfizer	None	No action required.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Pfizer	None	No action required.
The technology/ intervention	Novarits	The approved generic name for LDK378 is ceritinib. A brand name is not yet available.	Comment noted. The scope has been amended to reflect the approved generic name ceritinib.
	Pfizer	There are two ongoing Phase 3 clinical trials for LDK378 as registered in Clinicaltrials.gov: - NCT01828099: LDK378 Versus Chemotherapy in Previously Untreated Patients With ALK Rearranged Non-small Cell Lung Cancer - NCT01828112: LDK378 Versus Chemotherapy in ALK Rearranged (ALK Positive) Patients Previously Treated With Chemotherapy (Platinum Doublet) and Crizotinib The current scope proposed does not accurately reflect the clinical trial based evidence for LDK378.	Comment noted. Beside the phase 3 trial NCT01828112, there are 2 relevant phase 2 trials for ceritinib, NCT01685138 and NCT01685060, one of which included patients who have not previously received crizotinib. No action required.
Population	Pfizer	This should be modified to reflect the population included in the clinical trial program for LDK378 in previously treated patients, whereby LDK378 is appraised for ALK positive NSCLC in patients who have previously been treated with platinum doublet cytotoxic chemotherapy and crizotinib.	Comment noted. After receiving positive opinion from the Committee of Medicinal Products for Human Use for adult patients with ALK-positive advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib, the scope has been updated to reflect the wording of the approved indication.

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Comparators	Novartis	In the 2nd-line setting (post-chemotherapy), pemetrexed may be a comparator. In the 3rd-line setting (post crizotinib), it is possible that crizotinib itself may be a comparator since patients remain on treatment post-progression. The extent to which this is occurring in clinical practice should be confirmed with clinical experts. Best supportive care may include steroids, bisphosphonates, radiotherapy and pain relief	Comment noted. It was agreed at the scoping workshop that pemetrexed was not a valid comparator for ceritinib after chemotherapy or after chemotherapy and crizotinib because patients are likely to have received pemetrexed before being considered for ceritinib. After receiving positive opinion from the Committee of Medicinal Products for Human Use for adult patients with ALK-positive advanced non-small cell lung cancer previously treated with crizotinib, the scope has been updated and the comparator now is best supportive care.

Section	Consultees	Comments	Action
	Pfizer	As per the trial protocol for NCT01828112, pemetrexed and docetaxel are the appropriate treatment options for patients as an alternative to LDK378 who have previously been treated with platinum doublet cytotoxic chemotherapy and crizotinib, therefore should be included as relevant comparators in this appraisal. As described in the Appropriateness section, the inclusion criteria (point #2) for this trial requires that patients receive previous treatment with crizotinib and one regimen of platinum doublet cytotoxic chemotherapy, therefore crizotinib is not a relevant comparator in this appraisal. This is in line with current clinical practice, where crizotinib is routinely used in patients with ALK positive NSCLC previously treated with chemotherapy. As per the draft scope, best supportive care is also an appropriate comparator. If NICE was to proceed with the appraisal of LDK378 for people with ALK-positive NSCLC who have received prior chemotherapy only, Pfizer agree with NICE's decision to include drugs available through the Cancer Drugs Fund (CDF) as relevant comparators in this technology appraisal, as crizotinib is routinely used for the treatment of patients with ALK-positive NSCLC. Not including these technologies would reflect an inaccurate representation of how patients with previously treated ALK positive NSCLC are treated in England.	Comment noted. Although the phase 3 trial compared ceritinib with docetaxel or pemetrexed in patients who had received chemotherapy and crizotinib, the clinician at the scoping workshop indicated that neither docetaxel nor pemetrexed would be considered to be in routine use in the UK at that stage in therapy, and that best supportive care would be offered instead. No action required.
Outcomes	Novartis	Yes	Comment noted. No action required.
	Pfizer	None	No action required.

