National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Crizotinib for previously untreated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer [ID865]

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

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments	Action
Appropriateness	British Thoracic Society	The British Thoracic Society supports the intended appraisal for this topic.	Comment noted. No action required.
	Pfizer	It is appropriate to refer this topic to NICE for appraisal. There is an unmet need in anaplastic lymphoma kinase-positive NSCLC with no first-line targeted therapy currently available.	Comment noted. No action required.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Wording	Pfizer	We suggest adding 'previously' in the draft remit, so that it reads: *"Crizotinib for previously untreated…"* In addition to the above change, we also suggest adding 'non-squamous' to the draft remit, so that it reads: *"Crizotinib for previously untreated non-squamous anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer."* Crizotinib's pivotal Phase III trial in this first-line setting ('PROFILE 1014') included only advanced NSCLC patients with a non-squamous histological subtype.	Comment noted. The remit has been amended to read: 'To appraise the clinical and cost effectiveness of crizotinib within its marketing authorisation for previously untreated, anaplastic lymphoma kinase-positive (ALK-

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			positive) advanced non-small cell lung cancer.' The remit does not specify 'non-squamous' to be consistent with the wording of the marketing authorisation.
	Royal College of Pathologists	Yes	Comment noted. No action required.
Timing Issues	Pfizer	As there is an unmet need in the first-line setting for anaplastic lymphoma kinase-positive NSCLC due to no targeted therapies currently being available in the UK, it will be appropriate to appraise crizotinib as soon as possible after its marketing authorisation for this indication.	Comment noted. No action required.
	Royal College of Pathologists	Urgent as this appears to be an effective therapy on a selected group of patients with non-small cell lung cancer	Comment noted. No action required.
Additional comments on the draft remit	Pfizer	None.	No action required.
	Royal College of Pathologists	The main relevance for RCPath is the question "Are there any subgroups of people in whom crizotinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?", to which the answer is "yes" . This impacts on laboratory work as the test is either a FISH test, done in selected laboratories or immunohistochemistry, which can be done in greater numbers of laboratories, but requires validation for robust application.	Comment noted. No action required.

Comment 2: the draft scope

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Background information	Pfizer	1. *"It is estimated that approximately 3-5% of people with stage III or IV non-small-cell lung cancer 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 indicated the ALK+ incidence in NSCLC to be around 3%, rather than 5%. • Pfizer suggests the figure is changed to *"around 3%"* as opposed to *"3-5%".* 2. *"For most people with non-small-cell lung cancer, the aim of treatment is to extend survival, and quality of life."* • Pfizer suggests adding two further aims of treatment to this list: to delay progression, and to control or improve lung cancer symptoms. 3. *Burden of illness* • As well as the morbidity burden to patients, it is important to note that there is a considerable cost burden to the NHS from lung cancer. For example, in 2012-13, there were 84,876 hospital admissions for malignant neoplasm of the bronchus and lung (ICD code C34) in England, resulting in 295,114 bed days and 104,273 finished consultant episodes. (HSCIC, 2014) *Solomon et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.* *Thomas, A genomics-based classification of human lung tumors. CLCGP and NGM. Sci Transl Med 2013. 5, 2019ra153.* *The Health and Social Care Information Centre (HSCIC), Hospital Episode Statistics for England. Inpatient statistics, 2012-13. 2014. http://www.hscic.gov.uk/*	Comment noted. The scope has been amended to reflect that 3% of people with stage III or IV non-small-cell lung cancer have ALK fusion genes. Extending survival and improving quality of life are considered to capture most of the benefits from delaying progression, and controlling or improving symptoms. The budget impact of lung cancer would not normally be included in the background section of the scope.

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The technology/ intervention	Pfizer	Yes, it is accurate.	Comment noted. No action required.
Population	Pfizer	• Crizotinib's Phase III clinical trial in the first-line setting included non-squamous patients only. There are no Phase III first-line data for patients with histological tumours other than non-squamous. Consequently, Pfizer suggests the population is specified as non-squamous ALK+ NSCLC. • Pfizer does not think there are any subgroups that need to be considered separately.	Comment noted. The population does not specify 'non-squamous' to be consistent with the wording of the marketing authorisation. No action required.
Comparators	Pfizer	<u>1. Pemetrexed with cisplatin, non-squamous</u> • Pfizer understands from clinical expert opinion that pemetrexed in combination with platinum-based chemotherapy is the standard of care for non-squamous patients in the UK, and that carboplatin and cisplatin are equally used in combination with pemetrexed in UK clinical practice. • In order to accurately reflect practice, Pfizer requests *"cisplatin"* is amended to either *"cisplatin/carboplatin"* or *"platinum-based chemotherapy",* for example: *"Pemetrexed in combination with cisplatin/carboplatin (for people with non-squamous tumour histology only)"* <u>2. Platinum-based therapy, with gem/doc/pac/vin</u> • Pfizer understands from clinical expert opinion that it is it is uncommon for docetaxel, paclitaxel or vinorelbine with platinum-based chemotherapy to be used in non-squamous patients in the first line setting. These are instead comparators more commonly used to treat squamous patients.	Comment noted. It was agreed at the scoping workshop to include cisplatin or carboplatin in combination with pemetrexed. To reflect this comment and feedback received from clinical experts at the scoping workshop, single-agent chemotherapy with a third-generation drug has been included as comparator for people for whom treatment with

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		• It is also understood that gemcitabine is not commonly used in non-squamous patients, however may be an alternative therapy offered to a small number of non-squamous patients who are not be able tolerate pemetrexed. • Pfizer suggests removing the comparators in the second bullet (gem/doc/pac/vin) as these patients do not reflect the patients who would be looking to receive crizotinib.	a platinum drug is not appropriate. A third-generation drug in combination with platinum chemotherapy has been included as a comparator for people with squamous tumour histology to include comparators for all the populations covered by the marketing authorisation.
Outcomes	Pfizer	Yes, these outcomes are sufficient to capture the health related benefits of the technology.	Comment noted. No action required.
Economic analysis	Pfizer	No comments	No action required.