Section	Consultees	Comments	Action
Economic analysis	Pfizer	Pfizer believe this appraisal should evaluate the clinical and cost-effectiveness of LDK378 in ALK-positive NSCLC patients following treatment with platinum doublet cytotoxic chemotherapy and crizotinib. If NICE proceed with the appraisal of LDK378 following chemotherapy only, and therefore consider crizotinib as a comparator as it is currently available through the CDF, Pfizer would like to request clarity on NICE's new methods, as it is unclear how exploring cost-effectiveness against a therapy that has been deemed to be not cost-effective by the Institute will be integrated into the decision making process.	Comment noted. Sections 6.2.1–4 of the Guide to the methods of technology appraisal 2013 outline the Committee's approach to the relevance and appropriateness of comparators. In particular, section 6.2.3 states that when the assessment suggests that an established practice may not be considered a good use of NHS resources, the Committee will decide whether to include it as a comparator in the appraisal after reviewing an incremental cost–utility analysis. No action required.
Equality and Diversity	Pfizer	Pfizer note that the purpose of STAs, as described in the directions of the Secretary of State for Health and captured in section 1.2.2 of NICE's "Guide to the methods of technology appraisal 2013", is to appraise the health benefits and the costs of those technologies referred by the Secretary of State for Health and to make recommendations to the NHS in England and Wales. The CDF provides additional funding to enable patients within NHS England to access drugs that are not routinely funded by the NHS. As the CDF does not provide funding for the treatment of patients in Wales, Pfizer would like to request clarity on the impact this technology appraisal will have for patients in Wales, as including technologies that are only available through the CDF will not reflect the reality of patient treatment in Wales.	Comment noted. As part of the Health and Social Care Act in 2012, NICE became a non-departmental public body in England only in April 2013. Therefore, NICE issues guidance for England only. No action required.
Innovation	Pfizer	No comments	

Section	Consultees	Comments	Action
Other considerations	Pfizer	While we support the decision of including drugs available via the CDF as relevant comparators in technology appraisals, Pfizer would like to understand how NICE proposes to proceed with technology appraisals once the funding scheme ends in 2016.	Comment noted. The Committee will be guided by established practice in the NHS when identifying the appropriate comparators, irrespective of how established practice is funded. When the assessment suggests that an established practice may not be considered a good use of NHS resources, the Committee will decide whether to include it as a comparator in the appraisal after reviewing an incremental cost–utility analysis. No action required.
NICE Pathways	Novartis	In terms of the NICE pathway for lung cancer, it is expected that ceritinib will appear after treatment with chemotherapy. Licence extensions could move ceritinib forwards in the treatment pathway	Comment noted. No action required.
	Pfizer	"Where do you consider LDK378 will fit into the existing NICE pathway, Lung Cancer?" As stated previously, Pfizer believe LDK378 evaluated in the context of patients who have previously been treated with platinum doublet cytotoxic chemotherapy and crizotinib. Please refer to Pfizer's comments on the "Appropriateness" section for more information.	Comment noted. No action required.
Questions for consultation	*No comments received*.		

Section	Consultees	Comments	Action
Additional comments on the draft scope.	*No comments received*.		

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

Department of Health
Healthcare Improvement Scotland
The Royal College of Nursing

Response to consultee and commentator comments on the provisional matrix of consultees and commentators (pre-referral)

Version of matrix of consultees and commentators reviewed: Provisional matrix of consultees and commentators sent for consultation					
Summary of comments, action taken, and justification of action:					
	Proposal:	*Proposal made by:*		*Action taken:* Removed/Added/Not included/Noted	*Justification:*
1.	Remove Commissioning Support Appraisals Service from general commentators.	NICE Secretariat		Removed	Commissioning Support Appraisals Service no longer exists, and therefore has been removed from the matrix.

2.	Remove Cancer Network Pharmacists' Forum from professional groups.	NICE Secretariat		Removed	Cancer Network Pharmacists's Forum has disbanded, and therefore been removed from the matrix.
3.	Remove Research Institute for the Care of Older People from research groups.	NICE Secretariat		Removed	Research Institute for the Care of Older People is no longer involved in appraisals of this nature and has been removed from the matrix.
4.	Rename Public Health Wales NHS Trust.	NICE Secretariat		Renamed	'Public Health Wales NHS Trust' has been renamed 'Public Health Wales'
5.	Move British Thoracic Oncology Group to professional groups.	NICE Secretariat		Moved	British Thoracic Oncology Group has asked to be consulted as a professional group rather than a research group; this was agreed, and they have been moved accordingly.