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Equality and Diversity	Pfizer	• ALK diagnostic testing is now established in England and has been routinely conducted over the past three years. • A potential inequity in the consideration for the treatment of ALK+ NSCLC was raised in the appraisal of crizotinib as a second-line therapy: *"…testing could be restricted to patients with a diagnosis of adenocarcinoma."* (NICE, 2013) • It is important that whole patient population in England and Wales that the drug might be approved for (non-squamous) have equitable access to efficient ALK diagnostic testing. *NICE TA296: Crizotinib for previously treated non-small-cell lung cancer associated with an anaplastic lymphoma kinase fusion gene. 2013. Available at: http://www.nice.org.uk/guidance/ta296/chapter/1-Guidance*	Comment noted. The potential equality issues raised at the scoping process will be considered by the Committee during the course of the appraisal.
Innovation	Pfizer	<u>Step-change in disease management</u> • There is an unmet need in patients who have ALK+ NSCLC as no targeted therapies are available in the first-line. Crizotinib is innovative as it presents as the first targeted treatment option for these patients. • The impact to patients of this innovative targeted therapy is demonstrated through the tumour response data. With standard of care (an untargeted therapy) the majority of patients do not respond to treatment (pemetrexed objective response rate of 45%, Solomon 2014). With crizotinib however, the majority of patients do respond to treatment (objective response rate of 74%, Solomon 2014), a result of the drug being a targeted therapy. • Furthermore, crizotinib is innovative in that it is an oral therapy which offers an alternative to the standard of care which is intravenously administered. Not only does this ease the disease management for the patient, but it also provides a solution to those patients who have difficulties with intravenous administration.	Comment noted. The company is encouraged to describe the innovative nature of crizotinib in its evidence submission. No action required.

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		<u>Not captured by the QALY</u> • Crizotinib's ability to not only control disease but actually improve symptoms and functioning whilst on treatment (Solomon, 2014) would be captured in the QALY for the patient. Advanced NSCLC is associated with considerable indirect costs due to loss of productivity from patients and carers (Stanisic, 2010). However, the alleviation of carer burden as a result of this benefit would not be captured in the QALY. • Younger patients with progression-free disease may be able to return to work and thus reduce costs associated with loss of productivity (Stanisic, 2010). At presentation, ALK+ patients are typically younger than the typical NSCLC patient and are commonly still of working age. This, combined with crizotinib's ability to alleviate symptoms, can lead to wider societal benefits less commonly seen with chemotherapy. *Solomon et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.* *Stanisic S et al. (2010) Societal cost savings through bevacizumab-based treatment in non-small cell lung cancer (NSCLC). Lung Cancer. 2010 Aug;69 Suppl 1:S24-30*	
Other considerations	Pfizer	No other considerations.	Comment noted. No action required.
	Royal College of Pathologists	Will the costs for the test(s) that identify the selected group of patients be included within the cost of the drug	Comment noted. The cost of testing for ALK mutations would be expected to be included in the economic model. No action required.

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NICE Pathways	Pfizer	As a first-line treatment option for advanced NSCLC immediately after diagnosis in patients who are identified as being non-squamous and ALK+.	Comment noted. No action required.
Questions for consultation	Pfizer	Have all relevant comparators for crizotinib been included in the scope? • Please see above comments in 'Comparators' Which treatments are considered to be established clinical practice in the NHS? • Pemetrexed in combination with cisplatin/carboplatin is considered to be the established standard of care in UK clinical practice for non-squamous NSCLC. Have the most appropriate outcome measures been included in the scope? • Yes Should other outcome measures be considered? • No suggestions Are there any subgroups of people in whom crizotinib is expected to be more clinically effective? • No Are there any subgroups of people in whom crizotinib is expected to be more cost effective? • No Exclusion of any people - equality • ALK diagnostic testing is essential for access to crizotinib. If regional variations in ALK testing exist, this could lead to inequitable access. Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts. • Existing levels of ALK testing at second line may suggest what testing rate	Comment noted. The comparators in the scope have been amended to include pemetrexed in combination with platinum chemotherapy (cisplatin or carboplatin), and single-agent chemotherapy with a third-generation drug for people for whom treatment with a platinum drug is not appropriate. A third-generation drug in combination with platinum chemotherapy has also been included as a comparator for people with squamous tumour histology to include comparators for all the populations covered by the marketing authorisation.

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		could be expected in the first line. Do you consider crizotinib to be innovative? • Yes, see 'Innovation' above. Health-related benefits that are unlikely to be included in the QALY calculation • The wider societal impact of patients returning to work is an outcome unlikely to be included in the QALY calculation, along with care burden alleviation. See 'Innovation' above. Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits. • Crizotinib's Phase III trial (Solomon, 2014). Innovation is demonstrated through the significant improvement in the response rate vs. standard of care, the speed of response vs. standard of care, the reversal of symptom progression on treatment, and the availability of an oral administration optional. *Solomon et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. N Engl J Med. 2014 Dec 4;371(23):2167-77.*	The company is encouraged to describe the innovative nature of crizotinib, and the health-related benefits that are unlikely to be included in the QALY calculation, in its evidence submission.

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

Department of Health
Li Lilly
Royal College of Nursing